The Cost of Tuberculosis Care – Assessing the Economics of Tuberculosis for Patients and the Health Care System

Olivia D'Silva

Thesis submitted to the University of Ottawa
in partial fulfillment of the requirements for the
Masters of Science in Epidemiology

School of Epidemiology and Public Health

Faculty of Medicine

University of Ottawa

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Preface:

This thesis will be presented as a manuscript consisting of two related projects: a systematic review analyzing patient costs associated with tuberculosis (TB) care in low-, middle-, and high-income settings and a cost-effectiveness analysis of second generation (SG) lateral-flow urine lipoarabinomannan assays (LF-LAM) in human immunodeficiency virus (HIV) positive patients from Sub-Saharan Africa.

Ethic approval was not required for either study as data was collected solely from published literature and publicly available data.

The first manuscript was conducted in collaboration with the Baylor College of Medicine in Houston, Texas and the U.S. Centre for Disease Control (CDC) in Atlanta, Georgia as part of the TB GAPS Project. Ms. Olivia D'Silva was involved in the design, data collection and analysis of the study along with Ms. Samantha Lancione, Ms. Oviya Ananthakrishnan, and Dr. Alice Zwerling. Ms. D'Silva wrote the manuscript under the guidance of Dr. Zwerling including feedback and approval from all co-authors.

The second manuscript consisted of a cost-effectiveness analysis for SG LF-LAM assays in HIV-positive patients from Sub-Saharan Africa. This study was designed by Ms. D'Silva along with Dr. Zwerling and Dr. Shrestha. Ms. D'Silva was responsible for building the decision analytic model, determining the key input parameters, and performing the data analysis. Ms. D'Silva was also responsible for writing the manuscript under Dr. Zwerling with feedback and approval from all co-authors.

The final thesis manuscript was written by Ms. D'Silva with support from her thesis advisory committee members – Dr. Zwerling, Dr. Alsdurf and Dr. Thavorn.

Abstract:

Background:

Tuberculosis (TB) is a major global health threat that results not only in health consequences but also economic consequences. Since 2015 the World Health Organization (WHO) has developed a strategy with the aim of ending the global burden of TB by reducing TB related deaths, reducing TB incidence and eliminating the burden of TB related catastrophic costs for patients and their families. In order to reach these targets, we need to implement effective TB diagnostic and care strategies that are feasible for both patients as well as the health care system.

Methods:

This study consists of two manuscripts which assess the economic burden of TB – one from the patient perspective and the other from the health system perspective. The first manuscript is a systematic review aimed to determine the costs incurred by patients and their households while receiving TB care with direct (medical and non-medical) as well as indirect costs being examined for the pre-diagnostic, post-diagnostic and total phase of care. It analyzed studies with varying patient populations from low-, middle-, and high-income settings to help estimate key factors that drive patient costs. Furthermore, it assessed the proportion of patients that incurred catastrophic costs and the coping strategies that they resorted to in order to offset the costs of TB care.

The second manuscript is a modelling study which aimed to develop, parameterize and analyze a decision analytic model to determine the cost, health outcomes as measured by disability adjusted life years (DALYs) averted and the cost effectiveness of second-generation lateral flow lipoarabinomannan assay (SG LF-LAM) diagnostic algorithms in people living with HIV (PLHIV) per DALY averted. This model examined four different strategies – 1) the standard of care (SOC) Gene Xpert MTB/RIF only, 2) Gene Xpert MTB/RIF plus LF-LAM for all patients, 3) Gene Xpert MTB/RIF plus LF-LAM for patients with a negative Xpert result, and 4) Gene Xpert MTB/RIF plus LF-LAM for patients who are symptom negative.

Results:

A systematic review showed that total patient costs related to TB care ranged from a mean of $2.80 to $19,153.80 (2019 USD) with costs largely dependent on geographic location as well as patient population, Direct medical and indirect cost components were the largest source of costs for patients and their families while receiving TB care. Direct medical costs included the cost of medication, consultations,

diagnostics, follow-up testing and hospitalization while indirect costs mainly consisted of loss of income. The costs of TB care were considered catastrophic for the majority of patients resulting in them using coping strategies to offset the burden of costs. In the second manuscript, the cost-effectiveness analysis Xpert only was found to be dominated by Xpert + FujiLAM conditional on a negative Xpert with an ICER of 1,000 USD/per DALY averted compared to the standard of care (SOC) Xpert only. Sensitivity analysis found that variations in the key model parameters had an impact on the cost and effectiveness calculations obtained through the model.

Conclusions:

The burden of TB related costs impact both patients and the health care system at all stages of TB care. Novel diagnostic strategies like the inclusion of FujiLAM for TB diagnosis in PLHIV are cost-effective tools that can aid in case detection and reduce severe outcomes of TB. In order to reduce TB burden and achieve the "End TB" strategy goals, studies need to work to understand the key components involved in these costs as well as work to develop and implement effective, feasible interventions for TB diagnostics and care.

Acknowledgments:

First and foremost, I would like to thank Dr Alice Zwerling for supporting me and guiding me not only through this project but through my whole master's degree. I would also like to thank Dr Hannah Alsdurf and Dr Kednapa Thavorn for their invaluable expertise and feedback on this project. Finally, I would like to thank my family and friends for their never-ending love and support.

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List of Abbreviations:

- TB – Tuberculosis
- WHO – World Health Organization
- LTBI – Latent TB Infection
- DS-TB – Drug Susceptible TB
- DR-TB – Drug Resistant TB
- MDR-TB – Multidrug Resistant TB
- ACF – Active Case Finding
- PCF – Passive Case Finding
- USD – United States Dollar
- LMIC – Low- and Middle-Income Countries
- CHE – Catastrophic Health Expenditure
- CTC – Catastrophic Total Costs
- NTP – National TB Program
- SAEs – Severe Adverse Events
- Xpert – GeneXpert mycobacterium tuberculosis (MTB)/rifampicin (RIF)
- LF-LAM – Lateral flow lipoarabinomannan assay
- SG – Second generation
- FujiLAM – Fujifilm SILVAMP TB LAM
- AlereLAM – Abbott's (formerly Alere) Determine TB LAM
- ICER – Incremental cost-effectiveness ratio
- DALY – Disability adjusted life years
- HIV – Human immunodeficiency virus
- ART – Antiretroviral therapy
- CDC – Centres for Disease Control and Prevention
- HCW – Healthcare worker
- PRISMA – Preferred reporting in systematic reviews and meta-analysis
- AFRO – African regional office
- EMRO – Eastern Mediterranean regional office
- SEARO – South-East Asia regional office
- WPRO – Western Pacific regional office
- EURO – European regional office
- PAHO – Pan American Health Organization
- DOT – Directly observed therapy
- CHC – Community health centre
- NGO – Non-government Organization
- RR-TB – Rifampicin resistant TB
- RMR-TB – Rifampicin mono-resistant TB
- RS-TB – Rifampicin sensitive TB
- SD – Standard deviation
- IQR – Interquartile range
- CI – Confidence interval
- 4SS – 4 symptom screening
- CXR – Chest x-ray
- SOC – Standard of care

Chapter One – General Introduction:

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium tuberculosis* and is spread through droplets that are released through coughing, sneezing or talking. Individuals infected with the disease can present symptoms including coughing, fever, night sweats and weight loss. TB can present in two ways – active TB in which an individual is symptomatic and able to transmit the disease to others, or latent TB infection (LTBI) where an individual is exposed to TB but able to contain the disease[1,2]. According to the World Health Organization (WHO), it is estimated that ~25% of the global population is infected with the disease however, only 10-15% of individuals experience a shift from latent TB infection (LTBI) to active TB disease. Furthermore, in 2021 it was reported that 10.6 million people fell ill with TB resulting in 1.6 million deaths[1–3]. TB is considered to be the leading cause of death amongst individuals living with human immunodeficiency virus (HIV) who are 16 times more likely to contract TB[3,4]. Of the 1.6 million people who died from TB in 2021, 187,000 were people living with HIV (PLHIV). Due to challenges with TB diagnosis and treatment, 30% of PLHIV are undiagnosed and left lacking TB treatment[3].

Prior to the COVID-19 pandemic, TB was considered to be a disease of the past despite being the deadliest infectious disease[3]. Although COVID-19 resulted in more deaths in 2020 than TB, the pandemic negatively impacted TB care and increased the number of people who were not able to seek proper TB diagnosis and treatment[5]. In order to help address the burden of TB the WHO developed the "End TB" strategy with the goal of eliminating TB. The three main targets of this strategy consist of 1) to have a 95% reduction in the number of TB related deaths, 2) to have a 90% reduction in TB prevalence and 3) to have 0% of TB affected families suffer from catastrophic costs associated with TB care. Over the past two decades numerous global efforts have worked to achieve these targets and been successful in reducing TB incidence and mortality however, because of the pandemic this was all reversed[6,7].

TB is a disease predominately impacting low- and middle-income settings which have inadequate resources and limited funding when it comes to providing TB care[3,8–10]. Using the latest diagnostic tools and providing the newest treatment options is often not feasible unless it has been recommended as a cost-effective intervention. Furthermore, despite programs offering free TB care many patients in these settings cannot afford to take time off work or are hesitant to seek care due to additional costs resulting in delayed diagnosis and poor outcomes[9,10]. In order to achieve "End TB" strategy goals of eliminating TB and the costs associated with its care research needs to be conducted on understanding the burden of costs from both a societal and a healthcare systems perspective as well as examining TB care algorithms to identify cost-effective strategies.

Thesis Overview and Objectives:

This thesis consisted of two studies presented as Manuscript One and Manuscript Two. Manuscript One is a systematic review which examines the burden of patient incurred costs associated with TB care. The study assesses direct and indirect costs incurred by patients in low-, middle-, and high-income settings across all stages of TB care – pre-diagnostic, post-diagnostic and total. Manuscript two consisted of a simple decision analytic model which was used to run a cost-effectiveness analysis for using second generation FujiLAM assays for TB diagnostic compared to the standard of care GeneXpert MTB/RIF only.

The two main objectives of this thesis are as follows:

1. To summarize the burden of catastrophic costs faced by patients and their families while receiving TB care across differing global setting and patient populations
2. To assess the cost-effectiveness of implementing FujiLAM diagnostic assays to assist in TB diagnosis for PLHIV from South Africa

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Chapter Two – Manuscript One:

The Catastrophic Cost of TB Care: Understanding costs incurred by individuals undergoing TB care in low-, middle-, and high-income settings

Olivia D'Silva[1], Samantha Lancione[1] MSc, Oviya Ananthakrishnan[2], Hannah Alsdurf[3] PhD, Kednapa Thavorn[1,4] PhD, Alice Zwerling[1] MSc, PhD

1. University of Ottawa, School of Epidemiology and Public Health – Ottawa, Canada
2. University of Western Ontario, Department of Microbiology and Immunology – London, Canada
3. GSK GlaxoSmithKline
4. The Ottawa Hospital Research Institute, Ottawa Hospital – Ottawa, Canada

2.1 Abstract:

Background:

Eliminating the burden of catastrophic costs at >20% a household's pre-tuberculosis (TB) annual income is one of the World Health Organization (WHO) End TB Strategy targets. Historically, data on the costs incurred by individuals and their families while undergoing TB care has been sparse limiting our ability to mitigate the financial and social impact of these costs but growing interest in this area has resulted in numerous new research. In order to improve the current knowledge and help inform decisions on cost effective TB care, this study was conducted to provide a clear understanding of the burden of costs incurred by individuals while undergoing TB treatment and identify the main drivers of costs.

Methods:

We conducted a systematic review to examine the costs incurred by patients undergoing TB care in low-, middle-, and high-income country settings. We performed literature searches using Embase, Web of Science, Scopus and Medline online databases and included studies that used WHO, or WHO adapted patient costing questionnaires, to measure direct (medical and non-medical) and indirect (time lost and loss of income) patient-related costs associated with TB care. Studies were screened and data were extracted independently by three reviewers. We extracted key cost data and patient baseline characteristics, such as geographic setting, patient subgroups, and economic setting, to identify main drivers of cost.

Results:

Of 790 studies screened, 45 meet the inclusion criteria. A large proportion of studies were conducted within the last 5 years (73% from 2017-2021), while 35% included patient populations with drug resistant TB (DR-TB), and 62% with HIV-positive patients. Total mean costs per person for TB care ranged from a mean of $2.80 - $19,153.80; pre-diagnostic costs ranged from a mean of $13.41 - $2,682.10; while post-diagnostic costs ranged from a mean of $44.20-$4,894.39. Patient costs largely differed based on geographic setting and patient population with costs found to be consistently higher amongst persons with DR-TB and those identified through passive case finding. Direct medical and indirect costs significantly impacted the burden of patient incurred costs for both the pre- and post-diagnostic phase of TB care with medication, hospitalization and loss of income being the largest drivers of cost. Nearly all patients were found to suffer from catastrophic costs and resorted to coping strategies such as taking out loans, selling assets or using savings in order to offset costs.

Conclusions:

Despite many countries offering free TB care patients still incurred significant catastrophic costs. Future studies should aim to develop and implement cost-effective, country specific strategies that scale up the reach of TB programs, encourage evidence-based practices, and adopt social protection interventions like cash transfers and financial compensation to help eliminate the burden of patient costs and meet the END TB Strategy goal.

2.2 Introduction:

In 2021, tuberculosis (TB) impacted approximately 10.6 million people worldwide and was the second leading infectious cause of mortality following COVID-19[1]. With eighty-six percent of new TB diagnoses from the top 30 high TB burden countries, TB has been found to disproportionately impact the poor with the largest share of disease burden in India, China, Indonesia, and the Philippines[1,2,3]. According to the World Health Organization (WHO), 98% of all TB cases occur in individuals from low- and middle-income countries (LMIC) often with limited access to affordable and effective TB care[1,3].

In 2015, the WHO developed the End TB Strategy which includes a goal to eliminate the burden of catastrophic costs for patients impacted by TB and their households by 2030[45,6] Costs are defined as catastrophic when the total cost of TB care exceed 20% of a household's annual income pre-TB diagnosis[1]. These patient costs can be incurred at any stage of treatment – pre-diagnostic or post-diagnostic and consist of direct medical costs such as consultations by physicians or health care workers (HCW), additional diagnostic testing or medications and direct non-medical costs like those associated with transportation, accommodations and food. Individuals with TB also incur indirect costs resulting from time lost during illness and loss of income while seeking care[1,5,7]. For many, the burden of these additional costs has a catastrophic impact on their overall household income and can result in both financial as well as social consequences. In addition, the burden of the cost of TB care has also been found to deter individuals from seeking TB care in the first place and can lead to delayed diagnosis, poor adherence, and adverse TB outcomes[8,9]. While a majority of countries offer free TB diagnostic and treatment through public health systems or established global TB programs, patients and households with TB may still face severe costs associated with TB care[5,6]. In 2021, the WHO reported that 48% of individuals impacted by TB and their households incurred catastrophic patient costs.

Prior to the implementation of the End TB Strategy, economic evidence on the burden of patient costs associated with TB care had been sparse however, since 2015 the WHO has supported numerous national surveys to help understand the burden of patient incurred costs associated with TB care[1,6]. Previous systematic reviews found that a large proportion of patients incur catastrophic costs while receiving TB care and particular populations, and individuals with drug-resistant TB (DR-TB), human immunodeficiency virus (HIV)-TB coinfection and patients found using passive case finding (PCF) methods are groups that incur the highest burden of costs[5,7]. Yet these studies have not been able to provide a detailed understanding of the direct and indirect cost components associated with TB care, or the factors that influence patient incurred costs. Previous systematic reviews have been restricted to analysis of catastrophic costs at particular stages of treatment, or specific socioeconomic or population settings[5,7,10]. Research examining direct and indirect patient costs incurred throughout all stages of care is limited. To our knowledge, no systematic review to date has reported the direct and indirect patient costs incurred during all stages of TB-care – pre-diagnostic, post-diagnostic and overall, examined across all global socioeconomic settings – low-, middle-, and high-income. Thus, we conducted a systematic review to examine the costs incurred by patients throughout the TB care pathway in low-, middle-, and high-income country settings. Key costing data from the included studies was used to identify the main drivers of costs through examining direct medical, direct non-medical and indirect cost components. Finally, we assessed the variations in costs using a sub-group analysis.

2.3 Methods:

A systematic review was conducted using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to understand the burden of costs for patients undergoing TB care in low-, middle-, and high-income settings. We performed literature searches using the Embase, Scopus, Medline and Web of Science databases. The search strategy was developed with aid from the University of Ottawa's medical librarian and consisted of the terms "tuberculosis", "latent tuberculosis", "patient costs" and "catastrophic costs" etc. The search strategy contained no language, time or geographic restrictions (see complete search strategy in the supplemental for full details) and included all studies published until July 2021.

Studies were independently evaluated for inclusion by two reviewers (OD and SL) and underwent title and abstract as well as full text reviews. Any discrepancies were resolved by discussion and consensus or by a third reviewer (AZ) if necessary. Inclusion criteria for this systematic review consisted of primary research studies that collected and reported on patient incurred costs associated with TB care and used a WHO approved or WHO adapted patient costing survey (WHO – Tuberculosis Patient Costing Surveys: A Handbook, StopTB, USAID or the TB|CTA – Tool to Estimate Patient Costs) to collect direct (medical and non-medical) and indirect (time lost and loss of income) patient incurred costs[11–13]. We included studies that consisted of patient populations with latent tuberculosis infection (LTBI), active TB disease, drug resistant TB (DR-TB) or multi-drug resistant TB (MDR-TB) as well as patients with TB/HIV coinfection. Studies were excluded if they used a unique costing survey not based on the WHO approach or if they did not report patient costs. Abstracts, conference posters, letters and systematic reviews were also excluded however, references of systematic reviews and other relevant literature were examined to identify additional studies for inclusion. Once studies were identified, they were presented using a PRISMA diagram[14]. Key patient characteristic and costing data were independently extracted by three reviewers (OD, SL, and OA).

The primary outcome of this study was the total cost of TB care incurred by patients. Costs were obtained for both the pre-diagnostic as well as the post-diagnostic stage of care and were divided into direct medical, direct non-medical and indirect costs. Pre-diagnostic costs were defined as costs incurred from symptom onset to TB diagnosis while post-diagnostic costs were defined as any costs incurred following TB diagnosis to treatment completion. Direct medical costs were defined as any costs pertaining to medical services, examinations, and treatment[7,15,16]. Direct non-medical costs were defined as costs involved in but not pertaining to accessing treatment (i.e., accommodations, transportation, food, etc.)[15,16]. Indirect costs were defined as costs associated with a reduction in time and productivity at work or any form of paid labour due to illness[15,17]. In addition, we also examined the burden of catastrophic costs on patients which was defined as TB related costs exceeding more than 20% of a households annual income pre-TB diagnosis[7]. Due to the COVID-19 pandemic and its impact on global economies, all costs were converted from their original currency to 2019 USD using World Bank inflation and currency data for study. If year of cost valuation or original currency could not be confirmed with study authors, it was assumed that costs were collected in the local currency of the country where the study was conducted and valued at the final year of study conduct. Pre-diagnostic, post-diagnostic, and total costs were compared across geographic settings, patient demographics, treatment stages, and economic standings to understand the burden of patient costs as well as identify the main drivers of costs. Weighted averages were calculated using the extracted costing data and a sub-group analysis was conducted to understand the differences in patient costs across various subgroups. The subgroups analyzed include TB types (DS-TB vs DR/MDR-TB vs TB/HIV coinfection), geographic setting (WHO regions – AFRO, EMRO, SEARO, WPRO, EURO and PAHO) and TB burden settings (low-TB vs high-TB). TB burden settings were defined using the WHO Global List of High Burden Countries for Tuberculosis (TB), TB/HIV and multidrug/rifampicin-resistant TB (MDR/RR-TB), 2021 – 2025[18]. Data pertaining to the proportion of patients that incurred catastrophic costs and the cut-off range that was used was analyzed to understand the burden of catastrophic costs. This systematic review was conducted in accordance with PRISMA 2020 guidelines and has been registered in PROSPERO (Registration number: CRD42021293600).

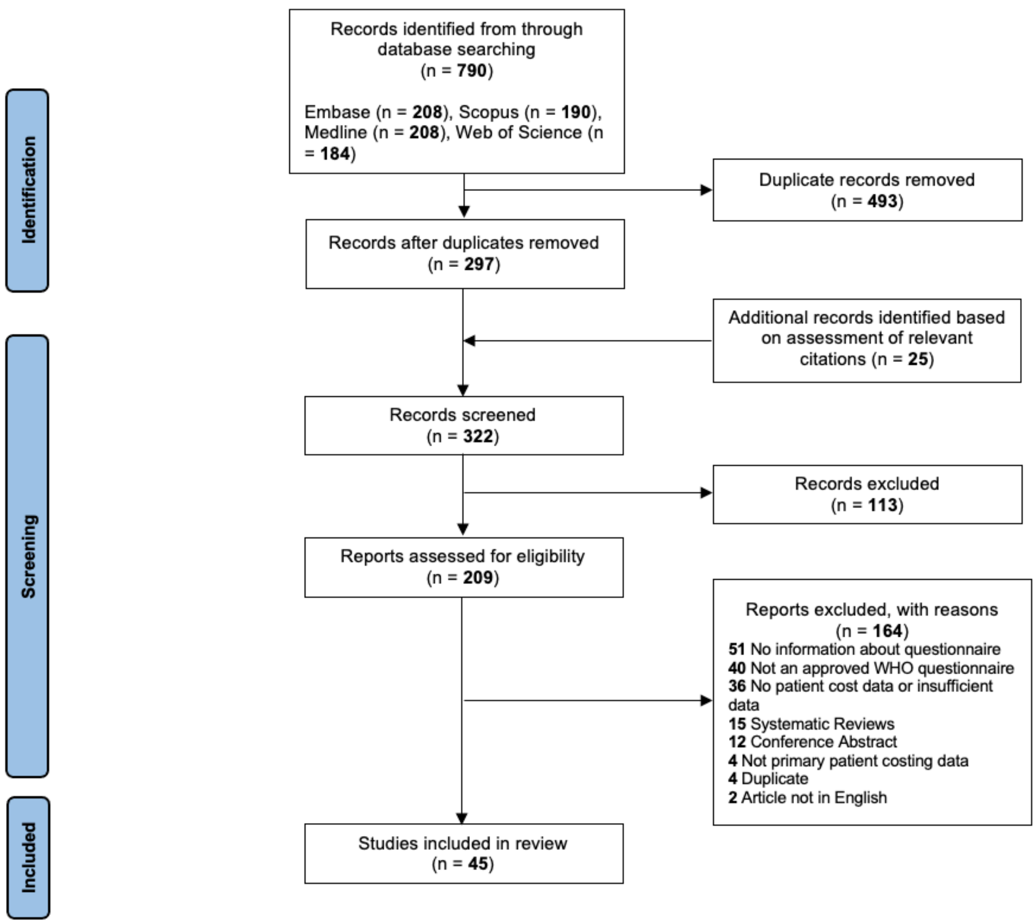
2.4 Results:

PRISMA:

Our search identified 790 studies of which 493 duplicates were removed. We identified 25 additional articles through reference lists of key systematic reviews. An initial title and abstract review were performed by independent reviewers (ODS, OA, and SL) on 322 studies with 113 studies excluded.

Two studies were excluded due to no members of our team speaking the language that they were published in. The remaining 209 studies underwent full-text review, and 45 studies were included in this systematic review (Figure 1).

Figure 2.1 – PRISMA 2020 flow diagram of patient costs associated with TB care in low-, middle-, and high-income settings.



Study Characteristics:

Key study characteristics for the included studies are highlighted in Table 1. Of the 45 studies identified for inclusion, 33 (73%) were published within the last five years (2017 – 2021) (Figure 2). All included studies were conducted in low- or middle-income countries with no studies conducted in a high-income setting. Studies were conducted across a combination of rural and urban settings globally with a large proportion conducted in African and Asian countries, 43.8% and 45.8% respectively (Figure 3). Study populations consisted mostly of adult patients; only 2 studies reported data on children <15 years of age. A total of 16 studies (35%) included patients with DR-TB or MDR-TB. Only 1 study included patients with LTBI (2%) while 28 studies (62%) included patients with HIV. Studies were conducted in either one health care setting or a combination of the two with the majority of studies conducted within public health centres (n=42) while a third of studies (n=14) conducted in private health centres (Table 1).

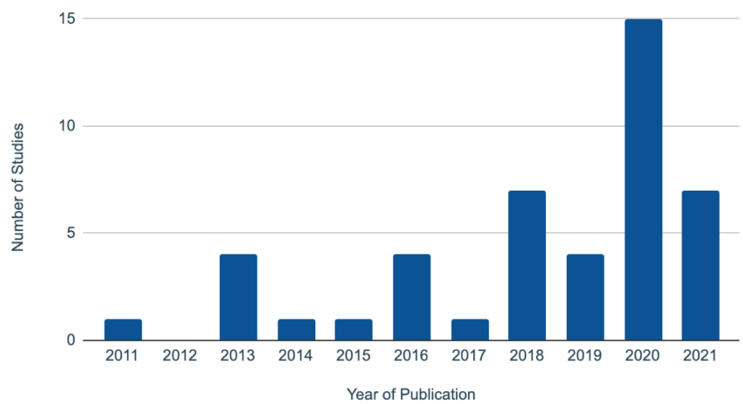


Figure 2.2 – Temporal Breakdown of Included Studies by Year of Publication

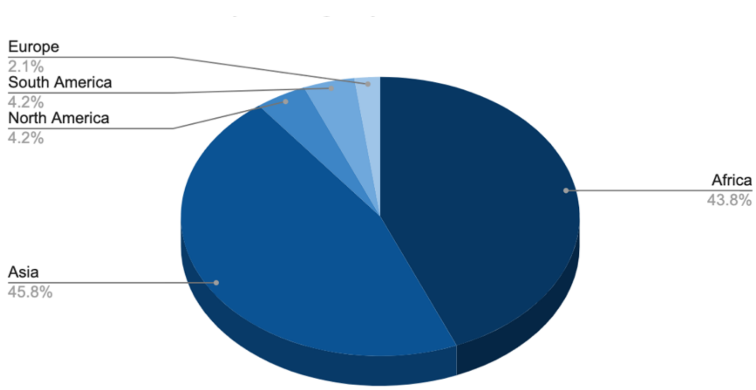


Figure 2.3 – Breakdown of Included Studies by Continent

Table 2.1 – Study Characteristics of Included Studies

Author name, Publication year	***Study Type***	***Year of study conduct***	***Study country (Urbanization status)***	***Study population***	***Sample size***	***Collected currency, Year of cost valuation***	***Health Centre Category***
Assebe, 2020[18]	Cross-sectional	2016 - 2019	Ethiopia (Urban, Rural)	TB patients, HIV+/- adult	n=787 (DR-TB=57)	Ethiopian Birr (ETB), 2019	Public
Aung, 2021[19]	Cross-sectional	2015 - 2016	Myanmar (NA)	TB patients, adult	n=967 (MDR-TB=66, DS-TB =901)	Myanmar Kyat (MMK), 2015	NA
Bogdanova, 2019[20]	Cost minimization analysis	2007 - 2009, 2011 - 2012	Russian Federation (Urban)	MDR-TB patients, adult	n=295	Russian Rubles (RUB), 2014	Public: Hospitals & Outpatient clinics
Chandra, 2021[(1)21]	Longitudinal	2019	North India (Urban, Rural)	New DS-TB patients, adults	n=110	Indian Rupee (INR), 2019	NA
Chandra, 2021[(2)22]	Cross-sectional	2019	North India (Urban, Rural)	New DS-TB patients, adults	n=109	Indian Rupee (INR), 2019	NA
Chittamany, 2020[23]	Cross-sectional	2018	Lao People's Democratic Republic (NA)	TB patients	n=848* (Nationally representative sample = 725, n=717 DS-TB, n=8 DR-TB; Additional sample = 123, n=30 DR-TB, n=123 TB-HIV)	Lao Kip (LAK), 2018	Public: Health facilities linked to the National TB Programme (NTP)
Collins, 2018[24]	Cross-sectional	2013	Ethiopia (Urban)	New MDR-TB patients	n=169	Ethiopian Birr (ETB), 2013	Public
De Siqueria Filha, 2018[25]	Pragmatic clinical trial	2015	Brazil (Urban)	New TB patients, HIV-positive adults	n=31 (TB/HIV=26, LTBI/HIV=5)	Brazilian Real (BRL), 2015	Public
Ellaban, 2021[26]	Prospective	2019 - 2020	Egypt (NA)	New TB patients, adults	n=151	Egyptian Pound (EGP), 2019	Public and Private: Private health centre, Public health centre, DOTS center
Fuady, 2020[27]	Cohort study	2016	Indonesia (Urban, Rural, Suburban)	New TB patients, adults	n=252	Indonesian Rupiahs (IDR), 2016	Public: Primary health centre
Fuady, 2020[28]	Cross-sectional	2016	Indonesia (Urban, Rural, Suburban)	New TB patients, adults	n=346 (DS-TB=282, MDR-TB=64)	Indonesian Rupiahs (IDR), 2015	Public: Primary health centre
Fuady, 2018[29]	Cross-sectional	2016	Indonesia (Urban, Rural, Suburban)	New DS-TB or MDR-TB patients, adults	n=346 (DS-TB=282, MDR-TB=64)	Indonesian Rupiahs (IDR), 2015	Public: Primary health centre
Getahun, 2016[30]	Cross-sectional	2015	Ethiopia (Urban, Rural, Homeless)	New TB patients, adults	n=576 (MDR-TB=16)	Ethiopian Birr (ETB), 2015	Public and Private: Private health centre and Public health centre

Author name, Publication year	***Study Type***	***Year of study conduct***	***Study country (Urbanization status)***	***Study population***	***Sample size***	***Collected currency, Year of cost valuation***	***Health Centre Category***
Gospodarevskaya, 2014[31]	Cross-sectional	2012	Bangladesh (subdistricts), Tanzania (Urban, Rural)	TB patients, adults	n=190 (Bangladesh=96, Tanzania=94)	Tanzanian Shillings, Bangladesh Takas (TZS, BDT), 2012	Public: Primary health centre, rural health facilities, DOTS centres
Gurung, 2021[32]	Longitudinal	2018 - 2019	Nepal (Urban, Rural)	New, retreated or relapsed DS-TB patients, adults	n=221	Nepal Rupee (NPR), 2018	Public and Private: Public Hospital, Private Hospital, Private health centre, Public health centre, NGOs, and informal providers such as pharmacists and traditional healers.
Gurung, 2019[33]	Cross-sectional	2018	Nepal (NA)	New, retreated or relapsed DS-TB patients, adults	n=99	Nepal Rupee (NPR), 2018	Public: Primary health centre, Public Hospital, Health posts, TB camps, DOTS centre
Kirubi, 2021[34]	Cross-sectional	2017	Kenya (Urban, Rural)	DS-TB patients	n=1071	Kenyan Shillings (KSH), 2020	Public and Private: Public and private health facilities that were within the NTLD - Program network.
Lu, 2020[35]	Cross-sectional	2014-2015	China (Urban)	DS-TB patients	n=248	Chinese Yuan (CNY), 2015	NA
Mauch, 2013(1)[36]	Cross-sectional	2010	Ghana, Viet Nam, Dominican Republic (Urban, Rural)	New DS-TB patients, ≥15 years	n=543 (Ghana=135, Viet Nam=258, Dominican Republic=150)	Dominican Republic Pesos (DOP), Ghanaian Cedi (GHC), Vietnamese Dong (VND), 2009	Public and Private: Primary health centre, Regional hospital, district hospital, private clinic, pharmacy, mission hospital, other
Mauch, 2011[37]	Cross-sectional	2008	Kenya (Urban, Rural)	New or re-treatment TB patients, ≥ 15 years	n=208	Kenyan Shilling (KSH), 2008	Public: Public health centre, Faith-based clinics, TB treatment centres
Mauch, 2013(2)[38]	Cross-sectional	2009	Dominican Republic (Urban, Rural)	New or re-treatment TB patients, adults under the age of 65	n=198 (New TB=150, Retreatment= 28, MDR-TB=20)	Dominican Republic Pesos (DOP), 2009	Public and Private: Private health centre, Public health centre
McAllister, 2020[39]	Cross-sectional	2017-2019	Indonesia (NA)	New TB patients, adults	n=469	Indonesian Rupiahs (IDR), 2017	Public and Private: Public Hospital, Private Hospital, Private health centre, Community health centres (CHC)
Morishita, 2016[40]	Cross-sectional	2014	Cambodia (NA)	New DS-TB patients, adults	n=208	Cambodian Riel (KHR), 2014⊥	Public: Primary health centres

Author name, Publication year	Study Type	Year of study conduct	Study country (Urbanization status)	Study population	Sample size	Collected currency, Year of cost valuation	Health Centre Category
Mudzengi, 2017[41]	Cross-sectional study nested within a cluster randomized trial—the MERGE trial.	2013	South Africa (NA)	New TB, HIV, or TB/HIV patients, adults	n=454 (TB/HIV=116, TB=40, HIV= 298)	South African Rand (ZAR), 2013	Public: Primary health care (PHC) clinics
Muniyandi, 2020[42]	Prospective cross-sectional	2018	South India (Urban)	DS-TB patients	n=384	Indian Rupee (INR), 2018	Public: Primary health centre
Muttamba, 2020[43]	Cross-sectional survey design with retrospective data collection and projections.	2017	Uganda (NA)	DS-TB or MDR-TB patients, children and adults	n=1178 (DS-TB=1134, MDR-TB=44)	Ugandan Shillings (UGX), 2017	Public: TB treatment facilities
Nhung, 2018[44]	National-level cross-sectional survey with retrospective data collection and projection	2016	Vietnam (NA)	DS-TB or MDR-TB patients, children and adults	n=735 (DS-TB=677, MDR-TB=58)	Vietnamese Dong (VND), 2015	Public and Private: Public and private facilities: Includes pharmacy/drugstore, herbalist/traditional practitioners, private clinic, private hospital.
Pedrazzoli, 2018[45]	Nationally representative survey	2016	Ghana (Urban, Rural)	TB patients, adults	n=691 (DS-TB=625, MDR-TB=66)	Ghanaian Cedi (GHC), 2016	Public: Public health facilities
Pedrazzoli, 2021[46]	Cross-sectional	2016	Ghana (Urban, Rural)	TB patients, adults	n=690	Ghanaian Cedi (GHC), 2016	Public: Primary, secondary and tertiary health centre
Prasanna, 2018[47]	Cross-sectional quantitative and in-depth qualitative interviews	2016-2017	South India (Urban, Rural)	New or re-treatment DS-TB patients	n=102	Indian Rupee (INR), 2017	Public and Private: Government hospital, private (Includes one each of Traditional Medicine Provider and pharmacist)
Ramma, 2015[48]	Cross-sectional cost-of-illness survey	2013	South Africa (Urban, Rural)	RR-TB or MDR-TB patients, adults	n=134	South African Rand (ZAR), 2013	Public: Primary health centre, Community health centre, TB hospital, and sub-acute care facility
Rupani, 2020[49]	Descriptive cross-sectional study	2019	Western India (Rural, Suburban)	DS-TB patients, adults	n=458	Indian Rupee (INR), 2019	Public: Public health centre
Shin, 2020[50]	Cross-sectional	2012-2017	Malawi (Rural)	Inpatients receiving TB care, adults	Primary population: Inpatients being treated for TB (n = 197); Comparison population: Outpatients being treated for TB (n=156) and outpatients consecutive adults who were recently	Malawian Kwacha (MWK), 2017	Public: Primary health centre, Public Hospital, Clinic

					diagnosed with HIV and undergoing screening for active TB (n=1530).		
Stracker, 2019[51]	Cross-sectional	2017-2018	South Africa (Rural)	New TB patients, adults	n=327 TB positive, n=263 Xpert negative	South African Rand (ZAR), 2018	Public: Public clinic
Author name, Publication year	***Study Type***	***Year of study conduct***	***Study country (Urbanization status)***	***Study population***	***Sample size***	***Collected currency, Year of cost valuation***	***Health Centre Category***
Sweeney, 2018[52]	Patient costing study nested within the TB FastTrack study, a pragmatic, cluster randomised trial	2014 - 2015	South Africa (Rural, Suburban)	Ambulant HIV-positive patients with no TB care, adults	n=66	South African Rand (ZAR), 2015	Public: Primary healthcare clinics
Timire, 2021[53]	Nationally representative health facility-based survey	2018	Zimbabwe (Urban, Rural)	DS-TB or DR-TB patients	n=860 (DS-TB=851; DR-TB=49)	South African Rand** (ZAR), 2018	Public: Health facilities
Tomeny, 2020[54]	Cross-sectional	2016	Philippines (NA)	TB patients, ≥16 years	n=194	Philippine Peso (PHP), 2016	Public and Private: Public Hospital, Public health centre, private clinic, NGO hospital
Trajman, 2016[55]	Cross-sectional costing study	2013-2014	Brazil (Urban, peri-urban)	TB patients	n=126	Brazilian Real (BRL), 2014	Public and Private: Family health clinic, classic health facilities and mixed clinics
Ukwaja, 2013[56]	Cross-sectional	2011	Nigeria (Rural)	New TB patients, ≥15 years old	n=452	Nigeria Naira (NGN), 2011	Public and Private: 3 rural hospitals (one public and two not-for-profit mission hospitals)
Ukwaja, 2013[57]	Cross-sectional	2011	Nigeria (Urban, Rural)	New TB patients, ≥15 years old	n=452	Nigeria Naira (NGN), 2011	Public and Private: Three rural hospitals; one secondary care public and two (not-for-profit) private from the three different zones in the State were selected as the study sites.
Van der Hof, 2016[58]	Cross-sectional	2012-2013	Ethiopia (Urban)	DS-TB or MDR-TB patients	n=603 (TB=197, MDR-TB=406) Ethiopia- 25 TB and 169 MDR-TB patients; Indonesia - 118 TB and 143 MDR-TB patients; Kazakhstan - 54 TB and 94 MDR-TB patients	Ethiopian Birr, Indonesia Rupiah, Kazakh Tenge (ETB, IDR, KZT), 2013	Public: Public hospitals and satellite hospitals

Author name, Publication year	Study Type	Year of study conduct	Study country (Urbanization status)	Study population	Sample size	Collected currency, Year of cost valuation	Health Centre Category
Viney, 2019[59]	Cross-sectional health-facility based survey	2016-2017	The Democratic Republic of Timor Leste (Urban, Rural)	TB patients	n=457	US Dollar (USD), 2017	Public: Public health centre, DOTS centres
Walcott, 2020[60]	Retrospective	2017	Uganda (Urban)	New TB patients, adults	n=196	Uganda Shillings (UGX), 2017	Public and Private: Medical facility (includes TB providers and private non-TB providers), pharmacy, traditional healer/ herbalist, or social contact (e.g., a parent or friend).
Wang, 2020[61]	Cross-sectional	2018	China (Urban, Rural)	MDR-TB patients	n=161	Chinese Yuan (CNY), 2018	Public: Public Hospital, Public health centre
Yang, 2020[62]	Cross-sectional	2018	China (Urban, Rural)	RS-TB or RR-TB patients	n=672 (RS=586, RMR=30 MDR=56)	Chinese Yuan (CNY), 2017	Public: Public Hospital; TB-designated hospitals

Abbreviations: TB – Tuberculosis, HIV – Human Immunodeficiency Virus, DR-TB – Drug-resistant TB, MDR-TB – Multi-drug resistant TB, DS-TB – Drug Sensitive TB, LTBI – Latent TB Infection, DOTs – Directly observed treatment, NGO – Non-governmental organization, RR-TB – Rifampicin-resistant TB, RS-TB – Rifampicin-sensitive TB

- The Chittamany et al., study reported costs for a nationally representative sample in addition and an additional sample with TB/HIV patients ** - study collected costs in South African Rand despite being conducted in Zimbabwe, ⊥ - costs were originally reported in 2011 - 2014 USD

Total Costs:

Total patient costs of TB care were reported in 40 studies (Table 2). Both mean and median costs are included in our study as the manner in which costs were reported varied between studies. Mean overall per person costs incurred during TB care ranged from $2.82 in out-patients in Malawi to $19,153.80 in MDR-TB patients in China. Median overall per person costs for TB care ranged from $7.00 in DS-TB adult patients from public health centres in Western India to $13,042.62 in MDR-TB patients from public hospitals in China. Average total costs of TB care across countries can be seen in Figure 4 with mean costs highest in China at $9,662.84 and lowest in Indonesia at $9.11 while median costs were highest in China at $8,052.64 and lowest in Ghana at $100.42.

DS-TB vs MDR-TB: Total cost per person for DS-TB patients ranged from a mean of $159.00 to $3,713.87 and a median of $45.77 to $2,443.05 while MDR-TB total patient costs were found to be significantly higher ranging from a mean of $1,510.00 to $19,153.80 and a median of $$964.88 to $13,042.62. When comparing the average total cost of TB care (Figure 5A), MDR-TB patients were found to incur the largest burden of costs (mean: $9,912.32, median: $4,564.75) followed by patients with DR-TB (mean: $13,598.50, median: $2,973.78) then DS-TB patients (mean: $2,128.70, median: $752.43).

Cost ranges incurred by patients for differing patient types like patients with TB/HIV coinfection, inpatients versus outpatients, and patients identified using different case finding methods like active case finding (ACF) compared to passive case finding (PCF) are highlighted in Figure 5B (additional details included in the supplement).

Total pre-diagnostic costs:

The total costs of TB ***pre-diagnostic*** care for patients were reported in 14 studies. Mean pre-diagnostic costs ranged from $13.41 in a population of newly diagnosed TB patients with LTBI/HIV from public hospitals in Brazil to $2,682.10 in a population of DS-TB patients from China. Median pre-diagnostic costs ranged from $5.38 in a population of newly diagnosed DS-TB patients from public hospitals in Indonesia to $187.00 in DS-TB patients from public hospitals in Nepal.

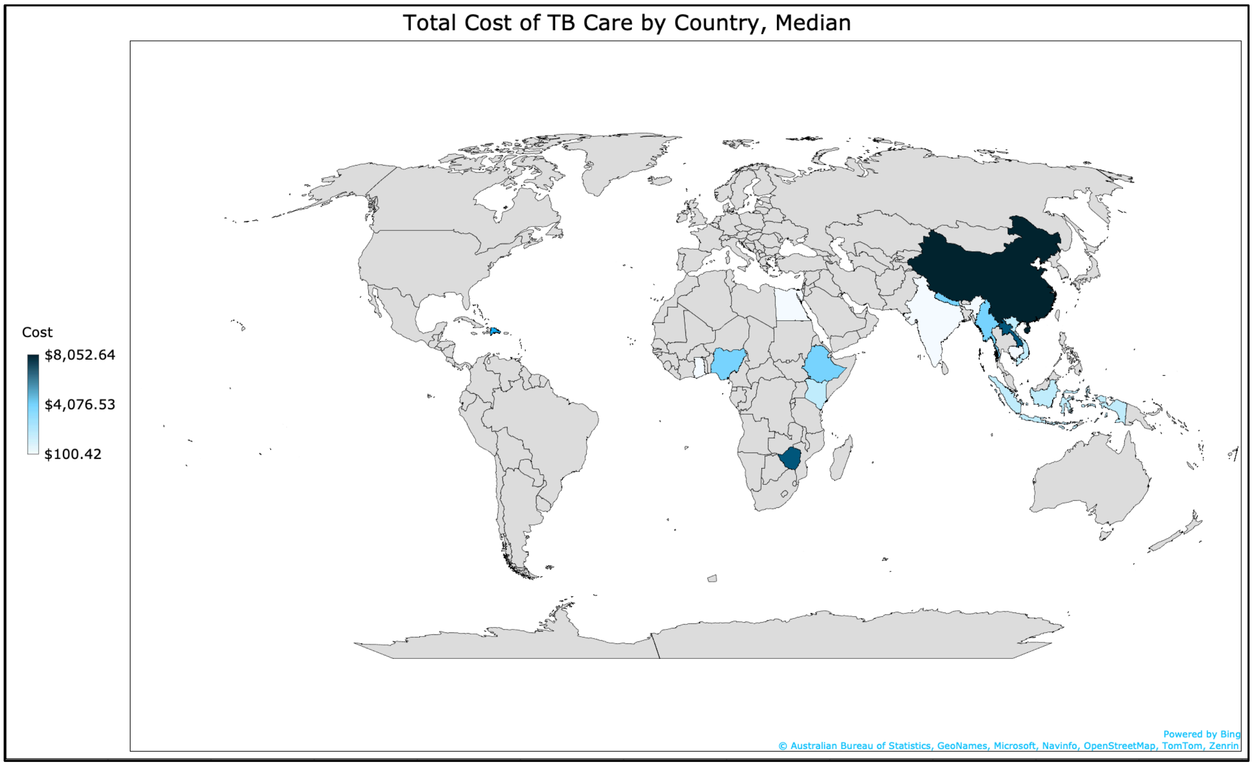
DS-TB vs MDR-TB: Two studies by Van der Hof *et al*., and Fuady *et al*., reported how pre-diagnostic costs varied between DS-TB and MDR-TB patients. Costs for DS-TB patients ranged between $5.38 to $17.50 while MDR-TB patient costs ranged between $11.18 to $93.76.

Total post-diagnostic costs:

The total ***post-diagnostic*** costs of TB care for patients were reported in 14 studies. Mean post diagnostic costs ranged from $44.20 in patients with LTBI/HIV coinfection from public hospitals in Brazil to $4,894.39 in DS-TB patients from China. Median post-diagnostic costs were found to range from $48.44 in DS-TB patients to $1,163.83 in MDR-TB patients from primary health centres in Ethiopia.

DS-TB vs MDR-TB: Post-diagnostic costs for patients with DR-TB compared to DS-TB were reported by two studies. Patients with DS-TB were reported to incur lower post-diagnostic costs as compared to patients with MDR-TB, ranging from $48.44 to $130.60 vs. $197.50 to $1142.78, respectively. A study by Van der Hof *et al.,* looked at the costs incurred by different TB patients across the intensive and continuous phase of TB treatment. TB treatment is divided into two stages – the intensive phase which is the first two month of treatment and the continuation phase which is the following months of treatment. Van der Hof *et al*., found that median costs incurred during the intensive phase ranged were $16.82 for DS-TB patients from Indonesia and $1,038.82 for MDR-TB patients from Ethiopia. Costs incurred during the continuation phase were reported to be $26.53 for DS-TB patients from Indonesia and $1,163.83 for MDR-TB patients from Ethiopia.

For a detailed breakdown of the total costs incurred by patients during the pre- and post-diagnostic phase see Table S2 in the supplemental.



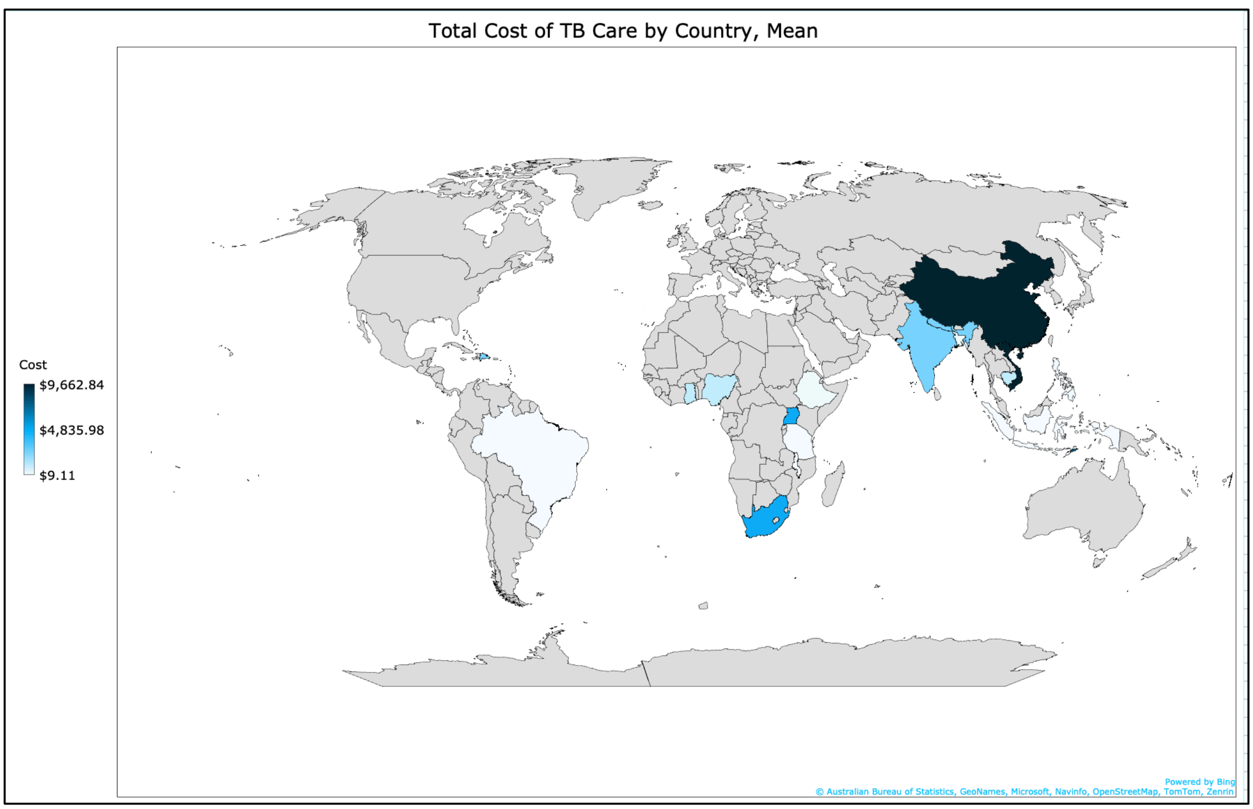
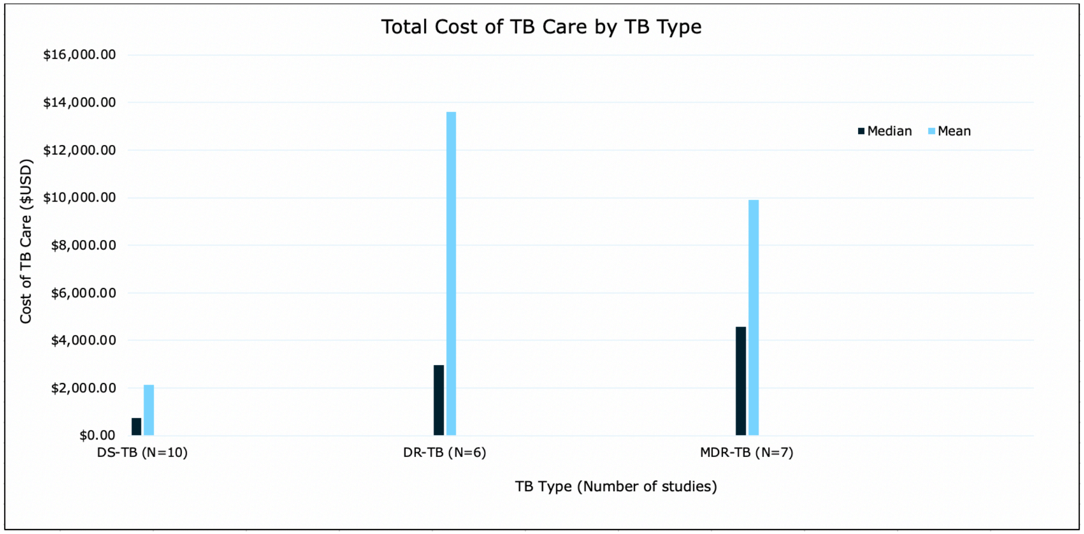


Figure 2.4 – Average total cost of TB care by country for median and mean costs



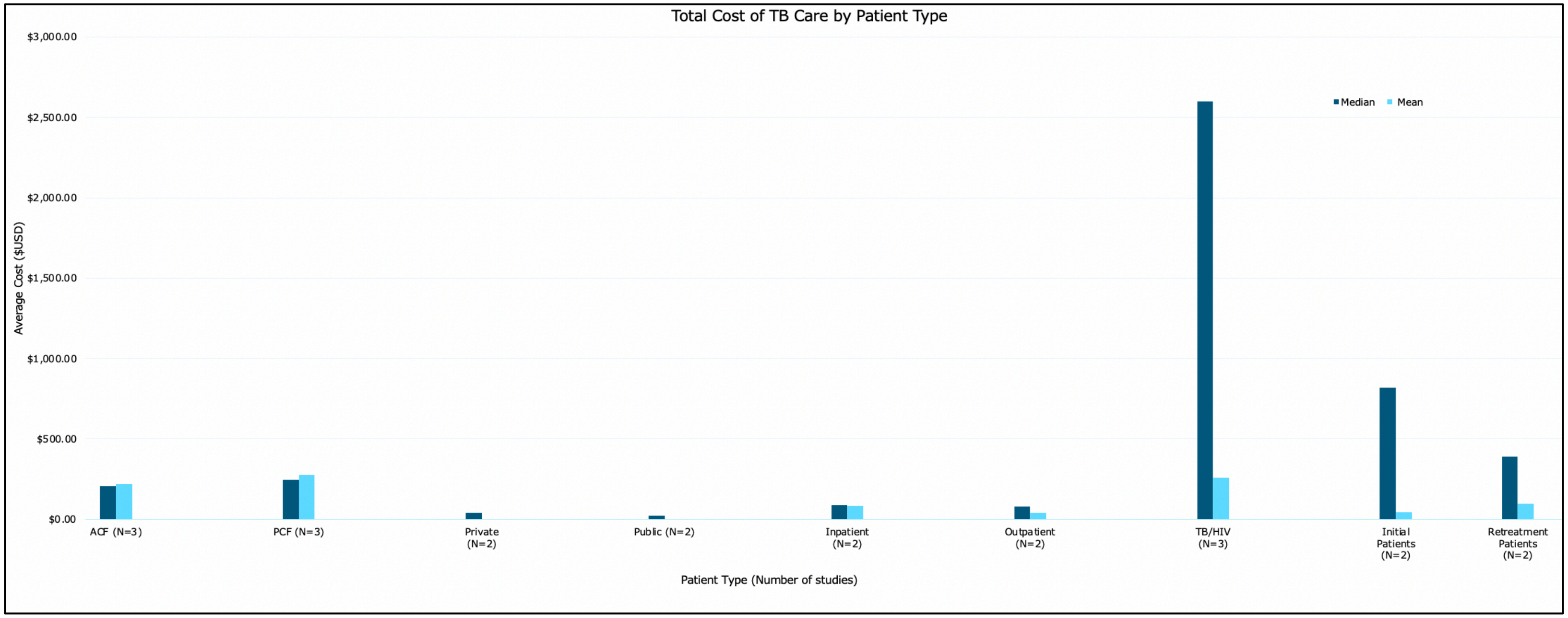


Figure 2.5 – Harvest plots for the total cost of TB care by TB type (A) and patient type (B)

Table 2.2 – Total costs incurred by patients stratified by patient type

	Overall costs		
Assebe, 2020[18]	*Outpatient*	Mean (SD): $110 (114)	
		Median (IQR): $79 (46–140)	
	Inpatient	Mean (SD): $105 (78)	
		Median (IQR): $87(39-158)	
	Total	Mean (SD): $115 (118)	
		Median (IQR): $81 (47–150)	
Aung, 2021[19]	*DS-TB*	Median (Range): $201.28 (42.07 – 4662.64)	
	MDR-TB	Median (Range): $1044.23 (42.07 – 4444.76)	
	Total	Median (Range): $214. 81(42.07 – 4662.64)	
Chandra, 2021[(1)][21]	Median (IQR): $150 (65-335)		
	Mean (SD): $270 (305)		
Chittamany, 2020[23]	*Nationally Representative Sample*	*DS-TB*	Median (IQR): $1189.90 (556.77 – 2277.99)
		DR-TB	Median (IQR): $3507.66 (1719.63 - 5206.60)
		Total	Median (IQR): $1201.03 (558.36 – 2312.99)
	Additional Sample	*DR-TB*	Median (IQR): $3568.11 (1958.24 – 4750.05)
		TB-HIV	Median (IQR): $2597.73 (1601.91 – 4220.32)
Collins, 2018[24]	Median: $1722.62		
De Siqueria Filha, 2018[25]	*TB/HIV*	Mean: $496.63	
	LTBI/HIV	Mean: $57.61	
Ellaban, 2021[26]	Median (IQR) - $129.4 (43.8–356.9)		
Fuady, 2020[(1)][27]	Median (IQR): $88.8 (342.41)		
Fuady, 2018[29]	*DS-TB*	Median (IQR): $45.77 (22.77 – 238.50)	
	MDR-TB	Median (IQR): $964.88 (417.36 – 1790.77)	
Fuady, 2020[(2)][28]	Mean (95% CI): $9.11(7.45 – 10.77)		
Getahun, 2016[30]	Mean (SD): $206.58 (91.70)		
	Median: $206.40 (538.07)		
Gospodarevskaya, 2014[31]	*Tanzania*	Mean: $43.47	
	Bangladesh	Mean: $134.00	
Gurung, 2019[33]	*ACF*	Median: $274.36 (87.8 – 491.42)	
	PCF	Median: $342.19 (136.53 – 590.29)	
	Total	Median: $314.84 (96.26 – 517.37)	
Gurung, 2021[32]	*ACF*	Mean (95% CI): $233.0 (204.6–261.4	
		Median (IQR) - $218.2 (97.1–340.6)	
	PCF	Mean (95% CI): $279.9 (244.8–315.2)	
		Median (IQR) - $ 252.0 (117.9–393.3)	
	Total	Mean (95% CI): $256.4 (233.7–278.9)	
		Median (IQR) - $245.2 (113.1–365.6)	
Kirubi, 2021[34]	Median: $266.64 (139.24 – 495.75)		
Lu, 2020[35]	*Residents*	Mean: $6889	
	Migrants	Mean: $3686	
Mauch, 2013[(1)][36]	*Ghana*	Mean: $78.76	
		Median: $29.57	
	Vietnam	Mean: $229.18	
		Median: $170.14	
	Dominican Republic	Mean: $254.71	
		Median: $149.05	
Mauch, 2013[(2)][37,38]	*New Patients*	Median: $817.64	
	Retreatment Patients	Median: $389.17	
	MDR Patients	Median: $3207.27	
Mauch, 2011[37]	Median: $82.28		
McAllister, 2020[39]	*CHC*	Median: $22.14 (10.38 – 29.39)	
	Public Hospital	Median: $36.15 (20.02 – 78.79)	
	Private Hospital	Median: $25.99 (5.78 – 70.12)	
	Private Practice	Median: $31.16 (18.59 – 47.47)	

	Overall costs		
Morishita, 2016[40]	*ACF*	Mean: $203.42 (212.10)	
		Median: $122.72 (33.39 – 303.15)	
	PCF	Mean: $272.71 (320.07)	
		Median: $148.11(57.92 – 414.70)	
Mudzengi, 2017[41]	*TB*	Mean: $32.86	
	TB/HIV	Mean: $19.43	
Muniyandi, 2020[42]		Mean: $624.35 (981.88)	
		Median: $206.89 (6372.98)	
Muttamba, 2020[43]	DS-TB	Mean: $159 (134.94 – 182.59)	
	MDR-TB	Mean: $1510 (1229.69 – 1750.64)	
	Total	Mean: $208 (162.97 – 253.06)	
Nhung, 2018[44]	*DS-TB*	Mean: $4630 (4028.21 – 5231.84)	
	MDR-TB	Mean: $18,898 (12,840.18 – 24,955.55)	
	Total	Mean: $5772 (4919.95 – 6625.36)	
Pedrazzoli, 2021[46]	*Uninsured*	Mean: $272.3	
		Median: $132.8 (48.02 – 269.86)	
	Insured	Mean: $273.8	
		Median: $138.9 (49.23 – 327.91)	
Prasanna, 2018[47]	*Study Population*	Median: $241.42 (64.24 – 607.74)	
	Those who incurred costs	Median: $245.86 (68.55 – 625.99)	
Ramma, 2015[48]		Mean: $2233.17	
Rupani, 2020[49]	*Private Provider*	Median: $61 (35 – 156)	
	Government Provider	Median: $7 (5-14)	
	Total	Median: $8 (5-28)	
Shin, 2020[50]	*Inpatient (Initial)*	Mean (SD): $44.28 (46.84)	
	Inpatient (Recurrent)	Mean (SD): $98.48 (123.13)	
	Outpatient (HIV)	Mean (SD): $3.92 (6.89)	
	Outpatient (TB)	Mean (SD): $2.82 (1.69)	
Stracker, 2019[51]	*TB+*	Mean: $297.98	
	Xpert-	Mean: $22.86	
Timire, 2021[53]	*Medical*	*DS-TB*	Median: $84.09
		DR-TB	Median: $169
		Total	Median: $88.99
	Non-Medical	*DS-TB*	Median: $335.53
		DR-TB	Median: $1261.32
		Total	Median: $354.8
	Total	*DS-TB*	Median: $967.41
		DR-TB	Median: $2913.84
		Total	Median: $1018.03
Tomeny, 2020[54]	*DS-TB*	Mean: $11.92	
	MDR-TB	Mean: $87.47	
Trajman, 2016[55]		*All*	*Patients Only*
	Minimum Wage	Mean: $135.12	Mean: $118.11
	SES income per capita	Mean: $135.12	Mean: $119.10
	Income per activity	Mean: $50.06	Mean: $122.36
	Reported income	Mean: $47.11	Mean: $134.47
Ukwaja, 2013(1)[56]	*Patient*	Median: $279.13	
	Household	Median: $313	
	Total	Mean: $372.53	
Ukwaja, 2013(2)[57]		Mean: $83.08	
Viney, 2019[59]	*Medical (pre- and post-diagnosis)*	Mean: $300.27	
	Non-medical (pre- and post-diagnosis)	Mean: $1899.09	
	Total (Overall)	Mean: $3579.98	
Wang, 2020[61]		Mean: 10,935.88	
		Median: 10,302.17	
Yang, 2020[62]	*RS-TB*	Mean: 3713.87	

		Median:2443.05
	RMR-TB	Mean: 13598.50
		Median: 6422.72
	MDR-TB	Mean: 19153.80
		Median:13,042.62

Abbreviations: TB – Tuberculosis, DS-TB – Drug sensitive TB, DR-TB – Drug resistant TB, MDR-TB – Multidrug resistant TB, RS-TB – Rifampicin sensitive TB, RMR-TB – Rifampicin mono-resistant TB, HIV – Human Immunodeficiency Virus, LTBI – Latent TB Infection, CHC – Community health centre, ACF – Active case finding, PCF – Passive case finding, SES – Socioeconomic status, SD – Standard deviation, IQR – Interquartile range

Pre-diagnostic costs:

Direct Costs: Pre-diagnostic costs were divided into direct medical costs, direct non-medical costs and indirect costs (Table 3). Direct pre-diagnostic costs ranged from a mean of $0.67 per patient in HIV-positive outpatients screened for TB at public health centres in Malawi to $81.00 in newly diagnosed TB patients from North India. Median direct costs ranged from $1.27 in DS-TB patients from public health centres using ACF in Cambodia to $138.95 in MDR-TB patients from public and private health centres in the Dominican Republic. Mean direct costs were highest in inpatient compared to outpatient settings (inpatient: $4.58 to $31.77, outpatient: $0.67 to $26.46) and higher among individuals found using PCF methods compared to ACF methods (PCF: $29.26 to $71.50, ACF: $6.32 to $47.90), while median direct costs were highest amongst patients that had DR-TB ($7.23 to $138.95), patients that were found using PCF methods ($7.55 to $40.90) and for patients that were treated at private health centres ($25.99 to $38.50). Patients with TB/HIV coinfection incurred mean direct costs ranging from $10.44 to $45.91 during the pre-diagnostic phase.

Medical costs were significantly higher than non-medical costs, ranging from a mean of $1.65 in MDR-TB patients from public health centres in Uganda to $1,908.65 in migrants in China and a median of $7.61 in TB patients from public and private health centres in Uganda to $112.94 in MDR-TB patients from public health centres in Lao People's Democratic Republic. Direct medical costs were highest for patients with DR-TB, ranging from a mean of $1.65 to $680.69 and a median of $8.42 to $112.94, while DS-TB patients incurred costs ranging from a mean of $3.42 to $175.71 and a median of $8.11 to $63.63. Factors that had the largest impact on the direct medical costs' patients incurred during the pre-diagnostic phase were medication (mean: $0.03 to $5,213.79, median: $0.59 to $31.29), diagnostic imaging (mean: $0.31 to $731.45, median: $0.54 to $7.85) and hospitalization (mean: $0.05 to $28.00, median: $6.36 to $48.64). These cost components were highest for inpatients, patients with DR-TB and those identified using PCF methods.

Non-medical costs were found to range from a mean of $3.60 in newly diagnosed TB patients in Ugandan public health centres to $724.81 in MDR-TB patients from public and private health centres in

Vietnam and a median of $0.88 in TB patients from public health centres in Ghana to $63.63 in MDR-TB patients from public health centres in Lao People's Democratic Republic. Factors that influenced the non-medical costs were nutritional supplements (mean: $5.95 to $505.73, median: $0.71 to 19.85), food (mean: $0.20 to $10.47, median: $0.12 to $14.69) and transportation (mean: $0.40 to $45.72, median: $0.15 to $11.14). As seen with the direct medical costs, patients with DR-TB and who were identified using PCF methods were found to incur higher non-medical costs however, it was found that food costs for patients with DS-TB were slightly higher than costs for patients with DR-TB.

Indirect Costs: Indirect costs made up the largest portion of pre-diagnostic costs incurred by patients ranged from a mean of $1.26 in HIV-positive outpatients being screened for TB at public health centres in Malawi to $271.46 in newly diagnosed TB patients from public health centres in Nigeria and a median of $0.34 in DS-TB patients from public health centres in Indonesia to $2,836.54 in MDR-TB patients from public and private health settings in the Dominican Republic. Mean indirect costs were found to be highest in inpatients ($21.34 to $114.79) and patients found using PCF methods ($15.30 to $30.13) while median costs were highest amongst patients with DR-TB ($0.97 to $2,836.59) as well as in patients that were identified using ACF method ($4.30 to $68.92). Patients with HIV incurred total indirect costs ranging from $2.91 to $158.50. The main cost component that impacted the burden of patient incurred indirect costs was loss of income (mean: $0.61 to $610.64, median: $0.43 to $2,836.59). Time and productivity loss in addition to caregiver costs incurred minimal patient costs during the pre-diagnostic phase.

For a detailed breakdown of the pre-diagnostic costs incurred by patients stratified by direct and indirect cost components see Table S3 – S5 in the supplemental.

Table 2.3 – Total direct and indirect costs incurred by patients during the pre-diagnostic phase of TB care

	Direct Costs						Indirect Costs	
	Total		**Medical**		**Non-Medical**			
Aung, 2021[21]			*MDR-TB*	Median: $19.31(4.60 – 77.40)				
			DS-TB	Median: $11.01				
			Total	Median: $11.01				
Chandra, 2021 (1)[21]	*Private*	Median (IQR): $38.5(19.5-84.2)					*Public*	*Median (IQR): $38.5(16.8-140.3)*
	Public	Median (IQR): $11.3(4.5-28.6)					*Private*	*Median (IQR): $70.1(16.6-192.4)*
	Total	Median (IQR): $31.7 (12.9-63.8)					*Total*	*Median (IQR): $43.6 (16.8-150.8)*
Chandra, 2021 (2)[22]	Median (IQR): $32 (13-67)		Median (IQR): $24 (8.1-57)		Median (IQR): $3.2 (1.1 - 10.7)			
	Mean (SD): $81 (183)		Mean (SD): $65 (153)		Mean (SD): $16 (70.5)			
Chittamany, 2020[23]			*DS-TB*	*Median: $63.63*	*DS-TB*	*Median: $17.50*		
			DR-TB	*Median: $112.94*	*DR-TB*	*Median: $63.63*		
			Total	*Median: $63.63*	*Total*	*Median: $17.50*		
Collins, 2018[24]	*MDR-TB*	*Median (Range): $93.75*					*MDR-TB*	Median: $0
De Siqueria Filha, 2018[25]	*TB/HIV*	Mean - $45.91	*TB/HIV*	Mean - $26.94			*TB/HIV*	*Mean - $158.50*
	LTBI/HIV	Mean - $10.47	*LTBI/HIV*	*Mean - $3.7*			*LTBI/HIV*	*Mean - $2.91*
Ellaban, 2021[26]	Median (IQR): $24.4 (12.0-59.4)		*Median (IQR): $15.6 (6.3-26.3)*				*Median (IQR): $0.0 (0.0-75.0)*	
Fuady, 2018[29]	*TB*	*Median: $3.79*					*TB*	*Median: $0.34*
	MDR-TB	*Median: $7.23*					*MDR-TB*	*Median: $1.38*
Fuady, 2020(1)[27]	*Mean: $5.51*						Mean: $2.06	
Getahun, 2016[30]	Mean: $28.79						*Mean: $16.67*	
	Median: $23.42						*Median: $13.19*	
Gurung, 2019[33]			*ACF*	*Median: $15.52*	*ACF*	Median: $3.69	*ACF*	*Median: $68.92*
			PCF	*Median: $34.30*	*PCF*	Median: $10.53	*PCF*	*Median: $50.00*
			Total	*Median: 20.84*	*Total*	Median: $5.86	*Total*	*Median: $55.46*
Gurung, 2021[32]	*ACF*	Mean (95% CI): $47.9 (32.8–63.0)	*ACF*	*Mean (95% CI): $41.1 (28.7–53.6)*	*ACF*	Mean (95% CI): $6.8 (3.7–9.9)	*ACF*	*Mean (95% CI) - $7.5 (5.6–9.5)*
		Median (IQR): $13.3 (1.4–59.9)		*Median (IQR): $12.3 (0–55.8)*		Median (IQR): $1.4 (0–5.8)		*Median (IQR) - $4.3 (1.9–8.7)*
	PCF	Mean (95% CI): $71.5 (56.2–86.8)	*PCF*	*Mean (95% CI): $53.1(41.6–64.6)*	*PCF*	Mean (95% CI): $18.4 (11.9–24.8)	*PCF*	*Mean (95% CI) - $15.3 (11.9–18.6)*

		Median (IQR): $40.9 (14.0–11.5)		*Median (IQR): $29.6 (10.2–79.2)*		Median (IQR): $5.3 (1.8–14.1)		*Median (IQR) - $10.0 (5.6–18.0)*
	Total	Mean (95% CI): $59.9 (49.1–70.7)	*Total*	*Mean (95% CI): $47.2 (38.8–55.7)*	*Total*	Mean (95% CI): $12.7 (9.0–16.4)	*Total*	*Mean (95% CI) - $11.5 (9.4–13.5)*
		Median (IQR): $28.4 (6.2–81.9)		*Median (IQR): $21.7 (3.5–70.3)*		Median (IQR): $3.0 (0.4–10.8)		*Median (IQR) - $6.7 (3.3–13.6)*
	Direct Costs						**Indirect Costs**	
	Total		**Medical**		**Non-Medical**			
Lu, 2020[35]			*Residents*	Mean: $919.70	*Residents*	*Mean: $167.78*		
			Migrants	Mean: $1,908.65	*Migrants*	*Mean: $79.44*		
Mauch, 2013[(1)36]	*Ghana*	Mean: $4.54					*Ghana*	*Mean; $55.78*
		Median (IQR): $2.05 (0.59 - 5.71)						*Median (IQR): $24.89 (6.30 – 49.78)*
	Vietnam	Mean: $20.65					*Vietnam*	*Mean: $186.30*
		Median (IQR): $1.80 (2.25 – 19.53)						Median (IQR): $161.84 (107.29 – 230.97)
	Dominican Republic	Mean: $7.63					*Dominican Republic*	*Mean: $211.12*
		Median (IQR): $1.61 (0.40 – 3.82)						*Median (IQR): $133.78 (55.24 – 238.24)*
Mauch, 2013[(2)38]	*New*	Median: $41.93						
	Retreatment	Median: $79.04						
	MDR-TB	Median: $138.95						
Mauch, 2011[37]	*Median: $3.06*						*Median: $69.16*	
McAllister, 2020[39]	*CHC*	*Median (IQR): $22.14*						
	Public Hospital	*Median (IQR): $36.15*						
	Private Hospital	*Median (IQR): $25.99*						
	Private Practice	*Median (IQR): $31.16*						
Morishita, 2016[40]	*ACF*	Mean (SD): $ 6.32					*ACF*	Mean (SD): $ 9.48
		Median (IQR): $ 1.27						Median (IQR): $ 0.00
	PCF	Mean (SD): $ 29.26					*PCF*	Mean (SD): $ 30.13
		Median (IQR): $ 7.55						Median (IQR): $ 0.71
	Direct Costs						**Indirect Costs**	
	Total		**Medical**		**Non-Medical**			

Muniyandi, 2020[42]	*Mean (SD): $82.56 (229.70)*						*Mean (SD): $153.61 (304.00)*	
	Median (IQR): $17.74 (0.00 – 3,042.65)						*Median (IQR): $0.00 (0.00 – 1709.74)*	
Muttamba, 2020[43]			DS-TB	Mean (95% CI): $3.42				
			MDR-TB	Mean (95% CI): $1.65				
			Total	Mean (95% CI): $3.40				
Nhung, 2018[44]			*DS-TB*	Mean (95% CI): $175.71	*DS-TB*	Mean (95% CI): $175.71		
			MDR-TB	Mean (95% CI): $680.89	*MDR-TB*	Mean (95% CI): $724.81		
			Total	Mean (95% CI): $276.75	*Total*	Mean (95% CI): $219.64		
Pedrazzoli, 2018[45]	*DS-TB*	*Median (IQR): $ 9.60*	*DS-TB*	*Median (IQR): $ 8.11*	*DS-TB*	*Median (IQR): $ 0.88*		
	MDR-TB	*Median (IQR): $ 9.97*	*MDR-TB*	*Median (IQR): $ 8.42*	*MDR-TB*	*Median (IQR): $ 0.88*		
	Total	*Median (IQR): $ 9.63*	*Total*	*Median (IQR): $ 8.11*	*Total*	*Median (IQR): $ 0.88*		
Pedrazzoli, 2021[46]			*Insured*	*Mean: $13.68*			*Insured*	*Mean: $ 1.43*
				Median (IQR): $ 8.21				*Median (IQR): $ 0.49*
			Uninsured	*Mean: $8.81*			*Uninsured*	*Mean: $ 3.34*
				Median (IQR): $ 8.21				*Median (IQR): $ 0.67*
Ramma, 2015[48]	*Inpatients*	*Mean (SD): $ 12.29*					*Inpatient*	Mean (SD): $ 114.79
	Outpatient	*Mean (SD): $ 26.46*					*Outpatient*	*Mean (SD): $ 29.87*
Timire, 2021[53]	DS-TB	*Median (IQR): $ 44.08*	DS-TB	Median (IQR): $20.41				
	DR-TB	*Median (IQR): $ 28.57*	DR-TB	Median (IQR): $10.61				
	Total	*Median (IQR): $ 42.45*	Total	Median (IQR): $20.41				
Ukwaja, 2013 (1)[57]	Median (IQR): $25.77						Mean (SD): $271.46	
	Mean (SD): $37.04							
Van der Hof, 2016[58]	Ethiopia DS-TB	Median (IQR): $17.50					Ethiopia DS-TB	Median (IQR): $0.00
	MDR-TB	Median (IQR): $85.01					MDR-TB	Median (IQR): $0.00

	Indonesia	DS-TB	Median (IQR): $10.68			*Indonesia*	DS-TB	Median (IQR): $1.29
		MDR-TB	Median (IQR): $12.62				MDR-TB	Median (IQR): $0.97
	Kazakhstan	DS-TB	Median (IQR): $1.78			*Kazakhstan*	DS-TB	Median (IQR): $1.07
		MDR-TB	-				MDR-TB	-
Walcott, 2020[60]	Mean (SD): $17.22			Mean (SD): $13.61	Mean (SD): $3.60			
	Median (IQR): $10.01			Median (IQR): $7.61	Median (IQR): $1.60			

Abbreviations: TB – Tuberculosis, DS-TB – Drug sensitive TB, DR-TB – Drug-resistant TB, MDR-TB – Multi-drug resistant TB, CHC – Community health centre, SD – Standard deviation, IQR – Interquartile range

**Shin - Costs for TB outpatients were extrapolated using the costing data from HIV outpatients*

Post-diagnostic costs:

Direct Costs: The direct costs incurred by patients during the post-diagnostic stage of TB care ranged from a mean of $0.67 in HIV-positive outpatients being screened for TB at public health centres in Malawi to $22,270.12 in MDR-TB patients from public health centres in China and a median of $5.16 in MDR-TB patients from primary health centres in Indonesia to $20,121.94 in MDR-TB patients from public hospitals in China (Table 4). Mean direct costs were found to be highest amongst inpatients ($4.58 to $31.77) compared to outpatients ($0.67 to $26.46) while median costs were highest amongst patients with DR-TB ($58.79 to $20,815.60). Median costs for patients who received treatment at private health centres were higher (private practice: $56.54, private hospitals: $21.58) than patients who were treated at public health centres (Community Health Centre (CHC): $8.10, public hospital: $29.01). Costs differed slightly for the intensive and continuation phase of care with patient costs for the intensive phase ranging from a median of $7.80 to $798.80 and the continuation phase ranging from $2.50 - $792.55. Mean costs for the intensive and continuation phase were only reported by Ramma *et al.,* with intensive costs being $13.80 while continuation costs were $27.65[19]. Total direct costs for patients with TB/HIV coinfection were found to range from a mean of $10.44 to $78.40 with LTBI/HIV coinfection patients incurring a cost of $31.66.

Direct medical costs were found to have the largest impact on post-diagnostic patient costs and were higher compared to non-medical costs. Direct medical costs ranged from a mean of $0.03 in TB patients from primary health care (PHC) clinics in South Africa to $17,139.85 MDR-TB patients from public hospitals in China while median costs ranged from $5.16 in MDR-TB patients from primary health centres in Indonesia to $14,093.21 in Chinese MDR-TB patients. Cost factors that had the biggest impact on the direct medical costs incurred by patients include medication (mean: $0.31 to $2,185.94, median: $0.13 to $209.00), follow-up tests (mean: $0.06 to $12.31, median: $0.67 to $228.73) and hospitalization (mean: $0.51 to $76.94, median: $1.25 to $278.66). Direct medical costs were highest amongst patients with DR-TB (mean: $2.19 to $17,139.85, median: $5.16 to $14,093.21) compared to patients with DS-TB (mean: $2.41 to $3,714.23, median: $22.49 to $2,521.78).

Non-medical costs ranged from a mean of $7.60 in DS-TB patients who were identified using ACF methods and were treated at public health centres in Nepal to $8,649.44 in MDR-TB patients treated at public and private health centres in Vietnam while median costs ranged from $1.41 in DS-TB patients identified using PCF methods and treated at public health centres in Nepal to $520.18 in DS-TB patients from public health centres in Lao People's Democratic Republic. Key factors that had the largest impact on patient incurred non-medical costs were food (mean: $0.02 to $4,647.59, median: $1.59 to $626.98), transportation (mean: $0.02 to $1,730.77, median: $0.43 to $143.74), and nutritional support (mean: $1.65 to $505.73, median: $0.71 to $783.72). Patients with MDR-TB were found to consistently incur the largest burden of non-medical costs (mean: $8,649.44, median: $294.56 to $423.15) except in the 2020 study by Chittamany *et al.*, found DS-TB patients incurred greater costs than DR-TB patients (median: DS-TB: $520.18, DR-TB: $423.15)[20].

Indirect Costs: Indirect costs incurred by patients post-diagnosis ranged from a mean of $1.26 in HIV-positive outpatients screened for TB at public health centres in Malawi to $6,044.51 in MDR-TB patients from public and private facilities in Vietnam while median costs ranged from $1.57 in DS-TB patients from public and private health centres in Vietnam to $2,836.59 in MDR-TB patients from public health centres in the Dominican Republic. Loss of time had the largest impact due to lost income while receiving care with patients incurring mean costs of $0.18 to $6,044.51 and median costs of $0.69 to $949.74. Indirect costs were found to be highest amongst patients with DR-TB (mean: $51.46 to $6,044.51, median: $80.89 to $2,836.59).

For a detailed breakdown of the post-diagnostic costs incurred by patients stratified by direct and indirect cost components see Table S6 – S8 in the supplemental.

Table 2.4 – Total post-diagnostic costs incurred by patients during the post-diagnostic phase of TB care stratified by direct and indirect cost components

	Direct Costs							**Indirect Costs**		
	Total			**Medical**		**Non-Medical**				
Chandra, 2021(2)[22]	Median (IQR): $13 (1.14 – 68)			*Median (IQR): $0 (0-0)*		*Median (IQR): $13 (1.14-63)*		*Median (IQR): $0 (0 – 105)*		
	Mean (SD): $43 (57)			*Mean (SD): $1.7 (10.6)*		*Mean (SD): $41 (56)*		*Mean (SD): $ 114 (230)*		
Chittamany, 2020[23]				*DS-TB*	*Median (IQR): $42.95*	*DS-TB*	*Median (IQR): $520.18*	*DS-TB*		*Median (IQR): $50.90*
				DR-TB	*Median (IQR): $334.06*	*DR-TB*	*Median (IQR): $423.15*	*DR-TB*		*Median (IQR): $2,106.19*
				Total	*Median (IQR): $46.13*	*Total*	*Median (IQR): $520.18*	*Total*		*Median (IQR): $90.67*
Collins, 2018*[24]	*MDR-TB*	*Intensive phase*	*Median (Range): $798.67*					*MDR-TB*	*Intensive phase*	*Median (Range): $0*
		Continuation Phase	*Median (Range): $792.42*						*Continuation Phase*	*Median (Range); $0*
De Siqueria Filha, 2018[25]	*TB/HIV*	*Mean: $78.40*						*TB/HIV*		*Mean: $212.80*
	LTBI/HIV	*Mean: $31.66*						*LTBI/HIV*		*Mean: $12.45*
Ellaban, 2021[26]	*First two months of treatment (intensive phase)*	*Median (IQR): $7.80 (3.80 – 15.00)*		*First two months of treatment (intensive phase)*	*Median (IQR): $0.00 (0.00 – 0.00)*			*First two months of treatment (intensive phase)*		*Median (IQR_: $0.00 (0.00 – 93.80)*
	Second two months of treatment	*Median (IQR): $3.80 (2.50 – 9.40)*		*Second two months of treatment*	*Median (IQR): $0.00 (0.00 – 0.00)*			*Second two months of treatment*		*Median (IQR): $0.00 (0.00 – 75.0)*
	Third two months of treatment	*Median (IQR): $2.50 (1.30 – 5.60)*		*Third two months of treatment*	*Median (IQR); $0.00 (0.00 – 0.00)*			*Third two months of treatment*		*Median (IQR): $0.00 (0.00 - 62.50)*
Fuady, 2018[29]				*DS-TB*	*Median (IQR): $0.00*	*DS-TB*	*Median (IQR): $11.36*	*DS-TB*		*Median (IQR): $2.75 (0.00 – 154.16)*
				MDR-TB	*Median (IQR): $5.16*	*MDR-TB*	*Median (IQR): $294.56*	*MDR-TB*		*Median (IQR): $462.48 (0.69-886.77)*
Getahun, 2016[30]	*Mean (SD): $143.29*							*Mean (SD): $63.21*		
	Median (R): $146.53							*Median (R): $51.97*		

Gurung, 2019[33]			*ACF*		*ACF*	*Median (IQR): $0.00*	*ACF*	*Median (IQR): $59.58*
			PCF	*Median (IQR): $0.00*	*PCF*	*Median (IQR): $1.41*	*PCF*	*Median (IQR): $64.68*
			Total	-	*Total*	*Median (IQR): $0.00*	*Total*	*Median (IQR): $59.80*
Gurung, 2021[32]	*ACF*	*Mean (95% CI): $27.20 (20.20 – 34.10)*	*ACF*	*Mean (95% CI): $19.50 (13.50 – 25.50)*	*ACF*	*Mean (95% CI): $7.60 (5.10 – 10.20)*	*ACF*	*Mean (95% CI): %38.70 (33.20 – 44.10)*
		Median (IQR): $16.20 (9.50 – 31.10)		*Median (IQR): $10.80 (6.30 – 20.70)*		*Median (IQR) $1.90 (0.30 – 9.40)*		*Median (IQR): $29.60 (21.20 – 50.10)*
	PCF	*Mean (95% CI): $30.60 (23.30 – 37.90)*	*PCF*	*Mean (95% CI): $21.10 (14.90 – 27.40)*	*PCF*	*Mean (95% CI): $9.50 (6.80 – 12.10)*	*PCF*	*Mean (95% CI): $44.10 (33.40 – 54.80)*
		Median (IQR): $17.90 (12.00 – 37.70)		*Median (IQR): $ 12.20 (7.20 – 21.20)*		*Median (IQR): $3.40 (0.70 – 13.20)*		*Median (IQR): $27.90 (17.00 – 51.50)*
	Total	*Mean (95% CI): $28.90 (23.90 – 33.90)*	*Total*	*Mean 95% CI): $20.30 (16.00 – 24.60)*	*Total*	*Mean (95% CI): $8.60 (6.70 – 10.40)*	*Total*	*Mean (95% CI): $41.40 (35.40 – 47.30)*
		Median (IQR): $17.90 (10.70 – 32.30)		*Median (IQR): $11.80 (6.60 – 20.70)*		*Median (IQR): $2.70 (0.70 – 10.80)*		*Median (IQR): $29.10 (19.50 – 50.20)*
Kirubi, 2021[34]			*Median (IQR): $10.86*		*Median (IQR): $170.85*		*Median (IQR): $35.55*	
Lu, 2020[35]			*Residents*	*Mean: $3321.78*	*Residents*	*Mean: $230.53*		
			Migrants	*Mean: $1938.93,*	*Migrants*	*Mean: $113.31*		
Mauch, 2013[(1)36]	*Ghana*	*Mean: $16.69*					*Ghana*	*Mean: $1.76*
		Median (IQR): $2.64						*Median (IQR): $0.00*

	Vietnam	*Mean: $16.39*					*Vietnam*	*Mean: $5.84*
		Median (IQR): $4.94						*Median (IQR): $1.57*
	Dominican Republic	*Mean: $22.10*					*Dominican Republic*	*Mean: $13.86*
		Median (IQR): $2.41						*Median (IQR): $11.25*
Mauch, 2013[(2)38]	*New*	*Median: $121.64*					New	*Median: $654.98*
	Retreatment	*Median: $88.45*					Retreatment	*Median: $199.18*
	MDR	*Median: $232.54*					MDR-TB	*Median: $2836.59*
Mauch, 2011[37]	*Cost per visit*	*Median: $0.38*						
	Overall treatment cost	*Median (IQR): $5.31 (2.12 – 9.64)*						
McAllister, 2020[39]	*CHC*	*Median (IQR): $8.10*					*CHC*	*Median (IQR): $102.69*
	Public Hospital	*Median (IQR): $29.01*					*Public Hospital*	*Median (IQR): $169.81*
	Private Hospital	*Median (IQR): $21.58*					*Private Hospital*	*Median (IQR): $233.39*
	Private Practice	*Median (IQR): $56.54*					*Private Practice*	*Median (IQR): $198.81*
Mudzengi, 2017[41]	*TB/HIV*	*Mean (SD):* $10.44	*Study Clinic*	*TB/HIV*	*Mean (SD): $0.00 (0.00)*		*TB/HIV*	*Mean (SD):* $25.17
				TB	*Mean (SD): $0.00 (0.00)*			
	TB	*Mean (SD):* $4.74		*HIV*	*Mean (SD): $0.00 (0.00)*		*TB*	*Mean (SD):* $28.12
			Other Facilities	*TB/HIV*	*Mean (SD):* $0.82			
	HIV	*Mean (SD):* $8.79		*TB*	*Mean (SD): $0.03*		*HIV*	*Mean (SD):* $10.64
				HIV	*Mean (SD): $0.42*			
Muniyandi, 2020[42]	*Mean (SD): $67.50 (256.13)*						*Mean (SD): $320.68 (677.17)*	
	Median (IQR): $21.45 (0.00 – 4.40)						*Median (IQR): $0.00 (0.00 – 6114.57)*	

Muttamba, 2020[43]							*MDR-TB*	*Mean (95% CI): $488.11*
							DS-TB	*Mean (95% CI): $46.05*
							Total	*Mean (95% CI): $62.47*
Nhung, 2018[44]			*MDR-TB*	*Mean (95% CI): $2793.83*	*MDR-TB*	*Mean (95% CI): $8649.44*	*MDR-TB*	*Mean (95% CI); $6044.51*
			DS-TB	*Mean (95% CI): $412.92*	*DS-TB*	*Mean (95% CI): $1629.73*	*DS-TB*	*Mean (95% CI): $2231.55*
			Total	*Mean (95% CI): $601.81*	*Total*	*Mean (95% CI): $2196.41*	*Total*	*Mean (95% CI): $2534.65*
Pedrazzoli, 2018[45]			*MDR-TB*	*Median (IQR): $12.37*	*MDR-TB*	*Median (IQR): $387.86*		
			DS-TB	*Median (IQR); $22.49*	*DS-TB*	*Median (IQR): $146.39*		
			Total	*Median (IQR): $21.27*	*Total*	*Median (IQR): $157.81*		
Pedrazzoli, 2021[46]			*Uninsured*	*Mean (SD): $40.42*	*Uninsured*	*Mean (SD): $137.97*		
				Median (IQR): $25.22		*Median (IQR): $45.89*		
			Insured	*Mean (SD): $43.15*	*Insured*	*Mean (SD): $133.11*		
				Median (IQR): $25.22		*Median (IQR): $46.19*		
Prasanna, 2018[47]	*Study population*	*Median (IQR): $80.51*					*Study Population*	Median (IQR): $ 61.90
	Those who incurring costs	*Median (IQR): $84.34*					*Those who incurred costs*	Median (IQR): $ 164.36
Ramma, 2015[48]	*Inpatients*	*Mean (SD): $12.29*					*Inpatients*	*Mean (SD): $114.79*
	Outpatients	*Mean (SD): $26.46*					*Outpatients*	*Mean (SD): $29.86*
	Intensive Phase	*Mean (SD): $13.80*					*Intensive Phase*	*Mean (SD): $91.44*

	Continuation Phase		*Mean (SD); $27.65*					*Continuation Phase*	*Mean (SD): $60.01*
Rupani, 2020[49]				*Private Provider*	*Median (IQR): $30.00 (10-76)*	*Private Provider*	*Median (IQR): $4.00 (2-5)*	*Private Provider*	*Median (IQR): $20.00 (3-76)*
				Public Provider	*Median (IQR): $0.00 (0-0)*	*Public Provider*	*Median (IQR): $3.00 (2-4)*	*Public Provider*	*Median (IQR): $4.00 (3-10)*
				Total	*Median (IQR): $0.00 (0-0)*	*Total*	*Median (IQR): $3.00 (2-4)*	*Total*	*Median (IQR): $6.00 (3-13)*
Shin, 2020[50]	*Patient OOP*	Inpatient (Initial)	Mean (SD): $11.98 (15.63)					Inpatient (Initial)	Mean (SD): $21.34
		Inpatient (Recurrent)	Mean (SD): $18.30 (21.99)						
		Outpatient (HIV)	Mean (SD): $2.60 (4.05)						
		Outpatient (TB)	Mean (SD): $1.35 (1.13)					Inpatient (Recurrent)	Mean (SD): $66.71
	Self-Reported OOP	Inpatient (Initial)	*Mean (SD): $4.58 (10.44)*						
		Inpatient (Recurrent)	*Mean: $8.66 (22.11)*						
		Outpatient (HIV)	*Mean: $0.67 (1.55)*					Outpatient (HIV)	*Mean (SD):* $1.26
		Outpatient (TB)	-						
	Total OOP	Inpatient (Initial)	*Mean: $22.95 (23.29)*						
		Inpatient (Recurrent)	*Mean: $31.77 (36.86)*					Outpatient (TB)	*Mean (SD):* $1.43
		Outpatient (HIV)	*Mean: $2.60 (4.05)*						
		Outpatient (TB)	Mean (SD): $1.35 (1.13)						
	TB+		*Mean: $88.17*						

Stracker, 2019[51]	*Xpert-*		*Mean: $13.88*						
Sweeney, 2018*[52]				*Mean: $17.70*		*Mean: $23.18*	*Approach #1: Current income (prompted ranges)*		*Mean (SD):* $21.12
							Approach #2: Current income (detailed)		*Mean (SD):* $27.59
							Approach #3: Permanent income (MCA)		*Mean (SD):* $47.36
							Approach #4: National mean income		*Mean (SD):* $72.08
							Approach #5: Self-reported income loss		*Mean (SD):* $54.45
Timire, 2021[53]	*DS-TB*		*Median (IQR): $438.40*	*DS-TB*	*Median (IQR): $72.29*		*DS-TB*		*Median (IQR): $195.93*
	DR-TB		*Median (IQR): $1354.88*	*DR-TB*	*Median (IQR: $168.99*		*DR-TB*		*Median (IQR): $979.66*
	Total		*Median (IQR): $453.09*	*Total*	*Median (IQR): $74.45*		*Total*		*Median (IQR): $244.92*
Tomeny, 2020*[54]				DS-TB	Mean: $2.45		DS-TB		*Mean:* $4.94
				MDR-TB	Mean: $2.19		MDR-TB		*Mean:* $51.46
Trajman, 2016[55]	All	Minimum Wage	Mean (SD): $31.41	*Minimum Wage*	*Mean (SD): $26.83 (34.35)*		All	*Minimum Wage*	Mean (SD): $103.38
								SES Income per Capita	Mean (SD): $103.38
		Reported Income	Mean (SD): $37.30					*Income per Activity*	*Mean (SD):* $108.62
								Reported Income	Mean (SD): $116.80
	Patients Only	Minimum Wage	Mean (SD): $16.69	*Reported Income*	*Mean (SD): $34.35 (51.69)*		*Patients Only*	*Minimum Wage*	*Mean (SD):* $101.42
								SES Income per Capita	*Mean (SD):* $102.40
		Reported Income	Mean (SD): $18.65					*Income per Activity*	Mean (SD): $105.67
								Reported Income	Mean (SD) $115.82
Ukwaja, 2013$^{(1)}$[56]	Mean: $21.17						*Mean: $42.86*		
Ukwaja, 2013$^{(2)}$[57]	Mean: $21.17								
		DS-TB	MDR-TB					DS-TB	MDR-TB

Van der Hof, 2016[58]	Ethiopia	Intensive Phase	Median (IQR): $130.00	Median (IQR): $798.80					Ethiopia	Intensive Phase	*Median (IQR): $0.00*	*Median (IQR): $275.02*
		Continuation Phase	Median (IQR): $100.00	Median (IQR): $792.55						Continuation Phase	*Median (IQR): $0.00*	*Median (IQR): $91.26*
	Indonesia	Intensive Phase	Median (IQR): $13.26	Median (IQR): $192.81					Indonesia	Intensive Phase	*Median (IQR): $3.24*	*Median (IQR): $101.90*
		Continuation Phase	Median (IQR): $19.08	Median (IQR): $315.74						Continuation Phase	*Median (IQR): $2.91*	*Median (IQR): $82.17*
	Kazakhstan	Intensive Phase	Median (IQR): $0.00	Median (IQR): $58.79					Kazakhstan	Intensive Phase	*Median (IQR): $143.96*	*Median (IQR): $547.71*
		Continuation Phase	Median (IQR): $63.78	Median (IQR): $268.69						Continuation Phase	*Median (IQR): $37.06*	*Median (IQR): $80.89*
Viney, 2019[59]					*Mean (95% CI): $293.09*			*Mean (95% CI): $1889.77*	*Mean (95% CI): $1392.81*			
Wang, 2020[61]					*Direct medical costs*	*Mean: $7850.66*		*Mean: $505.48*	*Mean: $2579.84*			
						Median (IQR): $6900.75						
					OOP medical costs	*Mean: $4914.93*		*Median (IQR): $460.40*	*Median (IQR): $1575.69*			
						Median (IQR): $4147.59						
Yang, 2020[62]	Hospitalized	RS-TB	Mean (SD): $5,748.04		*Hospitalized*	RS-TB	Mean (SD): $3,714.23					
			Median (IQR): $4,321.18				Median (IQR): $2,521.78					
		RMR-TB	Mean (SD): $20,815.60			RMR-TB	Mean (SD): $15,000.89					
			Median (IQR): $19,741.06				Median (IQR): $7,644.25					
		MDR-TB	Mean (SD): $22,270.12			MDR-TB	Mean (SD): $17,139.85					
			Median (IQR): $20,121.94				Median (IQR): $14,093.21					
	Non-Hospitalized	RS-TB	Mean (SD): $ 1,888.41		*Non-Hospitalized*	RS-TB	Mean (SD): $1,247.24					

			Median (IQR): $1,523.67			Median (IQR): $919.38		
		RMR-TB	Mean (SD): $4,021.69		RMR-TB	Mean (SD): $1,744.25		
			Median (IQR): $2,731.90			Median (IQR): $1,352.92		
		MDR-TB	Mean (SD): $2,416.81		MDR-TB	Mean (SD): $1,517.11		
			Median (IQR): $2,994.68			Median (IQR): $617.24		

Abbreviations: TB – Tuberculosis, DS-TB – Drug sensitive TB, DR-TB – Drug-resistant TB, MDR-TB – Multi-drug resistant TB, RS-TB – Rifampicin sensitive TB, RMR-TB – Rifampicin mono-resistant TB, HIV – Human Immunodeficiency Virus, LTBI – Latent TB Infection, CHC – Community health centre, ACF – Active case finding, PCF – Passive case finding, SES – Socioeconomic status, DOT – Directly observed therapy, SD – Standard deviation, IQR – Interquartile range, CI – Confidence Interval

**Costs reported are a combination of pre- and post-diagnostic costs*

Sub-Group Analysis:

Weighted costs were calculated by compiling all of the reported patient costs for each subgroup multiplying the cost by the patient population size and summing the costs together. Since costs were reported differently across studies both weighted mean and weighted medians were calculated for each of the sub-groups of interest.

Weighted Median of Costs for DS-TB Patients: The weighted median for patients with DS-TB was $52.12 for pre-diagnostic costs, $88.15 for post-diagnostic costs and $469.49 for total costs (Table 5).

Subgroup analyses were conducted to analyze how weighted medians for DS-TB patients varied across WHO regions and settings with differing degrees of TB, MDR-TB and TB/HIV burden. DS-TB patients incurred the highest total cost for TB care in the WPRO region with a weighted median of $1,332.25 while DS-TB patients from the SEARO region incurred the lowest total costs with a weighted median of $119.39. Weighted medians for DS-TB patients pre-diagnostic and post-diagnostic costs were calculated for two regions – AFRO and SEARO. Patients from the SEARO region had higher pre-diagnostic costs than patients from the AFRO region ($58.89 versus $12.99) while post-diagnostic costs were higher in the AFRO region compared to the SEARO region ($137.45 versus $57.91).

Across high TB burden settings, total costs for DS-TB patients were highest in high MDR-TB burden settings and lowest in high DS-TB burden settings with a weighted median of $585.23 and $385.61 respectively. Similar findings were observed for the pre-diagnostic weighted medians in high TB burden settings while post-diagnostic costs were found to be highest in high DS-TB burden settings and lowest in high TB/HIV burden settings ($76.52 versus $61.63).

Across low TB burden settings, the weighted medians for total costs were highest in patients from low DS-TB burden settings with a weighted median of $607.16 and lowest in patients from low TB/HIV burden settings with a weighted median of $457.77. Weighted medians for pre-diagnostic and post-diagnostic costs were identical in settings with low burden of DS-TB and TB/HIV.

Weighted Mean of Costs for DS-TB Patients: For patients with DS-TB the weighted mean was $466.77 for pre-diagnostic costs, $667.27 for post-diagnostic costs and $1,234.18 for total costs incurred during TB care.

Across WHO regions, patients from the WPRO region incurred the highest burden of costs during all stages of TB care (total, pre-diagnostic and post-diagnostic). The total cost of TB care had individuals from the WPRO region incurring a weighted mean of $3,323.40, while patients from the AFRO region incurred the lowest costs of $202.77. The weighted mean for pre-diagnostic costs for patients from the WPRO region was $1,719.01 compared to patients from the SEARO region who incurred a weighted median of $166.88. Analysis of post-diagnostic costs for WHO regions found patients from the WPRO region incurred a weighted mean of $3,435.28 compared to patients from the AFRO region who incurred a weighted mean of $58.63.

Patients from high MDR-TB burden countries incurred the highest total costs compared to high TB/HIV burden settings ($2,038.68 versus $1,046.19). Weighted means for pre-diagnostic costs were highest in high DS-TB burden settings and lowest in high TB/HIV burden settings ($760.51 versus $556.95) while the opposite was found for post-diagnostic weighted means ($1,196.72 versus $557).

In low TB burden settings, only total costs and post-diagnostic costs were comparable as a pre-diagnostic weighted mean could only be calculated for low MDR-TB burden settings. Among DS-TB patients, the weighted mean for total costs was found to be highest in low TB/HIV burden settings compared to low MDR-TB burden settings ($1,793.23 versus $663.27). Post-diagnostic costs were highest in patients from low MDR-TB burden stings with a weighted mean of $173.96 and lowest in patients from low TB/HIV burden settings with a weighted mean of $79.36.

Weighted Median of Costs for DR-TB and MDR-TB Patients: Weighted medians for patients with DR-TB/MDR-TB was $59.43 for pre-diagnostic costs, $1,134.61 for post-diagnostic costs and $5,123.26 for total costs incurred by patients.

When compared across WHO regions total costs incurred by DR/MDR-TB patients were found to be highest in patients from the WPRO region and lowest in patients from the SEARO region ($9,532.71 versus $1,005.17). Pre-diagnostic and post-diagnostic weighted medians could only be calculated for two WHO regions in DR-MDR-TB patients – AFRO and SEARO. Weighted medians for both costs were found to be higher in the AFRO region and lower in the SEARO region (pre-diagnostic: $98.75 versus $13.74 and post-diagnostic: 1,630.75 versus $868.68).

Across high TB burden settings, the weighted medians for total costs incurred by DR/MDR-TB patients were found to differ slightly with the highest values in high MDR-TB burden settings and lowest in high TB/HIV burden settings ($6,702.27 versus $5,287.80). Weighted medians for pre-diagnostic and post-diagnostic costs were both found to be highest in high DS-TB burden settings and lowest in high MDR-TB settings.

Across low TB burden settings, weighted medians for the total costs incurred by DR/MDR-TB patients were found to be highest in low TB/HIV burden settings and lowest in low MDR-TB burden settings ($3,435.34 versus $2,160.01). Weighted medians for pre-diagnostic costs in DR/MDR-TB patients were only able to be calculated for low MDR-TB settings. Post-diagnostic costs were found to be highest in low MDR-TB settings and identical for both low DS-TB and low TB/HIV settings ($1,630.75 versus $733.82).

Weighted Mean of Costs for DR-TB and MDR-TB Patients: The weighted mean for total costs incurred by DR/MDR-TB patients were $9,737.09.

A comparison of the weighted means for pre-diagnostic and post-diagnostic costs across WHO region could not be conducted due to limited studies reporting mean costs in these settings. However, the weighted mean for total costs could be obtained and was found to be highest in the WPRO regions with a weighted mean of $1,220.75 compared to the AFRO region with a weighted mean of $2,054.41.

Across high TB burden settings, weighted mean total costs incurred by DR/ MDR-TB patients were highest in patients from high MDR-TB burden settings and lowest in patients from high TB/HIV burden settings. ($10,561.67 versus $8,486.89).

Weighted means for low TB burden settings could not be obtained due to limited number of studies.

Weighted Median of Costs for Mixed Populations: Only two studies consisted of mixed populations where patient costs were not separated by TB type and patients could have either DS-TB or DR-TB. Both studies were conducted in Ethiopia with a weighted median of $134 for the total costs incurred by patients while receiving TB care. Weighted medians for the pre- and post-diagnostic phase could not be calculated due to limited data.

Weighted Mean of Costs for Mixed Populations: Weighted means for mixed populations were calculated from the same two Ethiopian studies mentioned above and values could only be calculated for the total cost due to limited data on pre- and post-diagnostic costs. The weighted mean for the total cost incurred by patients while receiving care in the two studies was $154.

Weighted Mean of Costs for HIV-Positive Patients: Median costs incurred by HIV-positive patients were only reported in one study and therefore a weighted median cost could not be calculated for a population of HIV-positive patients. Mean costs for HIV-positive patients were reported in four studies and highlighted pre-diagnostic, post-diagnostic and overall costs incurred by HIV-positive patients while receiving TB care. The weighted mean for pre-diagnostic costs incurred by HIV-positive patients was calculated to be $173.96 while for post-diagnostic costs it was calculated to be $602.43. For overall costs incurred by HIV-positive patients the weighted mean was $97.61

Table 2.5 – Weighted median and means for pre-diagnostic, post-diagnostic and total costs incurred by patients during TB care based on study population

	Pre-Diagnostic		Post-Diagnostic		Total	
Median						
DS-TB	N=9	$52.12	N=8	$88.15	N=20	$469.49
DR-TB/MDR-TB	N=3	$59.43	N=4	$1,134.61	N=8	$5,123.26
Mixed Population	N=0	-	N=0	-	N=2	$134
HIV+	N=0	-	N=0	-	N=0	-
Mean						
DS-TB	N=6	$466.77	N=7	$667.27	N=21	$1,234.18
DR-TB/MDR-TB	N=0	-	N=0	-	N=5	$9,737.09
Mixed Population	N=0	-	N=0	-	N=2	$154.00
HIV+	N=1*	$173.96	N=1*	$602.43	N=4	$97.61

Abbreviations: TB – Tuberculosis, DS-TB – drug sensitive TB, DR-TB – drug resistant TB, MDR-TB – multi-drug resistant TB, HIV – human immunodeficiency virus

**Studies with N=1 included costs and population sizes for different subgroups within the patient population*

Table 2.6 – Subgroup analysis on the weighted median and means for pre-diagnostic, post-diagnostic and total costs incurred by DS-TB patients during TB care

	Pre-Diagnostic Cost		Post-Diagnostic Cost		Total Cost	
Median						
WHO Regions						
AFRO	N=2	$12.99	N=2	$137.45	N=5	$413.39
EMRO	N=0	-	N=0	-	N=0	-
SEARO	N=7	$58.89	N=6	$57.91	N=10	$119.39
WPRO	N=0	-	N=0	-	N=4	$1,332.25
PAHO	N=0	-	N=0	-	N=2	$475.31
High TB Burden						
High TB	N=6	$45.67	N=4	$76.52	N=12	$385.61
High MDR-TB	N=7	$56.71	N=6	$69.49	N=14	$585.23
High TB/HIV	N=6	$47.54	N=4	$61.63	N=12	$474.26
Low TB Burden						
Low TB	N=4	$64.03	N=5	$109.35	N=9	$607.16
Low MDR-TB	N=3	$23.21	N=3	$129.82	N=6	$536.77
Low TB/HIV	N=4	$64.03	N=5	$109.35	N=8	$457.77
Mean						
WHO Region						
AFRO	N=0	-	N=2	$58.63	N=9	$202.77
EMRO	N=0	-	N=0	-	N=0	-
SEARO	N=3	$166.28	N=4	$236.13	N=6	$1,275.87
WPRO	N=1*	$1,719.01	N=1*	$3,425.28	N=5	$3,323.40
PAHO	N=1*	$173.96	N=1*	$602.43	N=3	$204.71
High TB Burden						
High TB	N=5	$557	N=6	$760.51	N=16	$1,326.12
High MDR-TB	N=4	$566.15	N=5	$979.91	N=12	$2,038.68
High TB/HIV	N=5	$556.95	N=5	$1,196.72	N=13	$1,046.19
Low TB Burden						
Low TB	N=0	-	N=0	-	N=5	$1,114.97
Low MDR-TB	N=2	$45.20	N=2	$173.96	N=9	$663.27
Low TB/HIV	N=0	-	N=2	$79.36	N=7	$1,793.23

Abbreviations: WHO – World Health Organization, AFRO – African region, EMRO – Eastern Mediterranean region, SEARO – South-East Asia region, WPRO – Western Pacific region, PAHO – Pan American region, TB – Tuberculosis, MDR-TB – Multidrug resistant TB, HIV – Human Immunodeficiency Virus

**Studies with N=1 included costs and population sizes for different subgroups with the patient population*

Table 2.7 – Subgroup analysis on the weighted median and means for pre-diagnostic, post-diagnostic and total costs incurred by DR-TB/MDR-TB patients during TB care

	Pre-Diagnostic Cost		Post-Diagnostic Cost		Total Cost	
Median						
WHO Regions						
AFRO	N=2	$98.75	N=3	$1,630.75	N=2	$1,990.14
EMRO	N=0	-	N=0	-	N=0	-
SEARO	N=2	$13.74	N=2	$868.68	N=2	$1,005.17
WPRO	N=0	-	N=0	-	N=3	$9,532.71
PAHO	N=0	-	N=0	-	N=0	-
High TB Burden						
High TB	N=3	$59.43	N=3	$1,302.59	N=5	$5,500.84
High MDR-TB	N=2	$13.74	N=2	$944.16	N=5	$6,702.27
High TB/HIV	N=3	$54.19	N=3	$1,205.73	N=6	$5,287.80
Low TB Burden						
Low TB	N=0	-	N=2	$733.82	N=2	$3,194.05
Low MDR-TB	N=2	$98.75	N=3	$1,630.75	N=3	$2,160.01
Low TB/HIV	N=0	-	N=2	$733.82	N=2	$3,435.34
Mean						
WHO Region						
AFRO	N=0	-	N=0	-	N=2	$2,054.41
EMRO	N=0	-	N=0	-	N=0	-
SEARO	N=0	-	N=0	-	N=0	-
WPRO	N=0	-	N=0	-	N=3	$14,220.75
PAHO	N=0	-	N=0	-	N=0	-
High TB Burden						
High TB	N=0	-	N=0	-	N=5	$9,737.09
High MDR-TB	N=0	-	N=0	-	N=4	$10,561.67
High TB/HIV	N=0	-	N=0	-	N=4	$8,486.89
Low TB Burden						
Low TB	N=0	-	N=0	-	N=0	-
Low MDR-TB	N=0	-	N=0	-	N=0	-
Low TB/HIV	N=0	-	N=0	-	N=0	-

Abbreviations: WHO – World Health Organization, AFRO – African region, EMRO – Eastern Mediterranean region, SEARO – South-East Asia region, WPRO – Western Pacific region, PAHO – Pan American region, TB – Tuberculosis, MDR-TB – Multidrug resistant TB, HIV – Human Immunodeficiency Virus

**Studies with N=1 included costs and population sizes for different subgroups within the patient population*

Catastrophic Costs and Use of Coping Strategies:

Patients in the majority of studies reported incurring catastrophic costs as a consequence of seeking TB care (Table 8). Using the WHO definition for catastrophic costs at a cut-off point of 20%, the proportion of patients that incurred catastrophic costs while seeking care ranged from 0% to 98%. Patients with MDR-TB were found to incur a higher burden of catastrophic costs ranging from 62% to 98% compared to patients with DS-TB where the proportion that incurred catastrophic costs ranged from 28% to 62%. In addition, the proportion of patients that suffered from catastrophic costs was lower in patients that were found using ACF methods (36% to 45%) compared to patients that were found using PCF methods (45% to 61%). A number of studies also examined a range of cut-off points to understand its effect on the proportion of patients burden by catastrophic costs. The cut-off points ranged from 5% to 40% and found that overall, the proportion of patients suffering from catastrophic costs decreased as the cut-off point increased.

Patients that suffered from catastrophic costs were found to use coping strategies to offset the costs of TB care such as: borrowing money (n=24, range:0% to 94%), selling assets (n=19, range: 0% to 52%), using savings (n=7, range: 10% to 40%), or a combination of strategies (n=7, range: 12% to 81%) (Appendix Table 1).

Table 2.8 – Proportion of patients that suffered from catastrophic costs and their cut-off point

	Cut-Off Point	***Catastrophic Costs***	
Assebe, 2020[18]	*10%*	*DS-TB*	*40%*
		DR-TB	*62%*
Aung, 2021[19]	*20%*	*60%*	
Chandra, 2021 [(1)] [21]	*20%*	*18% (95% CI 12 – 27%)*	
Chittamany, 2020[23]	*20%*	*Total*	*62.6%*
		DS-TB	*62.2%*
		DR-TB	*86.7%*
		TB/HIV	*81.1%*
Ellaban, 2021[26]	*20%*	*33%*	
Fuady, 2020 [(1)] [27]	*10%*	*46%*	
	15%	*38%*	
	20%	*33%*	
	25%	*26%*	
	30%	*22%*	
	35%	*17%*	
Fuady, 2018[29]	*20%*	*DS-TB*	*36%*
		MDR-TB	*83%*
Getahun, 2016[30]	*40%*	*63%*	
Gurung, 2019[33]	*20%*	*ACF*	*45%*
		PCF	*61%*
		Total	*53%*
Gurung, 2021[32]	*20%*	*32%*	
Kirubi, 2021[34]	*20%*	*27%*	
Lu, 2020[35]	*20%*	*22.2%*	

	Cut-Off Point	Catastrophic Costs			
McAllister, 2020[39]	10%	38.6%			
	20%	26.5%			
	25%	21.7%			
Morishita, 2016[40]		ACF	PCF		
	10%	54.6%	63%		
	20%	36.1%	45%		
	30%	24.1%	34%		
	40%	17.6%	21%		
Mudzengi, 2017[41]		TB/HIV	TB	HIV	
	5%	73%	55%	72%	
	10%	67%	53%	60%	
	15%	65%	47%	55%	
	20%	64%	47%	52%	
	25%	61%	45%	49%	
Muniyandi, 2020[42]	20%	31%			
Muttamba, 2020[43]	20%	53.1%			
Nhung, 2018[44]		MDR-TB	DS-TB	Total	
	20%	98%	59.6%	63%	
	30%	98%	43%	48%	
	40%	89%	30%	35%	
Pedrazzoli, 2021[46]	20%	Insured	65%		
		Uninsured	59%		
		Total	64%		
Pedrazzoli, 2018[45]	20%	64.1%			
Prasanna, 2018[47]	10%	49%			
	20%	32.5%			
Rupani, 2020[49]	20%	4%			
Stracker, 2019 [51]	20%	28%			
Sweeney, 2018[52]	20%	0-36%			
Timire, 2020[53]	20%	80%			
Tomney, 2020[54]	20%	DS-TB	28%		
		MDR-TB	80%		
Ukwaja, 2013[(2)][57]	5%	OOP Expenditure	95%		
	10%		65%		
	15%		37%		
	25%		9%		
	40%	Non-food Expenditure	44%		
Viney, 2019[59]	20%	83%			
Walcott, 2020[60]	20%	41.8%			
Wang, 2020[61]	20%	CHE	63.8%		
		CTC	87%		
Yang, 2020[62]		RS	RMR	MDR	Total
	15%	43.3%	46.7%	73.2%	46%
	20%	33.6%	43.3%	69.6%	37.1%
	25%	26.3%	40%	66.1%	30.2%

Abbreviations: TB – Tuberculosis, DS-TB – Drug sensitive TB, DR-TB – Drug-resistant TB, MDR-TB – Multi-drug resistant TB, RS-TB – Rifampicin sensitive TB, RMR-TB – Rifampicin mono-resistant TB, HIV – Human Immunodeficiency Virus, LTBI – Latent TB Infection, ACF – Active case finding, PCF – Passive case finding, CHE – Catastrophic health expenditure, CTC – Catastrophic total cost, OOP – Out of pocket

2.5 Discussion:

Through analysis of the current literature on the cost of TB care to patients and their households, our study shows that despite many countries offering free TB care, for a large portion of individuals it is not free. In reality while seeking care these individuals and their families can incur a large, potentially catastrophic, burden due to the costs for TB diagnostics and care. Total costs incurred while receiving TB care were found to range from a mean of $2.80 to $19,153.80 and a median of $7.00 to $13,042.62. Pre-diagnostic costs were found to range from a mean of $13.41 to $2,682.10 and a median of $5.38 to $187.00. Finally, post-diagnostic costs were found to range from a mean of $44.20 to $4,894.39 and a median of $48.44 to $1,163.83. Overall, pre-diagnostic costs were found to be lower than post-diagnostic costs despite previous literature finding that patients incurred a larger burden of costs during the pre-diagnostic period of care[5,21]. However, it is important to note that this discrepancy may be due to differences in reporting methods with some studies in this review combining pre-diagnostic costs and post-diagnostic costs together making post-diagnostic costs present a larger burden.

This study found the main drivers of financial burden for patients to be direct medical and indirect costs. While direct medical costs are covered in many countries through global and national free TB programs, medical costs still had a significant impact on the patient costs. During the pre-diagnostic phase the main drivers of costs were direct medical costs (i.e., patient consultations, medication, diagnostic imaging, and hospitalization) and indirect costs, namely loss of income. Similar results were found for the post-diagnostic phase with the main drivers of costs being direct medical costs particularly costs associated with TB medication, diagnostic imaging, follow-up tests and hospitalization as well as indirect costs, particularly loss of income, in addition to time/productivity loss and caregiver/guardian costs. Indirect costs accounted for a significant portion of patient incurred costs, with loss of income being the largest contributor to indirect costs incurred by patients in this review. This coincides with previous literature which cites income loss as the biggest financial risk for patients and their families while receiving TB care[5,22]. Income loss consists not only of wages loss due to inability to work while receiving TB care but also income lost to premature death due to TB resulting in limited income[23]. While patients in the post-diagnostic stage of care reported incurring larger direct medical costs, direct non-medical costs were also found to have a significantly higher burden on patients during the post-diagnostic stage compared to the pre-diagnostic stage. Direct non-medical factors that influenced the burden of costs incurred by patients include food, nutrition and costs related to transportation for TB care that were not covered under TB programs.

Certain patient subgroups, DR-TB and patients that were found using PCF methods, were consistently found to incur a larger burden of costs compared to other patient subgroups. This could be due to worse outcomes for these patients resulting in additional care like longer hospitalizations, longer, more complicated treatment regimens and higher risk of severe adverse events (SAEs)[24]. There was not enough costing data among many subgroups (e.g., insured versus uninsured patients, inpatients versus outpatients, TB/HIV versus LTBI/HIV coinfected patients, and patients treated in public versus private health clinics) to fully understand the burden of costs that these patients may face while receiving TB care. Our study calculated the weighted averages for studies with DS-TB, DR-TB, mixed patient and HIV-positive patient populations, and was able to compare how costs differed across WHO regions and varying TB burden settings. The weighted averages calculated for DR-TB patients were consistently higher than the weighted averages for any other subgroup for pre-diagnostic, post-diagnostic and total TB costs. In addition, patient populations with HIV-positive patients had the lowest weighted averages despite previous literature predicting that patients with TB/HIV coinfection may suffer additional financial burdens associated with HIV care [25–29]. Due to limited cost data for HIV-positive patient populations in this review we could only calculate overall weighted averages and not for differing geographical settings which restricted our grasp on the total burden of costs for this population[25–29].

Despite similarities between the study populations and settings, there were large variations in the patient incurred costs. Weighted averages for DS-TB and DR-TB patient subgroups were calculated and used to examine costs differences across varying geographical and TB burden settings. For DS-TB and DR-TB patients, total TB costs were highest in countries from the WPRO which consists of Cambodia, China, Lao People's Democratic Republic, the Philippines and Viet Nam[30]. Studies conducted in China by Lu *et al*., Wang *et al*., and Yang *et al*., reported some of the highest patient incurred costs and state that it is largely due to where as well as how patients in this region receive TB care[23,31,32]. In China, many patients have low socioeconomic status and are unable to qualify for medical assistance to cover the costs for services not covered through their government TB program. Furthermore, TB treatment is available solely at county and provincial TB designated hospitals, with high costs for services and low reimbursement rates which significantly add to the financial burden placed upon patients who are receiving TB care and their families[23,31–33]. In terms of high TB burden settings, weighted averages were calculated to be highest in countries with high MDR-TB burden such as China, India and Viet Nam[18,34]. This is not uncommon to see as due to the complicated nature of DR-TB, patients with DR-TB often incur a larger burden of costs associated with medication, severe adverse events and treatment adherence[35–37].

According to the WHO, patient incurred costs are considered catastrophic when they make up more than 20% of a household's pre-TB annual income[1]. Using the WHO cut-off, we found the proportion of patients to suffer from catastrophic costs while receiving TB care ranged from 0 – 98%[1]. Patients with MDR-TB and patients found using PCF methods reported the highest burden of catastrophic costs. Studies have found the occurrence of catastrophic patient costs to have a significant impact on patient outcomes with a study by Fuady *et al*., stating that patients who incur catastrophic costs are 2-4 times more likely to experience treatment failure compared to patients without catastrophic costs[38]. Patients who experience catastrophic costs often have to resort to coping mechanisms like borrowing money, selling assets or using savings to help offset some of the financial burden of TB care. Studies have found that a number of factors are associated with TB patients suffering catastrophic costs including age, employment status prior to illness, income level, financial security, insurance, distance to hospital, type of TB and severity[7,23,39]. Furthermore, Kirubi *et al*., noted that delayed treatment could also have an impact on the costs incurred by patients by increasing disease severity and requiring more complex, costly treatment options[40].

There are several strengths and limitations to this review. One strength of this study was that it used a comprehensive search strategy that covered studies with differing patient as well as geographical populations. A limitation of this review is that we restricted to studies that collected patient costing data using WHO or WHO adapted patient costing surveys. This prevented studies that were conducted prior to the development of the costing survey and studies that did not use the WHO patient costing survey from being included in this review. Despite this limitation, we were able to find a significant number of studies to include in this review. Furthermore, by using only studies that collected patients costs with a standardized WHO survey it provides comparability between studies that may not have been available with other costing survets. Another limitation of this review is that due to limited data on patient costs in high-income settings we were only able to report on costs in LMIC settings. This helps to highlight the need for economic research on patient incurred costs associated with TB care to be conducted in high income settings. Finally, the manner in which studies reported patient costs varied resulting in pre-diagnostic and post-diagnostic costs being combined in some studies, which may influence the interpretation of the burden of patient costs at different stages of TB care.

2.6 Conclusion:

Based on the findings of this review it can be determined that free TB care under TB programs is not enough to prevent patients from being severely burdened by the costs incurred during TB care. Throughout all stages of care, patients incur direct medical, non-medical and indirect costs with costs varying largely based on patient type and geographical location. For many patients these costs are catastrophic resulting in the use of various coping mechanisms to deal with the financial burden. Patients and their families are forced to resort to taking out loans, selling assets or using their savings to pay for their care which can have significant social consequences such as job loss, interrupted work or schooling, food insecurity, impact relationships and result in social exclusion[41–44]. These factors can isolate TB patients and their families from their community as well as further perpetuate poverty. In addition, patients may be hesitant to seek care in order to limit the financial and social consequences associated with receiving care which can increase the transmission of TB[2,45,46]. Despite a number of TB programs offering free screening and treatment, direct medical costs were found to significantly drive the burden of patient incurred costs for both the pre-diagnostic and post-diagnostic stages of care. In particular, the key factors that influenced this burden were medication, hospitalization in addition to diagnostic testing during the pre-diagnostic phase and follow-up testing during the post-diagnostic phase. Non-medical costs while not as consequential, still influenced patient incurred costs. Costs for food, transportation and additional nutritional support drove non-medical patient costs for both the pre- and post-diagnostic stage of care. Indirect were also found to have a large impact on patient incurred costs and consisted mainly of loss of income due to inability to work or premature death due to TB. Patient incurred costs were consistently higher for patients with MDR-TB and those who were identified using PCF methods who likely experience poor outcomes and therefore require treatment regimens that are longer with increased risk of SAEs.

Further social protection interventions are needed to better understand the factors influencing the burden of costs in order to develop and implement policies that protect patients from TB-related financial burdens. Studies should work to establish evidence- based strategies that are both cost-effective and can be easily implemented in addition to scaling up TB programs to allocate resource for transportation vouchers and food programs in order to eliminate or at least mitigate the burden of direct drivers of patient incurred costs [5,41,47,48]. Strategies like conditional (i.e., for patients with specific types of TB or at specific stages of care) or unconditional cash transfers and financial compensation have shown promising results for reducing the burden of patient costs, however additional data is needed[7,49,50]. “One-size-fits-all” health care policies fall short when it comes to TB care and countries need to work to adopt tailored policies that provide support to their most vulnerable populations without letting them slip through the cracks[23,39]. The COVID-19 pandemic had significant impacts on the fight against TB, reversing years of progress, in addition to highlighting where there are gaps in how TB care is provided. The socioeconomic impact of TB care faced by patients exacerbates poverty as well as further perpetuates the global burden of TB. By working to isolate and understand the factors that influence patient costs while receiving TB care we can develop tailored social protection strategies and policies that provide effective TB care resources while lowering catastrophic costs for patients in accordance with the WHO "End TB Strategy" goals[50,51].

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Chapter Three – Bridging Section:

The first manuscript in this thesis examined the economic burden of TB care in low-, middle-, and high-income settings specifically from a patient perspective. The findings of this study highlight how despite efforts from both national and international programs to eliminate catastrophic costs associated with TB care for patients and their families, the majority of patients still suffer a significant financial burden when seeking and receiving TB care. Direct medical costs consisting of consultations, diagnostics, medication, hospitalization and other related medical costs had the highest burden on patients followed by indirect costs such as loss of income and productivity loss then lastly direct non-medical costs including food, transportation, nutritional support and accommodations. Unfortunately, these cost components only highlight a fraction of the total costs associated with providing TB care[1,2].

Health care system costs account for the other half of costs associated with TB care. These include cost components like the cost of staff, equipment costs, consumables as well as overhead and maintenance. Economic evaluations are used as a crucial step to help understand the costs of novel strategies and assess their cost-effectiveness[1,3]. Health economic evaluations work to use available costing data to identify strategies to improve an individual's health and wellbeing[4–6]. By conducting economic evaluations, policy makers and decision makers can be provided with ample information to develop policies that improve health outcomes by being both effective at reducing the burden of disease as well as cost-effective[7]. One form of economic evaluations include cost-effectiveness analyses (CEAs) which calculates the incremental cost effectiveness ratio (ICER), quality adjusted life years (QALYS) or disability adjusted life years (DALYs) by comparing the cost of the intervention of interest to one or more reference interventions[5,6].

Development of novel TB diagnostic and treatment interventions are key to reducing TB burden as well as improving patient outcomes however before these strategies can be implemented, we first need to understand the economic impact of them. In order to target and address the funding of TB services, we need to understand the effectiveness as well as the cost of novel TB interventions so that they can be implemented as part of current TB regimens[3]. In the second manuscript of this thesis, a simple decision analytic model was used to conduct a CEA to assess the impact of including second generation urine base lateral flow lipoarabinomannan (LF-LAM) assays in combination with gold-standard Gene Xpert MTB/RIF tests to assist in TB diagnostics for people living with HIV from South Africa.

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Chapter Four – Manuscript Two:

<u>*Cost-Effectiveness of Second-Generation Lateral-Flow Urine Lipoarabinomannan for the Diagnosis of Tuberculosis in HIV-Positive Patients*</u>

Olivia D'Silva[1], Suvesh Shrestha[1], Alice Zwerling[1] PhD

1. University of Ottawa, School of Epidemiology and Public Health – Ottawa, Canada

<u>*4.1 Abstract:*</u>

Background:

In accordance with the World Health Organization (WHO) "End TB" strategy goal to reduce TB prevalence, use of LF-LAM diagnostic tests have been recommended by the WHO to assist in the detection of TB for HIV+ patients. LF-LAM tests like AlereLAM have been shown to be cost-effective and have improved diagnostic accuracy compared to other diagnostic algorithms for people living with HIV (PLHIV) but uptake has been slow. Second generation FujiLAM has been introduced as a replacement for AlereLAM however data on the cost effectiveness of this strategy is limited. This study aims to determine the cost-effectiveness of including FujiLAM to assist in TB diagnostics for PLHIV.

Methods:

A simple decision analytic model was developed to evaluate four diagnostic algorithms for HIV+ adults from South Africa – the standard of care Xpert Only, Xpert + FujiLAM for all, Xpert + FujiLAM conditional on a negative Xpert and Xpert + FujiLAM conditional on patients being symptom positive. Published literature was used to parameterize the model. The key outcomes that were analyzed include the cost, disability adjusted life years (DALY), and incremental cost per DALY averted. One-way sensitivity analyses were also conducted.

Results:

In the cost-effectiveness analysis two algorithms were found dominated by the algorithms Xpert only and Xpert + FujiLAM conditional on patients having a negative Xpert – Xpert + FujiLAM for all and Xpert + FujiLAM conditional on being symptom positive. In the base case analysis, Xpert only was found to be dominated by Xpert + FujiLAM conditional on a negative

Xpert with an ICER of 930.47 USD per DALY averted. One-way sensitivity analysis found that variations in the key model parameters had an impact on the ICER calculation though none of the variations were large enough change the threshold.

Conclusion:

Based on the findings of this CEA, it is recommended that the SG LF-LAM test FujiLAM be used as an additional diagnostic test to assist in TB diagnosis for HIV-positive patients that have a negative Xpert instead of using Xpert as the sole diagnostic test for PLHIV.

4.2 Introduction:

Tuberculosis (TB), an airborne respiratory disease is the second leading infectious cause of death following COVID-19. Individuals living with human immunodeficiency virus (HIV) can become immunocompromised due to the disease and are considered to be at a high-risk for developing TB compared to those without HIV[1]. According to the World Health Organization (WHO) the likelihood of developing active TB disease is approximately 16 (Range:14-18) times higher in people living with HIV (PLHIV) than those individuals living without HIV[1,2]. In 2021 it was estimated that 10.6 million individuals contracted TB with 1.6 million TB related deaths - 187, 000 of which were amongst PLHIV[1]. In addition, the largest burden of TB HIV coinfection was seen in African regions particularly southern Africa where prevalence exceeded 50%[1].

PLHIV continue to disproportionately suffer from TB and in order to reduce this burden, factors like quick, affordable access to ART, effective screening and TB prevention measures in addition to accurate diagnostic testing need to be implemented[1]. PLHIV can experience difficulties when trying to get diagnosed with TB mainly due to suboptimal performance concerns with current diagnostic tools, as well as the lack of strategies that can be implemented in settings with resource constraints[3,4]. Furthermore, according to the WHO there is an overdependence on clinical diagnosis for TB as opposed to bacteriological confirmation suggesting that the current TB diagnostic strategies are not able to be effectively implemented in various high TB burden settings. Due to this combination of factors, studies have found that nearly 30% of PLHIV who have TB are left undiagnosed and lacking proper care[1].

The WHO strategy for prevention, care and control of TB recognizes early detection as a key step in reducing the global burden of TB. Current diagnostic strategies consist of rapid molecular assays such as Gene Xpert MTB/RIF a sputum-based test which can detect both active TB disease and rifampicin drug resistance. Since 2010, Gene Xpert MTB/RIF and its updated version Gene Xpert MTB/RIF Ultra have been recommended by the WHO as a first-line diagnostic test for active TB in children and adults[5]. However, while Xpert MTB/RIF may be effective at diagnosing active TB in those without HIV, in PLHIV it has been found to have reduced specify and sensitivity[6–8]. In 2019, the WHO updated their policies to recommend lateral flow urine lipoarabinomannan assays (LF-LAM) like AlereLAM which have improved sensitivity compared to Xpert in PLHIV as the point-of-care (POC) test to ***assist*** in TB diagnosis amongst this population. The policy update states that "*LF-LAM should be used as an add-on to clinical judgement in combination with other test. It should not be used as a replacement or triage test"*[9].

LF-LAM is a point-of-care test that can detect the presence of lipoarabinomannan, a mycobacterial antigen excreted in the urine of individuals with TB. This non-sputum-based test has been found to be a crucial development for the diagnosis of TB in PLHIV by allowing for diagnostic testing in individuals unable to produce sputum samples[10]. Using LF-LAM as an additional tool to assist in the diagnosis of TB in PLHIV has been shown to reduce the proportion of PLHIV with undiagnosed TB as well as allow for earlier detection and implementation of treatment for these patients improving patient outcomes[9,10]. At the time that the 2019 policy update was published AlereLAM was the only LF-LAM strip test commercially available on the market however, since then Fujifilm SILVAMP TB-LAM (FujiLAM) a new LF-LAM strip test has been introduced and shows promising results.

While first generation AlereLAM has been an effective tool in diagnosing TB in PLHIV helping to improve diagnostic yield and reduce mortality from TB there are limitations to the sensitivity of this diagnostic test. AlereLAM falls short in its ability to detect low levels of LAM in urine samples and its restriction to adult patients with advanced HIV and low CD4 levels[11–13]. Second generation LF-LAM (SG LF-LAM) tests like FujiLAM have improved sensitivity compared to first generation assays making them the ideal POC test for PLHIV. Use of any LF-LAM assay as a screening test is yet to be recommended by the WHO however, when used in combination with Xpert, AlereLAM tests have been found to improve active case finding in PLHIV by 13.5%. In addition, studies have found the addition of AlereLAM to diagnostic algorithms to be a highly cost-effective strategy that greatly reduces TB morbidity and mortality in PLHIV[14–17]. As SG FujiLAM assays have improved sensitivity compared to their first-generation counterparts it is suggested that uptake of these assays can further improve active case finding for PLHIV. In order to fully understand the benefit of recommending SG LF-LAM assays for PLHIV we need to determine the effectiveness of these tests in diagnosing patients with TB and their cost effectiveness. This study aims to develop and parameterize a model to evaluate the cost-effectiveness of SG LF-LAM tests for TB diagnosis in HIV+ patients from sub-Saharan Africa. It will aim to determine the cost, health outcomes as measured by disability adjusted life years (DALYS) averted, and the cost-effectiveness of SG LF-LAM diagnostic algorithms for TB in PLHIV per DALY averted.

4.3 Methods:

Model Overview: This economic evaluation consisted of a cost effectiveness study for HIV+ patients in South Africa from a health care systems perspective. A basic decision analytic model was developed and analyzed the addition of FujiLAM in TB diagnostic algorithms for PLHIV using TreeAge Pro software (version 2019; TreeAge Software Inc., Williamstown, MA, USA). This was used to assess the cost-effectiveness of the SG LF-LAM diagnostic tools FujiLAM for PLHIV across several scenarios. The model for this study was kept simple with hope to expand the model for further studies.

A total of four diagnostic algorithms were compared as shown in Figure 1.

1) *Algorithm 1 – Xpert only:* Patients receive Gene Xpert MTB/RIF as the only diagnostic test. This is considered the standard of care for TB diagnostics in PLHIV[1,5].
2) *Algorithm 2 – Xpert + LF-LAM for all patients:* All patients receive Gene Xpert MTB/RIF as the initial diagnostic test followed by FujiLAM.

3) *Algorithm 3 - Xpert + LF-LAM conditional on negative Xpert:* All patients receive an initial Gene Xpert MTB/RIF diagnostic test followed by FujiLAM for patients who had a negative Xpert.
4) *Algorithm 4 – Xpert + LF-LAM conditional on being symptom positive:* All patients receive an initial Gene Xpert MTB/RIF followed by FujiLAM for patients who were symptom positive.

Model Assumptions: Our model assumed that all patients were South African adults (≥18 years of age) with a confirmed HIV diagnosis regardless of CD4 count and on ART consisting of tenofovir/lamivudine/efavirenz, the most common ART regimen in South Africa[18–20]. We included patients with active TB disease including pulmonary, extrapulmonary or disseminated TB. Active cases of TB in PLHIV were initially identified using a four-symptom screening (4SS) to detect one of the four common symptoms of TB consisting of fever, night sweats, cough and weight loss[21]. If diagnosed with TB through use of Xpert or LF-LAM diagnostic tests patients would start drug sensitive TB treatment unless they chose to decline treatment. Current treatment regimens for TB in PLHIV from South Africa consist of a 6-month regimen with 2-months of isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) followed by 4-months of HR (2HRZE/4HR)[22,23]. Patients with drug resistant TB (DR-TB) were excluded from this model.

Model Inputs: Key parameters including epidemiologic parameters, disability weights as well as the cost and performance of diagnostic tests are highlighted Table 1. All data was obtained from previously published literature through careful review and consensus amongst reviewers.

Model Outcomes: The primary outcome of this study was the incremental cost-effectiveness ratio (ICER) per DALY averted and the cost effectiveness of the SG LF-LAM assay FujiLAM for HIV+ patients in South Africa. This cost effectiveness analysis was conducted from a health care perspective with a time horizon of 1-year year and a discount rate of 3%. All costs are reported in 2021 USD. Strategies were considered to be cost-effective if the ICER is below the willingness to pay threshold (WTP)[24,25]. For this CEA study, we adopted the gross domestic product (GDP) per capital of South Africa ($7,055 USD) as the WTP [26].

Sensitivity Analysis: One-way sensitivity analyses were conducted using the ranges included in Table 1. Where the ranges for values were not available, we used a range of +/- 20% for the sensitivity analyses. In addition using the distributions noted in Table 1, a probabilistic sensitivity analysis was also conducted.

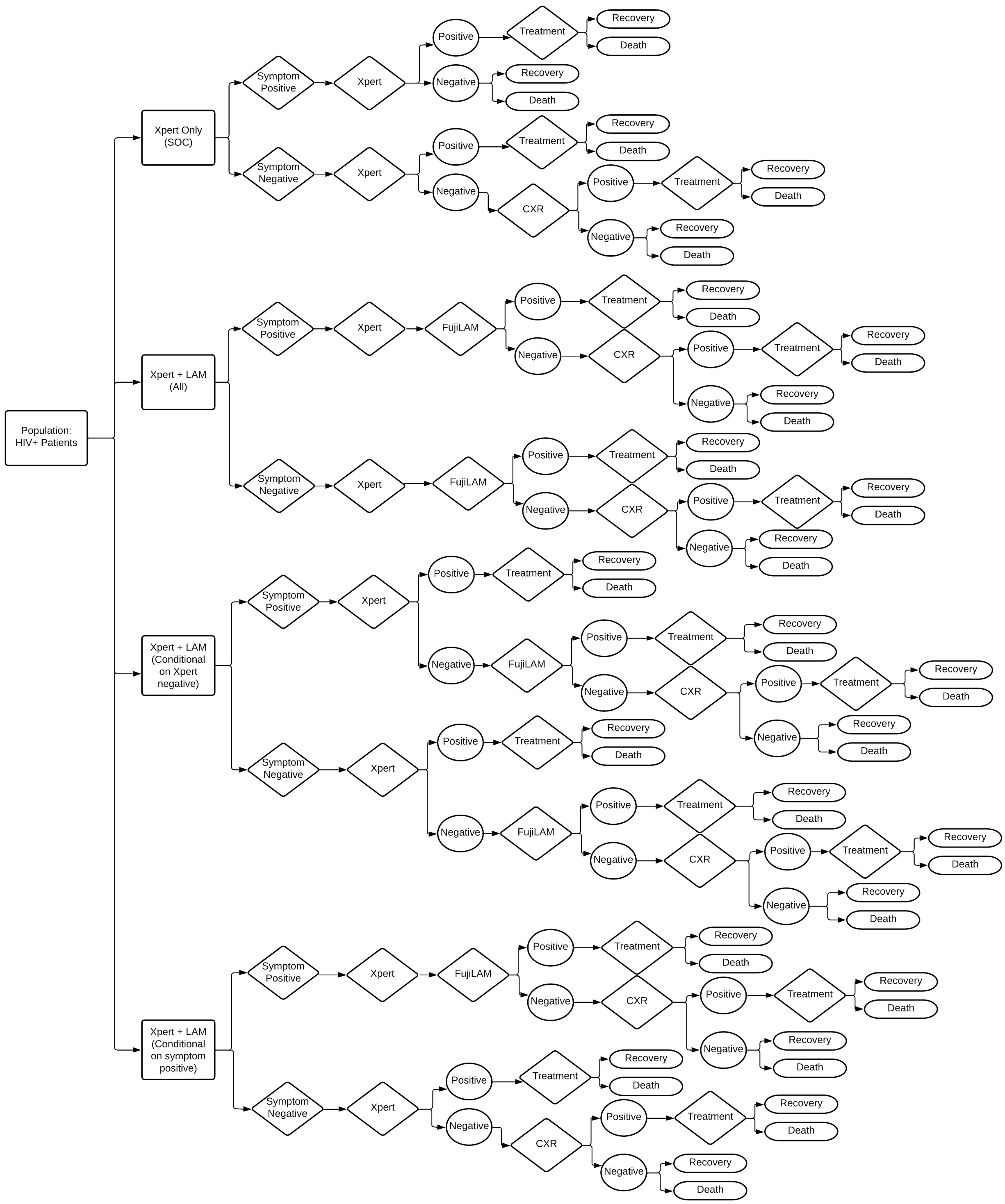

Figure 4.1- Simplified model of TB diagnostic strategies in PLHIV in South Africa

HIV – Human Immunodeficiency Virus, Xpert – Gene Xpert MTB/RIF, LAM – Lipoarabinomannan, CXR – Chest X-ray

Table 4.1 – Model Input Parameters

Parameter	*Value*		*Range*		*Distribution*	*Source*
Cost of TB diagnostic assay, per test (2021 USD)						
Urine FujiLAM	$4.59		$2.30 - $14.77		Gamma	18
Sputum GeneXpert MTB/RIF	$6.66		$5.96 - $12.89		Gamma	15
Symptom Screen	$27.56				Gamma	24,25
CXR	$0.77		$0.60 - $0.94		Gamma	26
Cost of TB treatment regimens, per patient						
DS-TB treatment	$413.86		$331.27 - $469.45		Gamma	27
First-line ART (TDF/3TC/EFV)	$821.56		$740.85 - $902.27		Gamma	28
Test Performance	***Sensitivity***	***Specificity***				
Urine FujiLAM	62%	90%	48% - 77%	75% - 94%	Beta	18,29
Sputum GeneXpert MTB/RIF	66.7%	77.1%	54.8% - 77.1%	62.7% - 88.0%	Beta	30
CXR	67.9%	53.7%	56.6% - 77.8%	47.7% - 59.6%	Beta	31
Symptom Screening	95%	23%	83% - 99%	15% - 33%	Beta	24
Epidemiological Parameters						
TB prevalence among HIV+ patients	29%		15% - 45%		Beta	18
Probability of treatment initiation (symptom positive patients)	55%		32% - 76%		Beta	32
Probability of treatment initiation (symptom negative patients)	21%		0% - 50%		Beta	33
Probability of DS-TB treatment completion	77%		62% - 95%		Beta	15
Mortality rate (TB/HIV coinfection on DS-TB treatment)	0.2		0.10 – 0.30		Beta	16,34
Mortality rate (untreated TB/HIV coinfection)	1		0.75 – 1.00		Beta	15,35
Disability Weights						
TB/HIV Coinfection	0.408		0.274 – 0.549		Triangular	36,37
HIV on ART	0.078		0.052 – 0.111		Triangular	36,37
Death	1.00				Triangular	36

Abbreviations: TB – Tuberculosis, LAM – Lipoarabinomannan, RIF – Rifampicin, CXR – Chest x-ray, DS-TB – Drug-sensitive TB, ART – Antiretroviral therapy, TDF – Tenofovir disoproxil fumarate, 3TC – Lamivudine, EFV – Efavirenz, HIV – Human immunodeficiency virus

4.4 Results:

Base-Case Analysis:

The base case results for the decision analytic model are presented in Table 2 below. Of the four strategies that were examined in the model, none of the FujiLAM strategies were found to be dominated by the SOC Xpert. The Xpert + FujiLAM conditional on patients having a negative Xpert result was found to be the most cost-effective algorithm with an ICER of 1,000 USD/per DALY averted. The other two FujiLAM algorithms can also be considered cost-effective though their ICERs were slightly higher at 1,350 USD/per DALY averted for the Xpert +FujiLAM for all algorithm and 1,150 USD/per DALY averted for the Xpert + FujiLAM conditional on patients being symptom positive. All FujiLAM algorithms were found to have identical incremental effectiveness when compared to the SOC with only minor differences in the incremental cost for each strategy. Xpert + FujiLAM conditional on patients having a negative Xpert result had the lowest incremental cost at $20 USD per patient while Xpert + FujiLAM for all had the highest incremental cost at $27 USD per patient. With a WTP threshold of $7,055 USD, the ICERs for all FujiLAM strategies is considered cost-effective however, Xpert + FujiLAM for Xpert negative patients is the most cost-effective strategy for TB diagnostics in PLHIV from South Africa.

Table 4.2 – Base-Case Analysis Results:

Testing Strategy	***Cost***	***Incremental Cost***	***DALY***	***DALY Averted***	***ICER***
Xpert only (SOC)	$948	-	0.30	-	-
Xpert + FujiLAM (All)	$975	27	0.28	0.02	1,350
Xpert + FujiLAM (Conditional on Xpert negative)	$968	20	0.28	0.02	1,000
Xpert + FujiLAM (Conditional on Symptom positive)	$971	23	0.28	0.02	1,150

Abbreviations: DALY – Disability adjusted life years, ICER – Incremental cost effectiveness ratio, Xpert – GeneXpert MTB/RIF
Note that all costs are reported in 2019 USD

One-Way Sensitivity Analysis:

One-way sensitivity analyses were conducted to assess how variations in the parameter values may influence the results of the model. The one-way sensitivity analyses analyzed the impact of two main factors - the cost and the effectiveness on the SOC Xpert only algorithm. The findings of the one-way sensitivity analyses are presented in the Figure 2 and Figure 3 tornado diagrams. The line in the middle of the diagram represents the base case value for each variable with the parameters that have the largest influence on the model reflected in the wider bars at the top while the parameters that have a smaller influence on the model are reflected in the smaller bars at the bottom. The factors that had the largest burden on the cost include the cost of first line ART, the probability of initiating DS-TB treatment and the probability of completing DS-TB treatment. The factors that had the largest burden on the effectiveness include the prevalence of TB, the DALY for death and the DALY for HIV positive patients on ART.

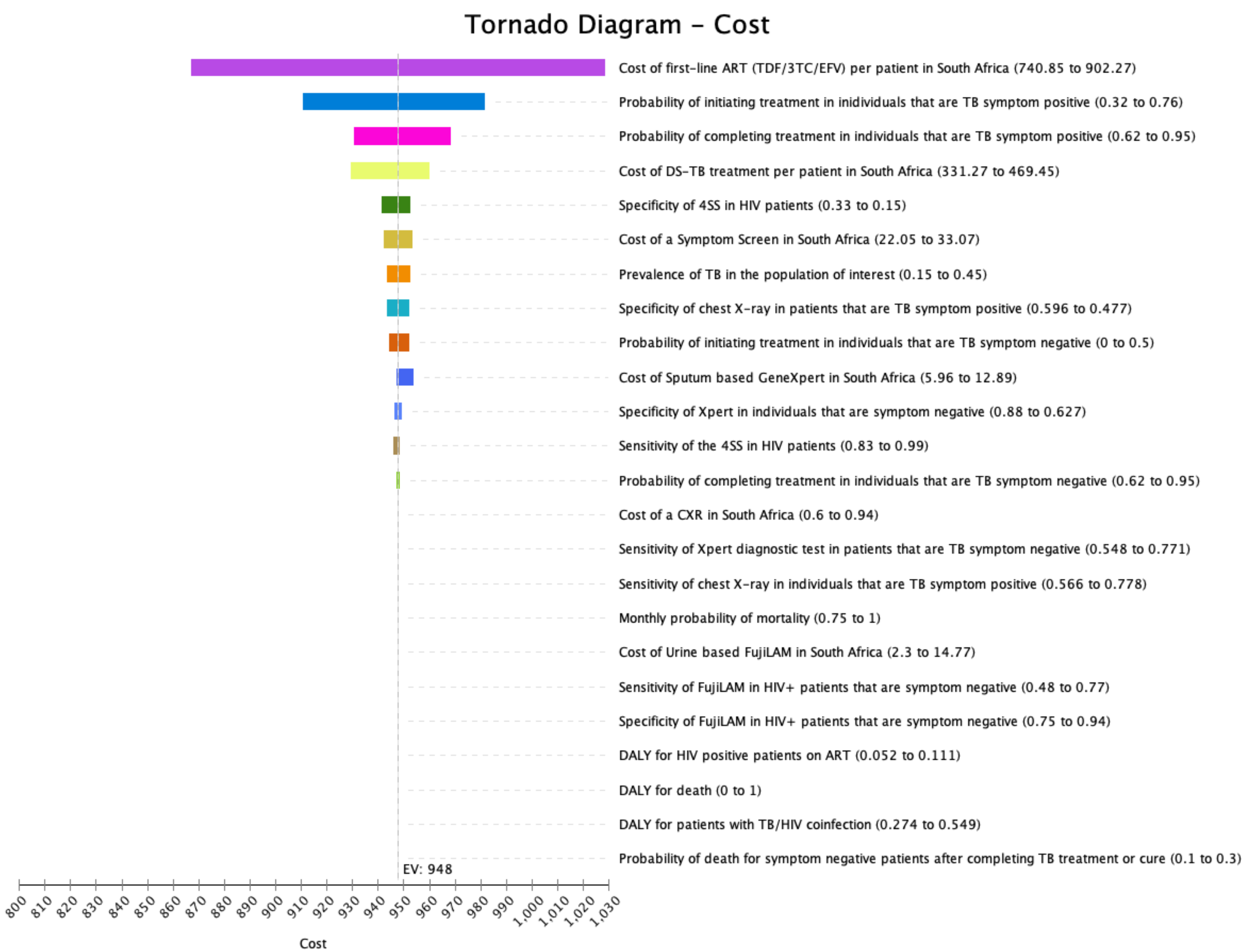

Figure 4.2 - Tornado diagram of key parameters that influence the cost per patient for the Xpert only (SOC) diagnostic algorithm using one-way sensitivity analysis

DALY – disability adjusted life year, Xpert – GeneXpert MTB/RIF, TB – Tuberculosis, HIV – Human immunodeficiency virus, DS-TB – Drug sensitive TB, 4SS – 4 Symptom Screening, CXR – Chest x-ray, ART – Antiretroviral therapy

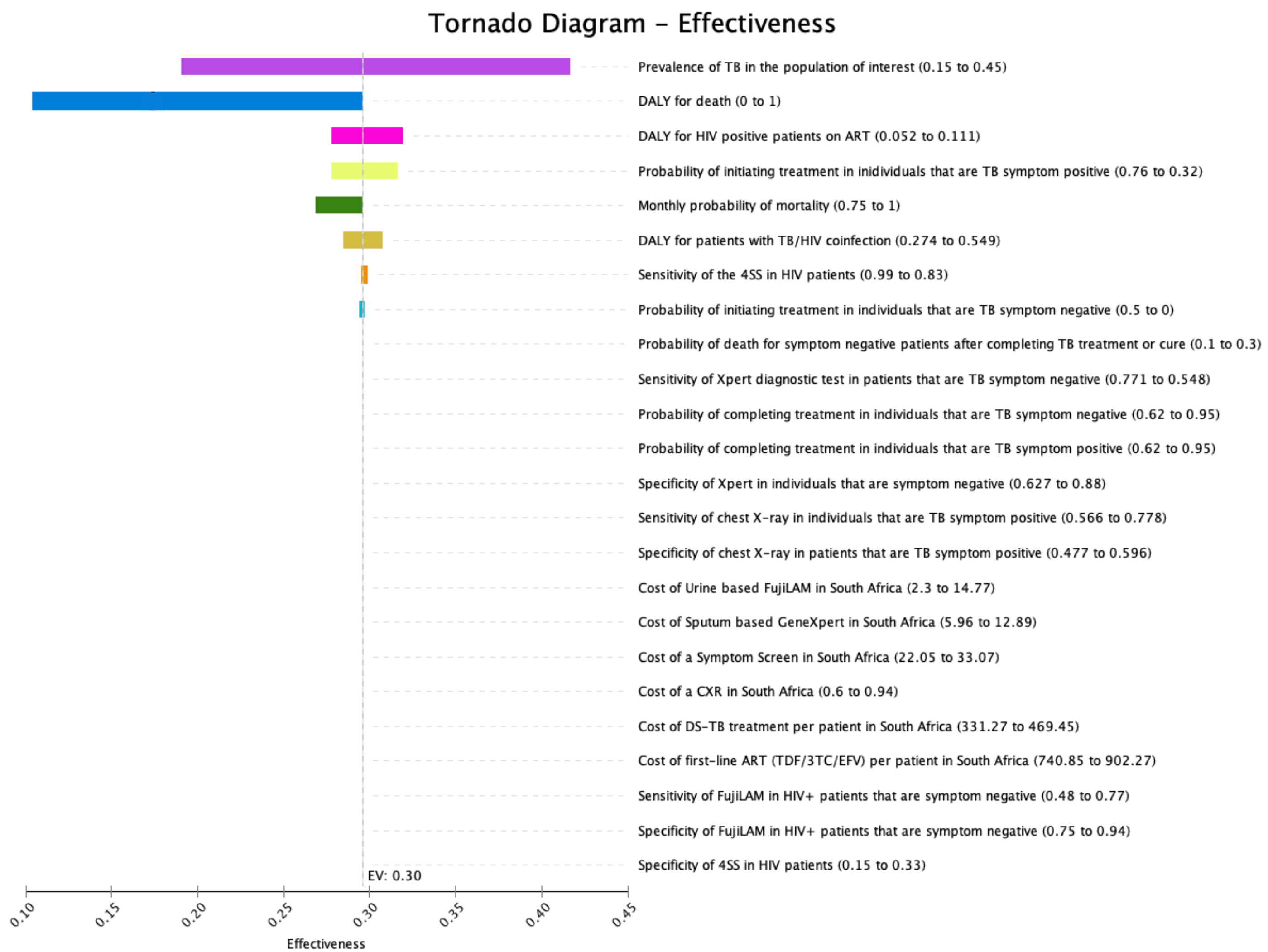

Figure 4.3 – Tornado diagram of key parameters that influence the effectiveness of the Xpert only (SOC) diagnostic algorithm using one-way sensitivity analysis

DALY – disability adjusted life year, Xpert – GeneXpert MTB/RIF, TB – Tuberculosis, HIV – Human immunodeficiency virus, DS-TB – Drug sensitive TB, 4SS – 4 Symptom Screening, CXR – Chest x-ray, ART – Antiretroviral therapy

Probabilistic Sensitivity Analysis:

A probabilistic sensitivity analysis was conducted to assess how the uncertainty of key model parameters may influence the model. The analysis analyzed cost and effectiveness as the two main factors of interest. A histogram presenting the probability distribution for each algorithm was generated. For the cost, the histograms for each algorithm are presented in Figure 4. The probability distribution histograms for all strategies had a normal distribution. The *SOC Xpert only strategy* had a range of $796 - $1,117 with a mean cost of $948 and a standard deviation of $46.87. The *Xpert + FujiLAM for all strategy* had a range of $820 - $1,156 with a mean cost of $975 with a standard deviation of $49.57. The *Xpert + FujiLAM conditional on patients having a negative Xpert result strategy* had a range of $812 – $1,147 with a mean cost of $968 and a standard deviation of $49.07. The *Xpert + FujiLAM conditional on patients being symptom positive strategy had a range* of $816 - $1,153 with a mean cost of $971 and a standard deviation of $49.24.

For the effectiveness, the Monte Carlo probability distribution histograms for each algorithm are presented in Figure 4. The histograms for each algorithm are all slightly skewed to the right. The *Xpert only strategy* had a range from 0.07 – 0.48 DALYs with a mean of 0.23 and a standard deviation of 0.06. The histograms for the three FujiLAM strategies were found to all have the same range of 0.08 – 0.44 DALYs with a mean of 0.22 and a standard deviation of 0.06.

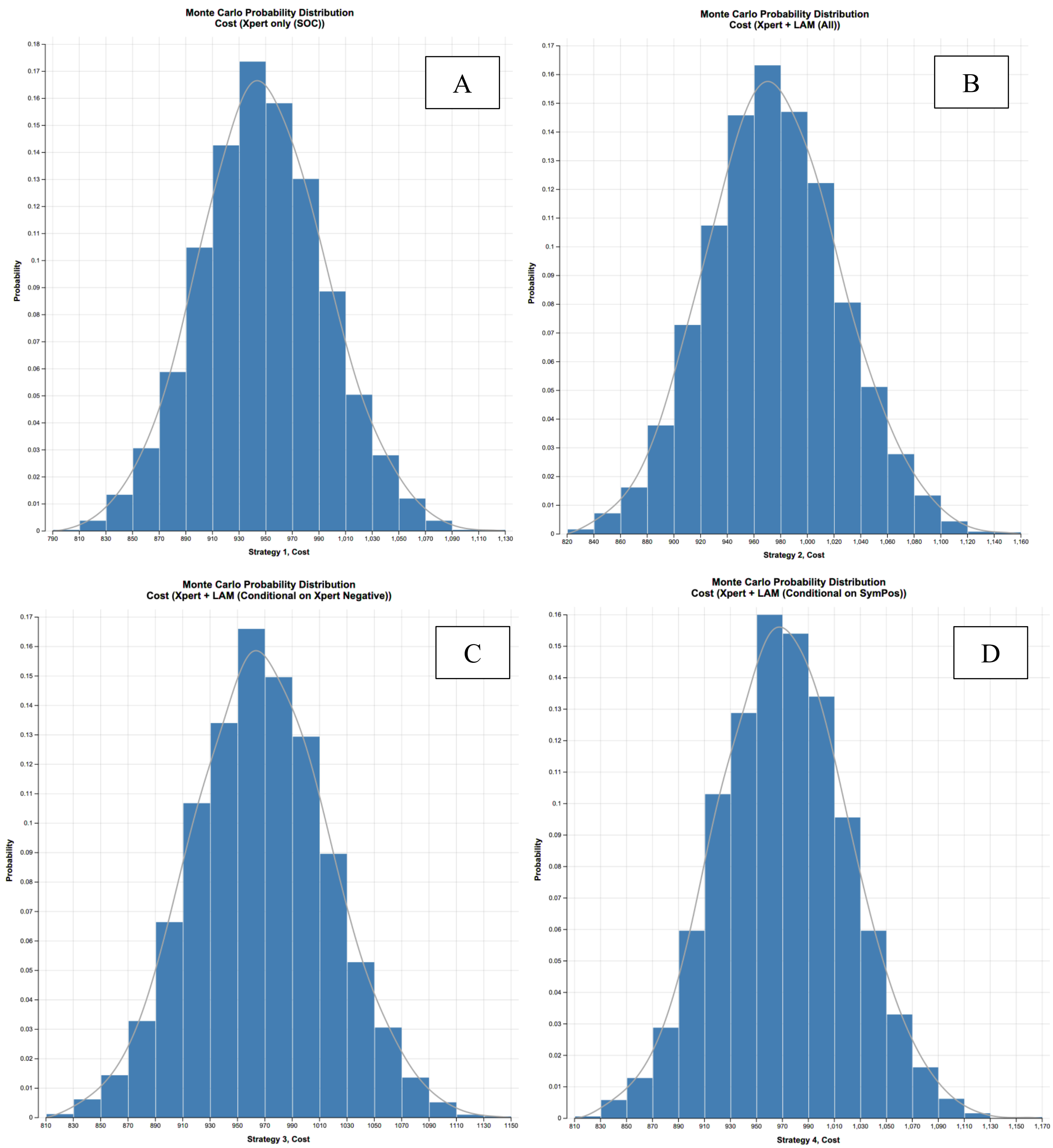

Figure 4.4 – The Monte Carlo probability distribution histograms for the cost of the four diagnostic strategies – Xpert only (A), Xpert + FujiLAM for all (B), Xpert + FujiLAM conditional on patients having anegative Xpert result (C) and Xpert + FujiLAM conditional on patients being symptom positive (D).

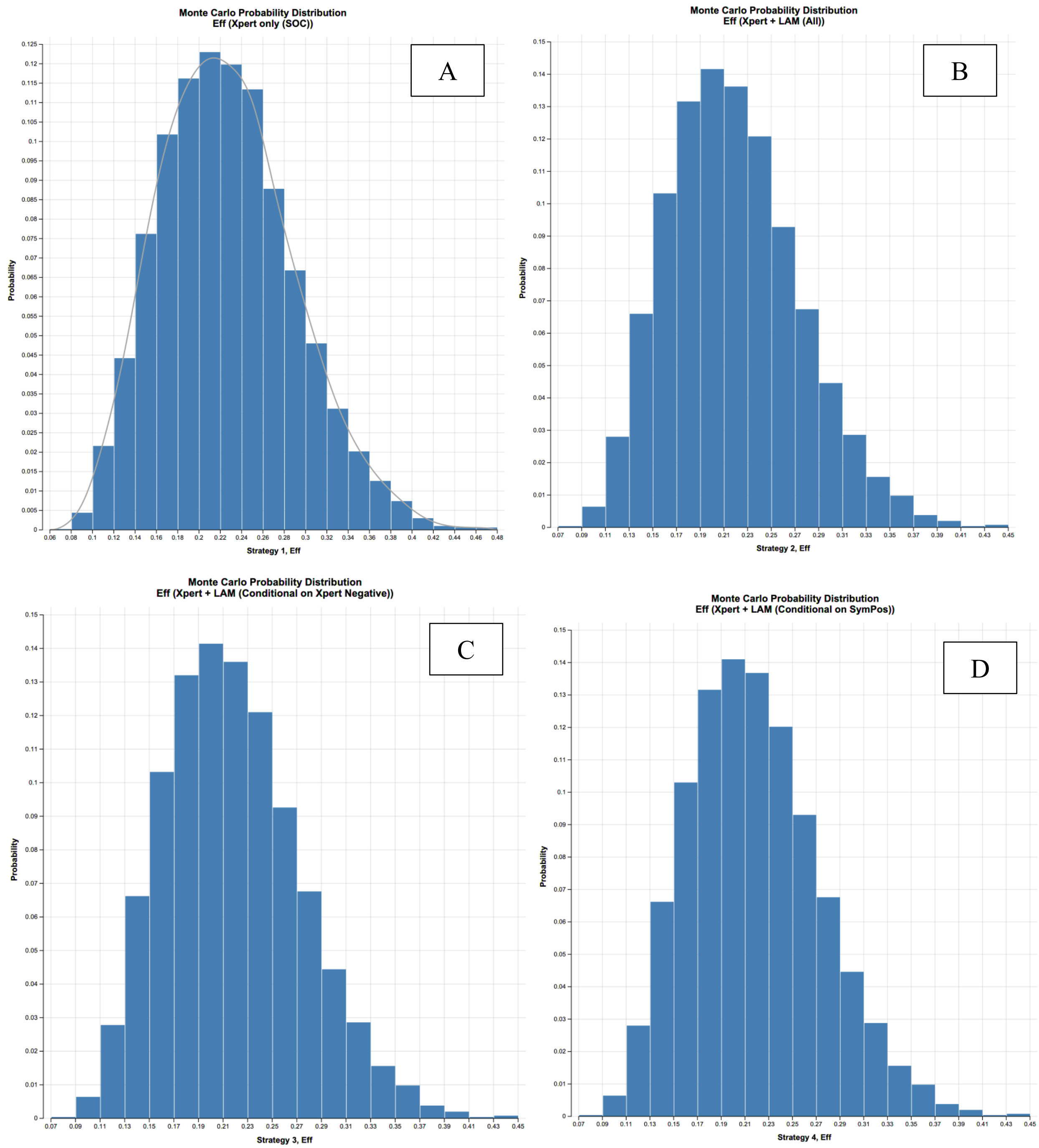

Figure 4.5 – The Monte Carlo probability distribution histograms for the effectiveness of the four diagnostic strategies – Xpert only (A), Xpert + FujiLAM for all (B), Xpert + FujiLAM conditional on patients having anegative Xpert result (C) and Xpert + FujiLAM conditional on patients being symptom positive (D)

4.5 Discussion:

This study developed and populated a decision analytic model to assess the cost effectiveness of implementing the SG LF-LAM diagnostic tool FujiLAM to assist in the diagnosis of TB in HIV+ adults from South Africa. The model assessed four different strategies with the three FujiLAM algorithms all being considered cost-effective compared to the SOC Xpert only. One strategy - Xpert + FujiLAM conditional on patients having a negative Xpert result was found to be slightly more cost-effective than the other two FujiLAM algorithms with an ICER of $1,000 USD/per DALY averted. Therefore, for the base case analysis assuming a WTP threshold of $7,055 USD, Xpert + FujiLAM conditional on patients having a negative Xpert result is the optimal strategy to use for PLHIV from South Africa. One-way sensitivity analyses were also conducted to assess the impact of variability with key model parameters on the cost and effectiveness. It was found that the parameters that had a large influence on costs were ART costs, the probability of treatment initiation and treatment competition while the parameters that influenced the effectiveness were TB prevalence, the DALY for death and the DALY for HIV.

Since the introduction of LF-LAM technology, a number of studies have been conducted supporting the cost-effectiveness of earlier AlereLAM diagnostic strategies and leading to policy updates encouraging their use[15–17,41,42]. Despite this, uptake of AlereLAM as a POC test to assist in the diagnosis of TB in PLHIV has been slow due to a number of barriers including lack of country specific data, limited applicability in clinical setting as well as lack of coordination between national TB and HIV programs to name a few[43,44]. Furthermore, while AlereLAM improved TB diagnostics by having higher diagnostic accuracy for PLHIV compared to other strategies it has limited use for children and individuals with higher CD4 levels[9]. Literature on the cost-effectiveness of FujiLAM is still limited, however, the findings of our study are supported by a 2021 Reddy et al., study which found that the inclusion of FujiLAM with Xpert for TB diagnostics in PLHIV from South African populations is cost-effective at an ICER of $830 USD/YLS when compared to Xpert only strategies[18]. Furthermore, feasibility and acceptability studies like the one by Rücker *et al.*, show that healthcare workers found uptake of FujiLAM to be relatively easy with the only downsides being the need for additional training and the fact that the assay procedures required multiple steps[45].

If we want FujiLAM to have better success than its predecessor, efforts need to be made to address the previously listed barriers and ensure that sufficient research on the use and benefits of FujiLAM as well as the cost-effectiveness of this strategy for PLHIV in various geographical settings is conducted. Current literature suggests that SG LF-LAM assays like FujiLAM have improved sensitivity compared to their first-generation counterparts however, accuracy and effectiveness of these assays has been found to vary greatly. A study by Huerga *et al*., found that when compared between lot numbers, FujiLAM sensitivity varied from 48% (95% CI 34-62) to 76% (95% CI 57-89) and specificity varied from 77% (95% CI 72-81) to 98% (95% CI 93-99)[44]. Until this variability among FujiLAM assays has been addressed large scale uptake of SG FujiLAM at a clinical level is unlikely. New TB diagnostic technology has shown improved sensitivity and specificity particularly in HIV+ populations working to improve case detection and reduce TB incidence rate. However, current strategies are nowhere near reaching the 4-5% TB incidence decline needed to achieve WHO "End TB Strategy" targets[46].

A limitation to this study is that it may overestimate the cost-effectiveness of the included diagnostic strategies by excluding additional cost factors like overhead, capital, materials and consumables etc. that are necessary in providing TB care. This may have underestimated the unit cost for each algorithm and therefore overestimated the cost-effectiveness. In order to mitigate this, we aimed to include a broad range of cost components in our model and ensure that we used the best available data. Furthermore, as this study is only conducted from a health care system prospective it completely overlooks the financial burden that may be taken on by the patients while undergoing TB diagnostics. It is possible that by excluding patient cost components in the model it may have misrepresented the cost effectiveness of the diagnostic algorithms. Another limitation of this study is that it used a very simple model to represent the TB diagnostic algorithms for PLHIV in South Africa. This may not accurately reflect how TB diagnostics are conducted and the strategies that are used impacting how the findings of this study can be interpreted.

4.6 Conclusion:

Based on the findings from this study, it is recommended that the SG LF-LAM test FujiLAM be used as an additional diagnostic test to assist in TB diagnosis for HIV-positive patients that have a negative Xpert over using Xpert as the sole diagnostic test for PLHIV. FujiLAM has the potential to be a crucial test for TB case detection in PLHIV however, it is important to note that before developing policies encouraging the uptake of FujiLAM, key issues with the variability of FujiLAMs diagnostic accuracy first need to be addressed.

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Chapter 5 – Final Conclusions:

This thesis project consisted of two manuscripts – a patient costs systematic review and a cost-effectiveness analysis analyzing the use of second generation FujiLAM assays for PLHIV in South Africa. In the first manuscript we found that patients were severely burdened by catastrophic costs associated with TB care despite access to free TB programs. Direct medical, direct non-medical, and indirect costs were found to all have a significant impact on patient costs and varied greatly by geographic setting or patient population. Particular patient populations like those with MDR-TB and patients who were identified using PCF methods were found to consistently incur significantly higher costs compared to patients with DS-TB. The burden of these catastrophic costs forced patients to seek out options such as taking out loans, selling assets or using savings to offset costs which had social consequences like interrupted work or schooling, food insecurity or social exclusion. Going forward, researchers should focus on examining the effectiveness of social protection interventions influences on the burden of catastrophic costs faced by patients.

In the second manuscript we used a decision analytic model to assess the cost-effectiveness of using the SG LF-LAM diagnostic tool FujiLAM to assist in TB diagnostics for PLHIV from South Africa. By comparing four algorithms – 1) Xpert only, 2) Xpert + FujiLAM for all, 3) Xpert + FujiLAM conditional on a negative Xpert and 4) Xpert + FujiLAM conditional on the patient being symptom positive it was found that Xpert + FujiLAM conditional on a negative Xpert was dominant over Xpert only. An ICER of 1,000 USD per DALY averted was calculated and sensitivity analyses were conducted to concluded that various parameters had an impact on the cost and effectiveness calculated. The findings of this study support the uptake of FujiLAM as an additional diagnostic test to assist in TB diagnostics for PLHIV in South Africa. Future analyses are needed to assess the cost-effectiveness of FujiLAM strategies in differing populations like children living with HIV and mixed patient populations. In addition, further work is needed to determine accurate test performance results as well as better understanding on the uptake and feasibility of these strategies.

By taking a multifaceted approach to examining the various economic components associated with TB care we are able to understand the health system costs and implications on TB care strategies on individual patients' financial burden. The findings of this study show the drastic costs associated with TB care, particularly from a patient perspective and help to highlight the need for universal health care services to help mitigate costs and make health care attainable for all. Furthermore, these findings can be used to inform decision makers and aid in helping to develop publicly funded TB programs that provide subsidized care that is both effective and cost-effective. Studies like this help to identify key strategies that are more cost-effectiveness than current regimens and can be implemented to help improve TB case finding as well as prevent poor treatment outcomes.

Appendix:

Appendix A – Search Strategy for Manuscript One:

Medline and Embase (OVID):

- 1. Latent Tuberculosis/ or Tuberculosis/ or Mycobacterium tuberculosis/ or Tuberculosis, Multidrug-Resistant/
- 2. tuberculos*.ti,ab,kw.
- 3. (latent adj1 tuberculos*).ti,ab,kw.
- 4. (latent adj2 tuberculos*).ti,ab,kw.
- 5. (latent adj2 infection*).ti,ab,kw.
- 6. (mycobacterium adj1 tuberculos*).ti,ab,kw.
- 7. (mycobacterium adj2 infection*).ti,ab,kw.
- 8. (mdr adj1 tuberculos*).ti,ab,kw.
- 9. (multi* adj2 tuberculos*).ti,ab,kw.
- 10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
- 11. patient cost*.ti,ab,kw.
- 12. catastrophic cost*.ti,ab,kw.
- 13. 11 or 12
- 14. 10 and 13

Web of Science/ Web of Knowledge:

- 1. (Tuberculosis OR TB OR Mycobacterium) (Topic)
- 2. ("Latent tuberculos*" OR "latent TB infection*") (Topic)
- 3. (MDR* TB" OR "MDR* Tuberculos*" OR "Multidrug-resistant Tuberculos*") (Topic)
- 4. (1 OR 2 OR 3) (Topic)
- 5.("Patient cost*" OR "catastrophic cost*") (Topic)
- 6. (3 AND 5)

Scopus:

- 1. (Tuberculos* OR TB OR mycobacterium) (title/abstract/keywords)
- 2. ("Latent tuberculos*" OR "latent TB infection*" OR LTBI) (title/abstract/keywords)
- 3. ("MDR* TB" OR "MDR* Tuberculos*" OR "Multidrug-resistant Tuberculos*") (title/abstract/keywords)
- 4. ("Patient cost*" or "catastrophic cost*") (title/abstract/keywords)
- 5. ((1 OR 2 OR 3) AND 4) (title/abstract/keywords)

Appendix B – Supplementary Results from Manuscript One:

Table S1 - Use of Coping Strategies in the Included Studies:

	N		Used Coping Strategies	Borrowed Money/Loans		Sold Assets		Use of Savings	Family Assistance	Combination of Mechanisms
Assebe, 2020[18]	787		68%	4%		19%			16%	
Aung, 2021[19]	967			32.5%		23.8%		36.8%		64.4%
Chandra, 2021(1)[21]	110		46.36%	94%						
Chittamany, 2020[23]	DS-TB	717		26.4%		17.7%		21.2%		49.9%
	DR-TB	8		25%		12.5%		37.5%		50%
	Total	725		26.3%		17.7%		21.4%		49.9%
Collins, 2018[24]	169			41%		Sold Property: 38%				
						Leased Property: 7%				
Ellaban, 2021[26]	151			67.6%		33.1%				
				Friends	56.3%	Household Property	45.7%			
				Family	39.4%	Jewelry & Gold	45.7%			
				Employers	3.2%	Means of Transport	8.7%			
				Other	1.1%					
Getahun, 2016[30]	576			18%		11%				
				Neighbours	34%					
				Family	23%					
				Friends	26%					
				Organizations	17%					
Gurung, 2019[33]	ACF	50		28%		8%				
	PCF	49		44%		10%				
	Total	99		36%		9%				
Gurung, 2021[32]	ACF	111								
	PCF	110								
Mauch, 2013 (1)[36]	Ghana	135		47%		37%				
	Vietnam	258		17%		5%				

	Dominican Republic	*150*			*45%*		*19%*					
***Mauch, 2013 (2)*[38]**	*198*				*45%*		*Property*	*20%*				
							Household Items	*43%*				
							Vehicles	*14%*				
							Land	*8%*				
							House	*3%*				
***Mauch, 2011*[37]**	*208*				*57%*		*52%*					
***McAllister, 2020*[39]**	*469*				*31%*							
***Morishita, 2016*[40]**	*ACF*	*108*		*46.30%*	*42.60%*		*13.90%*					
	PCF	*100*		*52%*	*46%*		*21%*					
***Muttamba, 2020*[42]**	*DS-TB*	*1134*			*25.90%*				*10%*			47.20%
	MDR-TB	*44*			*54.40%*				*39.90%*			81.20%
***Nhung, 2018*[44]**	*735*				*25%*		*5.8%*		*16%*			38%
***Pedrazzoli, 2018*[45]**	*DS-TB*	*625*		*51%*	*27%*		*10.7%*		*29.4%*			52%
	MDR-TB	*66*			*30.3%*		*15.2%*		*16.7%*			47%
	Total	*691*			*27.4%*		*11.1%*		*28.2%*			51.5%
***Prasanna, 2018*[47]**	*102*				*38%*		*8%*		*20.8%*			
***Rupani, 2020*[49]**	*458*			*18%*	*11%* *Median (IQR) amount borrowed: $71 (29 – 143)*							
***Sweeney, 2018*[52]**	*66*			*36%*	*30%*		*3%*					12%
***Tomeny, 2020*[54]**	*194*				*70%*		*7%*		*37%*			
***Ukwaja, 2013 (2)*[57]**	*452*			*88%*	*47%*		*9%*					32%
***Van der Hof, 2016*[58]**		*DS-TB*	*MDR-TB*		*DS-TB*	*MDR-TB*	*DS-TB*	*MDR-TB*		*DS-TB*	*MDR-TB*	
	Ethiopia	*25*	*169*		*56%*	*41%*	*24%*	*38%*		*-*	*-*	
	Indonesia	*118*	*143*		*9%*	*27%*	*9%*	*27%*		*32%*	*43%*	
	Kazakhstan	*54*	*94*		*0%*	*4%*	*0%*	*1%*		*57%*	*66%*	
***Walcott, 2020*[60]**	*196*			*26%*								

Abbreviations: TB – Tuberculosis, DS-TB – Drug sensitive TB, DR-TB – Drug resistant TB, MDR-TB – Multi-drug resistant TB, ACF – Active case finding, PCF – Passive case finding, IQR – Interquartile range

Table S2 – Total costs incurred by patients stratified by each phase of TB care – pre-diagnostic, post-diagnostic and overall.

	Pre-diagnostic		Post-diagnostic		Overall costs		
Assebe, 20208[1]					*Outpatient*	Mean (SD): $110 (114)	
						Median (IQR): $79 (46–140)	
					Inpatient	Mean (SD): $105 (78)	
						Median (IQR): $87(39-158)	
					Total	Mean (SD): $115 (118)	
						Median (IQR): $81 (47–150)	
Aung, 2021[19]					*DS-TB*	Median (Range): $201.28 (42.07 – 4662.64)	
					MDR-TB	Median (Range): $1044.23 (42.07 – 4444.76)	
					Total	Median (Range): $214. 81(42.07 – 4662.64)	
Chandra, 2021[(1)21]	*Median (IQR): $42 (19-313)*		*Median (IQR): $63 (10.2 - 190)*		*Median (IQR): $150 (65-335)*		
	Mean (SD): $113 (196.4)		*Mean (SD): $157 (238)*		*Mean (SD): $270 (305)*		
Chandra, 2021[(2)22]	*Private Health Facility*	*Median (IQR): $115.9 (46.3 - 204.3)*					
	Public Health Facility	*Median (IQR): $92.0 (48.6 - 194.8)*					
Chittamany, 2020[23]					*Nationally Representative Sample*	*DS-TB*	Median (IQR): $1189.90 (556.77 – 2277.99)
						DR-TB	Median (IQR): $3507.66 (1719.63 - 5206.60)
						Total	Median (IQR): $1201.03 (558.36 – 2312.99)
					Additional Sample	*DR-TB*	Median (IQR): $3568.11 (1958.24 – 4750.05)
						TB-HIV	Median (IQR): $2597.73 (1601.91 – 4220.32)
Collins, 2018[24]	*Median (Range): $103.74 (50-[22657].52*		*Intensive*	*Median: $826.16 (336.27 – 1210.08)*	*Median: $1722.62*		

Study							
				Continuation	Median: $792.42(572.54 – 1310.09)		
	Pre-diagnostic		**Post-diagnostic**			**Overall costs**	
De Siqueria Filha, 2018[25]	TB/HIV	Mean: $204.83	TB/HIV		Mean: $709.78	TB/HIV	Mean: $496.63
	LTBI/HIV	Mean: $13.41	LTBI/HIV		Mean: $44.2	LTBI/HIV	Mean: $57.61
Ellaban, 2021[26]	Median (IQR) - $67.5 (21.9–119.4)		Intensive		Median (IQR) - $18.8 (5.6–98.8)	Median (IQR) - $129.4 (43.8–356.9)	
			2nd two months of treatment		Median (IQR) - $9.4 (3.1–89.1)		
			3rd two months of treatment		Median (IQR) - $4.4 (1.9–67.5)		
Fuady, 2020(1)[27]						Median (IQR): $88.8 (342.41)	
Fuady, 2018[29]	DS-TB	Median (IQR): $5.38 (2.07 – 12.42)	DS-TB		Median (IQR): $48.44 (13.66 – 225.66)	DS-TB	Median (IQR): $45.77 (22.77 – 238.50)
	MDR-TB	Median (IQR): $11.18 (5.38 – 25.67)	MDR-TB		Median (IQR): $1142.78(409.50 – 1784.15)	MDR-TB	Median (IQR): $964.88 (417.36 – 1790.77)
Fuady, 2020(2)[28]						Mean (95% CI): $9.11(7.45 – 10.77)	
Getahun, 2016[30]						Mean (SD): $206.58 (91.70)	
						Median: $206.40 (538.07)	
Gospodarevskaya, 2014[31]			Tanzania	Intensive	Mean: $21.84	Tanzania	Mean: $43.47
				Continuation	Mean: $10.82		
			Bangladesh	Intensive	Mean: $66.43	Bangladesh	Mean: $134.00
				Continuation	Mean: $33.79		
Gurung, 2019[33]	ACF	Median (IQR): $143.58 (24.53 – 280.00)	ACF		Median: $91.92 (56.10 – 156.28)	ACF	Median: $274.36 (87.8 – 491.42)
	PCF	Median: $187.00 (65.01 – 439.98)	PCF		Median: $112.54 (49.16 – 209.68)	PCF	Median: $342.19 (136.53 – 590.29)
	Total	Median: $159.86 (45.15 – 330.90)	Total		Median: $104.84 (56.22 – 191.99)	Total	Median: $314.84 (96.26 – 517.37)
Gurung, 2021[32]	ACF	Mean (95% CI): $55.5 (39.0–71.9)	ACF		Mean (95% CI): $ 65.9 (55.1–76.6)	ACF	Mean (95% CI): $233.0 (204.6–261.4
		Median (IQR) - $20.4 (3.8–69.2)			Median (IQR) - $48.8 (35.4–78.5)		Median (IQR) - $218.2 (97.1–340.6)
	PCF	Mean (95% CI): $86.7 (69.7–103.8)	PCF		Mean (95% CI): $74.7 (60.6–88.8)	PCF	Mean (95% CI): $279.9 (244.8–315.2)
		Median (IQR) - $58.2 (22.3–127.2)			Median (IQR) - $51.2 (29.9–91.7)		Median (IQR) - $ 252.0 (117.9–393.3)
	Total	Mean (95% CI): $71.4 (59.5–83.3)	Total		Mean (95% CI): $70.3 (61.5–79.1)	Total	Mean (95% CI): $256.4 (233.7–278.9)

		Median (IQR) - $33.6 (10.3–97.1)		Median (IQR) - $ 49.8 (33.2–83.4)		Median (IQR) - $245.2 (113.1–365.6)
	Pre-diagnostic		***Post-diagnostic***		***Overall costs***	
Kirubi, 2021[34]					*Median: $266.64 (139.24 – 495.75)*	
Lu, 2020[35]	*Residents*	Mean: $2682.10	*Residents*	Mean: $4894.39	*Residents*	Mean: $6889
	Migrants	Mean: $1309.42	*Migrants*	Mean: $2800.48	*Migrants*	Mean: $3686
Mauch, 2013[(1)36]					*Ghana*	Mean: $78.76
						Median: $29.57
					Vietnam	Mean: $229.18
						Median: $170.14
					Dominican Republic	*Mean: $254.71*
						Median: $149.05
Mauch, 2013[(2)38]					*New Patients*	*Median: $817.64*
					Retreatment Patients	*Median: $389.17*
					MDR Patients	*Median: $3207.27*
Mauch, 2011[37]					Median: $82.28	
McAllister, 2020[39]					*Community Health Centre*	Median: $22.14 (10.38 – 29.39)
					Public Hospital	Median: $36.15 (20.02 – 78.79)
					Private Hospital	Median: $25.99 (5.78 – 70.12)
					Private Practice	*Median: $31.16 (18.59 – 47.47)*
Morishita, 2016[40]					*ACF*	Mean: $203.42 (212.10)
						Median: $122.72 (33.39 – 303.15)
					PCF	*Mean: $272.71 (320.07)*
						Median: $148.11(57.92 – 414.70)
Mudzengi, 2017[41]					*TB*	*Mean: $32.86*
					TB/HIV	*Mean: $19.43*
Muniyandi, 2020[42]	*Mean: $236.14 (380.35)*		Mean: $388.21 (727.18)		Mean: $624.35 (981.88)	
	Median: $91.52 (0 – 3042.65)		*Median: $60.44 (0 – 6274.95)*		Median: $206.89 (6372.98)	
Muttamba, 2020[43]					DS-TB	Mean: $159 (134.94 – 182.59)
					MDR-TB	*Mean: $1510 (1229.69 – 1750.64)*
					Total	*Mean: $208 (162.97 – 253.06)*
Nhung, 2018[44]					*DS-TB*	Mean: $4630 (4028.21 – 5231.84)
					MDR-TB	Mean: $18,898 (12,840.18 – 24,955.55)
					Total	*Mean: $5772 (4919.95 – 6625.36)*
Pedrazzoli, 2021[46]					*Uninsured*	*Mean: $272.3*
						Median: $132.8 (48.02 – 269.86)
					Insured	*Mean: $273.8*
						Median: $138.9 (49.23 – 327.91)
Pedrazzoli, 2021[45]			*DS-TB*	*Median: $130.6*		
			MDR-TB	*Median: $197.5*		
Prasanna, 2018[47]					Study Population	Median: $241.42 (64.24 – 607.74)

Study	Pre-diagnostic	Post-diagnostic	Overall costs		
			Those who incurred costs		*Median: $245.86 (68.55 – 625.99)*
Ramma, 2015[48]			Mean: $2233.17		
	Pre-diagnostic	***Post-diagnostic***	***Overall costs***		
Rupani, 2020[49]			*Private Provider*		*Median: $61 (35 – 156)*
			Government Provider		*Median: $7 (5-14)*
			Total		*Median: $8 (5-28)*
Shin, 2020[50]			Inpatient (Initial)		Mean (SD): $44.28 (46.84)
			Inpatient (Recurrent)		*Mean (SD):* $98.48 (123.13)
			Outpatient (HIV)		*Mean (SD):* $3.92 (6.89)
			Outpatient (TB)		Mean (SD): $2.82 (1.69)
Stracker, 2019[51]			TB+		Mean: $297.98
			Xpert-		*Mean: $22.86*
Timire, 2021[53]			Medical	DS-TB	Median: $84.09
				DR-TB	Median: $169
				Total	Median: $88.99
			Non-Medical	DS-TB	Median: $335.53
				DR-TB	Median: $1261.32
				Total	Median: $354.8
			Total	DS-TB	Median: $967.41
				DR-TB	Median: $2913.84
				Total	Median: $1018.03
Tomeny, 2020[54]			*DS-TB*		*Mean: $11.92*
			MDR-TB		*Mean: $87.47*
Trajman, 2016[55]				All	Patients Only
			Minimum Wage	Mean: $135.12	Mean: $118.11
			SES income per capita	Mean: $135.12	Mean: $119.10
			Income per activity	*Mean: $50.06*	*Mean: $122.36*
			Reported income	*Mean: $47.11*	*Mean: $134.47*
Ukwaja, 2013[(1) 56]	Mean: $308.50	Mean: $64.03	Patient		Median: $279.13
			Household		*Median: $313*
			Total		*Mean: $372.53*
Ukwaja, 2013[(2) 57]	*Mean:* $37.04	*Mean:* $21.17	Mean: $83.08		
Van der Hof, 2016[58]	*Ethiopia* | *Indonesia* | *Kazakhstan*	*Ethiopia* | *Indonesia* | *Kazakhstan*			
	DS-TB: *Median: $17.5* | *Median: $11.32* | *Median: $3.21*	*Intensive* *DS-TB*: *Median: $148.76* | *Median: $16.82* | *Median: $216.30*			

						MDR-TB	*Median: $1038.82*	*Median: $349.06*	*Median: $682.05*	
	MDR-TB	*Median: $93.76*	*Median: $14.88*	*NA*	*Continuation*	*DS-TB*	*Median: $160.01*	*Median: $26.53*	*Median: $113.68*	
						MDR-TB	*Median: $1163.83*	*Median: $396.94*	*Median: $428.33*	

	Pre-diagnostic	***Post-diagnostic***	***Overall costs***	
Viney, 2019[59]			*Medical (pre- and post-diagnosis)*	*Mean: $300.27*
			Non-medical (pre- and post-diagnosis)	*Mean: $1899.09*
			Total (Overall)	Mean: $3579.98
Walcott, 2020[60]	*Mean: $24.83*			
	Median: $12.41(4.81 – 24.83)			
Wang, 2020[61]			Mean: 10,935.88	
			Median: 10,302.17	
Yang, 2020[62]			RS-TB	Mean: 3713.87
				Median:2443.05
			RMR-TB	Mean: 13598.50
				Median: 6422.72
			MDR-TB	*Mean: 19153.80*
				Median:13,042.62

Abbreviations: TB – Tuberculosis, DS-TB – Drug sensitive TB, DR-TB – Drug resistant TB, MDR-TB – Multidrug resistant TB, RS-TB – Rifampicin sensitive TB, RMR-TB – Rifampicin mono-resistant TB, HIV – Human Immunodeficiency Virus, LTBI – Latent TB Infection, ACF – Active case finding, PCF – Passive case finding, SES – Socioeconomic status, SD – Standard deviation, IQR – Interquartile range

Breakdown of total patient costs:

Total Costs:

TB/HIV Coinfection: The median cost of care for patients with TB/HIV coinfection was reported in one study by Chittamany *et.,* who found that the median overall cost incurred by these individuals was $2,597.73 while the mean cost incurred by patients with TB/HIV co-infection ranged from $19.43 to $496.63.

Inpatient vs Outpatient: Two studies reported cost differences for inpatient versus outpatient care. Inpatient costs ranged from a mean of $44.28 to $105 per person with initial TB treatment incurring fewer costs than patients with reoccurring TB ($44.28 versus $98.48). Outpatient total costs ranged from $2.82 to $110. Like with the mean costs, median costs incurred by inpatients were found to be higher ranging from $44.28 to $98.48 while outpatient care ranged from $2.82 to $79.00.

Insured vs Uninsured: Pedrazzoli *et al*., was the only study in this review that examined cost differences between insured patients compared to uninsured and found there to be minimal differences between the two (Uninsured: $273.30 vs Insured: $273.80). Minimal differences were also seen with the median overall costs incurred by insured compared to uninsured individuals which were reported at $132.80 and $138.90, respectively.

ACF vs PCF: Mean total incurred costs by patients found using ACF methods were lower than PCF methods, with ACF ranging from $203.42 to $233.00 compared to $272.71 to $279.90 per person for PCF. Median costs incurred by patients identified through PCF methods ranged from $148.11 to $342.19 and were found to be higher than costs incurred by patients identified through ACF which ranged from $122.72 to $274.36.

Residents vs Migrants: Lu *et al*., examined cost differences between residents of the Songjiang district in Shanghai, China compared to individuals that migrated to the city for care. Their study found that residents incurred larger overall costs while receiving TB care compared to migrants at $6,889.00 vs. $3,686.00, respectively.

Total pre-diagnostic costs:

TB/HIV Coinfection in Patients with Active TB vs LTBI: De Siqueria Filha *et al*., reported differences in pre-diagnostic costs for patients with active TB/HIV co-infection ($204.83) against patients with LTBI/HIV ($13.41) and were the only study to report costs for patients with LTBI.

ACF vs PCF: Gurung *et al*., reported pre-diagnostic cost differences for patient identified using ACF methods versus PCF methods and found that patients identified using PCF incurred greater costs ranging from $58.20 to $187.00 per person than patients identified using ACF with costs ranging from $20.40 to $143.58. Median pre-diagnostic cost differences for patients identified with ACF ranging from $20.40 to $143.58 while PCF patient costs ranged from $58.20 to $187.00.

Residents vs Migrants*:* Lu *et al.,* reported that residents of Shanghai, China incurred greater mean pre-diagnostic costs for TB care then migrants at $2,682.10 and $1,309.42 respectively.

Public vs Private Health Care Centres*:* Differences in pre-diagnostic costs between public versus private health care centres in India were examined by Chandra *et al*., and found that patients who received care in private health centres incurred $115.90 in pre-diagnostic costs compared to public health centre patients who incurred $92.00.

Total post-diagnostic costs:

Intensive Phase vs Continuation Phase: TB treatment is divided into two stages – the intensive phase which is the first two months of treatment and the continuation phase which is the following months of treatment. Costs during the intensive phase were found to range from $21.84 to $66.43 while costs during the continuation phase of treatment ranged from $10.82 to $33.79. Median costs incurred by patients during the intensive and continuation phase of post-diagnostic care were reported by four studies. Costs incurred during the intensive phase were found to range between $16.82 in DS-TB patients from Indonesia to $1038.82 to MDR-TB patients from Ethiopia. Costs incurred by the continuation phase ranged from $4.40 in Egyptian patients during the last two months of care to $1,163.83 in MDR-TB patients from Ethiopia.

TB/HIV Coinfection in Patients with Active TB vs LTBI: Mean post-diagnostic costs for newly diagnosed patients with TB/HIV coinfection compared to newly diagnosed patients with LTBI/HIV were reported by De Siqueria *et al*. Costs were reported to be significantly higher in individuals with TB/HIV at a mean cost of $709.78 compared to individuals with LTBI/HIV who incurred a cost of $44.20.

ACF vs PCF: Gurung *et al*., compared post-diagnostic cost differences for patients identified using PCF compared to ACF and found that patients found using PCF methods incurred higher post-diagnostic costs at a mean of $74.70 while individuals identified using ACF methods incurred a cost of $65.90. Patients who were identified using PCF methods were reported to incur post-diagnostic costs ranging from a median of $51.20 to $112.54 with patients who were identified using ACF methods reporting lower post-diagnostic costs which ranged from $48.80 to $91.92.

Residents vs Migrants: Unlike with the overall and pre-diagnostic costs the study by Lu *et al*., found that for post-diagnostic costs migrants incurred significantly larger costs at a mean of $4,894.39 while residents incurred a mean post-diagnostic cost of $2,899.48

Table S3 – Breakdown of the direct medical costs incurred by patients during the pre-diagnostic stage of TB care.

Study		Total	Consultation	Medication	Diagnostic Imaging		Follow-up Tests		Hospitalization	Other
Assebe, 2020[18]					*Outpatient*	Mean (SD) - $2 (5)	*Outpatient*	Mean (SD) - $8 (13)		
						Median (IQR) - $1 (0-2)		Median (IQR) - $4 (0-12)		
					Inpatient	Mean (SD) - $11 (16)	*Inpatient*	Mean (SD) - $14 (16)		
						Median (IQR) - $7 (1-14)		Median (IQR) - $7 (3-18)		
					Total	Mean (SD) - $3 (7)	*Total*	Mean (SD) - $9 (15)		
						Median (IQR) - $1 (0-2)		Median (IQR) - $5 (0-13)		
Aung, 2021[19]	*MDR-TB*	Median: $19.31								
	DS-TB	Median: $11.01								
	Total	Median: $11.01								
Chandra, 2021 (1)[21]		Median (IQR): $23.3 (7.9-50.7)								

Chandra, 2021 [(2) 22]		Median (IQR): $24 (8.1-57*)*		Median (IQR): $0.43 (0-5.6)		Median (IQR): $2.8 (0 - 12)				Median (IQR): $ 5.6 (0-19)		Median (IQR): $ 0 (0)		
		Mean (SD): $65 (153)		Mean (SD): $3.4 (5)		Mean (SD): $11 (22)				Mean (SD): $16 (28)		Mean (SD): $28 (126)		
Chittamany, 2020[23]	*DS-TB*	*Median: $63.63*	*DS-TB*	Median: $60.45							*DS-TB*	*Median : $6.36*		
	DR-TB	*Median: $112.94*	*DR-TB*	Median: $112.94							*DR-TB*	*Median : $9.54*		
	Total	*Median: $63.63*	*Total*	Median: $60.45							*Total*	*Median : $6.36*		
De Siqueira Filha, 2018[25]	*TB/HIV*	Mean: $26.94	*TB/HIV*	Mean: $14.94	*TB/HIV*	*Mean: $5.65*			*TB/HIV*	*Mean: $6.35*				
	LTBI/HIV	*Mean: $3.7*	*LTBI/HIV*	Mean: $1.30	*LTBI/HIV*	*Mean: $0.03*			*LTBI/HIV*	Mean: $2.43				
Ellaban, 2021[26]		*Median (IQR): $15.6 (6.3-26.3)*												
Gurung, 2019[33]	*ACF*	*Median: $15.52*	ACF	Median: $0	*ACF*	*Median: $6.40*	*ACF*	*Median: $0.54*	*ACF*	Median: $1.19			*Medical Supplies* *ACF*	*Median: $0*

	PCF	Median: $34.30	PCF	Median: $0.22	PCF	Median: $19.86	PCF	Median: $3.47	PCF	Median: $2.93			PCF	Median: $3.58
	Total	Median: 20.84	Total	Median: $0	Total	Median: $8.79	Total	Median: $1.74	Total	Median: $1.95			Total	Median: $2.9
Gurung, 2021[32]	ACF	Mean (95% CI): $41.1 (28.7–53.6)												
		Median (IQR): $12.3 (0–55.8)												
	PCF	Mean (95% CI): $53.1(41.6–64.6)												
		Median (IQR): $29.6 (10.2–79.2)												
	Total	Mean (95% CI): $47.2 (38.8–55.7)												
		Median (IQR): $21.7 (3.5–70.3)												
Lu, 2020[35]	Residents	Mean: $919.70			Residents	Mean: $5,213.79	Residents	Mean: $731.45				Medical Supplies	Residents	Mean: $422.68
	Migrants	Mean: $1,908.65			Migrants	Mean: $417.88	Migrants	Mean: $425.38					Migrants	Mean: $79.44
Mauch, 2013[(1) 36]			Ghana	Mean: $0.44	Ghana	Mean: $1.76	Ghana	Mean:0.44	Ghana	Mean: $0.15				
				Median: $0.00		Median: $0.59		Median (IQR): $0 (0 – 0.44)		Median (IQR): $0 (0 – 0)				
			Vietnam	Mean: $1.80	Vietnam	Mean: $5.84	Vietnam	Mean: $2.47	Vietnam	Mean: $10.55				
				Median: $0.45		Median: $2.70		Median (IQR): $0.67 (0.40 – 1.32)		Median (IQR): $2.02 (0.92 – 10.57)				
			Dominican Republic	Mean: $2.81	Dominican Republic	Mean: $0.40	Dominican Republic	Mean: $3.42	Dominican Republic	Mean: $1.21				
				Median: $0.00		Median: $0.00		Median (IQR): $0 (0 – 1.11)		Median (IQR): $0 (0 - 0.08)				

Mauch, 2013 [(2) 38]		New	Median: $7.48	New	*Median: $14. 97*						
		Retreatment	Median: $1.00	Retreatment	*Median: $31.29*						
		MDR-TB	Median: $20.02	MDR-TB	*Median: $9.38*						
Mauch, 2011 [37]						*Pulmonary TB*	*Median: $2.92*				
						Extrapulmonary TB	*Median: $4.93*				
McAllister, 2020 [39]		*CHC*	*Median (IQR): $3.39 (1.52 – 6.89)*	*CHC*	*Median (IQR): $ 5.56 (*	*CHC*	*Median (IQR): $ 5.18*	*CHC*	*Median (IQR): $ 5.07*	*CHC*	*Median (IQR): $25.33*
		Public Hospital	*Median (IQR): $5.44 (2.53 – 8.11)*	*Public Hospital*	*Median (IQR): $5.86*	*Public Hospital*	*Median (IQR): $4.56*	*Public Hospital*	*Median (IQR): $3.80*	*Public Hospital*	*Median (IQR): $40.53*
		Private Hospital	*Median (IQR): $5.83 (1.52 – 11.65)*	*Private Hospital*	*Median (IQR): $7.08*	*Private Hospital*	*Median (IQR): $7.85*	*Private Hospital*	*Median (IQR): $9.13*	*Private Hospital*	*Median (IQR): $43.07*

			Private Practice	*Median (IQR): $5.07 (2.03 – 10.13)*	*Private Practice*	*Median (IQR): $7.67*	*Private Practice*	*Median (IQR): $6.51*	*Private Practice*	*Median (IQR): $ 6.40*	*Private Practice*	*Median (IQR): $48.64*	
Morishita, 2016[40]			*ACF*	Mean (SD): $0.82 Median (IQR): $0 (0 – 0.10)	*ACF*	Mean (SD): $3.88 Median (IQR): $0.00	*ACF*	Mean (SD): $0.31 Median (IQR): $ 0.00	*ACF*	Mean (SD): $ 0.36 Median (IQR): $ 0.00	*ACF*	Mean (SD): $0.05 Median (IQR): $0.00	
			PCF	Mean (SD): $0.05 Median (IQR): $0 (0-0)	*PCF*	Mean (SD): $18.66 *Median (IQR): $3.16*	*PCF*	Mean (SD): $1.07 Median (IQR): $0.00	*PCF*	Mean (SD): $ 1.17 Median (IQR): $ 0.00	*PCF*	Mean (SD): $1.89 Median (IQR): $0.00	
Muttamba, 2020[43]	DS-TB	Mean (95% CI): $ 3.42											
	MDR-TB	Mean (95% CI): $ 1.65											
	Total	Mean (95% CI): $ 3.40											
Nhung, 2018[44]	*DS-TB*	Mean (95% CI): $ 175.71											
	MDR-TB	Mean (95% CI): $ 680.89											

	Total	Mean (95% CI): $ 276.75							
Pedrazzoli, 2018[45]	*DS-TB*	*Median (IQR): $* 8.11							
	MDR-TB	*Median (IQR): $* 8.42							
	Total	*Median (IQR): $* 8.11							
Pedrazzoli, 2021[46]	*Insured*	*Mean: $* 13.68							
		Median (IQR): $ 8.21							
	Uninsured	*Mean: $* 8.81							
		Median (IQR): $ 8.21							
Ramma, 2015[48]			*Inpatient*	*Mean (SD): $0.66 (3.78)*					
				Median: $0					
			Outpatient	*Mean (SD): $* 0.52 (2.08)					
				Median: $0					
Timire, 2021[53]	DS-TB	Median (IQR): $20.41							

	DR-TB	Median (IQR): $10.61							
	Total	Median (IQR): $20.41							
Ukwaja, 2013 (1) [56]				*Non-TB Medication*	*Mean (SD):* $13.23	*Mean (SD):* $4.76	*Mean (SD):* $5.82		
Viney, 2019[59]		Mean (SD): $7.17							
Walcott, 2020[60]		Mean (SD): $13.61		*Non-TB Medication*	Mean (SD): $11.21	Mean (SD): $2.40			
		Median (IQR): $7.61			Median (IQR): $4.40	*Median (IQR):* $1.20			

Abbreviations: TB – Tuberculosis, DS-TB – Drug sensitive TB, MDR-TB – Multi-drug resistant TB, DR-TB – Drug resistant TB, RS-TB – Rifampicin sensitive TB, RMR-TB – Rifampicin mono-resistant TB, HIV – Human Immunodeficiency Virus, LTBI – Latent TB Infection, CHC – Community health centre, ACF – Active case finding, PCF – Passive case finding, SD – Standard deviation, IQR – Interquartile range, CI – Confidence Interval

Table S4 – Breakdown of the direct non-medical costs incurred by patients during the pre-diagnostic phase of TB care

	Total		*Transportation*		*Accommodation*		*Food*		*Nutritional Supplements*	*Other*
Chandra, 2021 [(1)] [21]	*Median (IQR): $3.2 (1.1 - 10.7)*									
Chandra, 2021 [(2)] [22]	Median (IQR): $3.2 (1.1 - 10.7)		Median (IQR): $3.1 (1.1 - 8.2)		Median (IQR): $0 (0)		*Food during travel*	Median (IQR): $0 (0-0.71)	Median (IQR): $0 (0-0)	
								Mean (SD): $1.1 (2.8)		
	Mean (SD): $16 (70.5)		Mean (SD): $7 (8.9)		Mean (SD): $7 (69)		*Special diet*	Median (IQR): $0 (0)	Mean (SD): $0 (0)	
								Mean (SD): $0.74 (3.9)		
Chittamany, 2020 [23]	*DS-TB*	*Median: $17.50*	*DS-TB*	*Median: $6.36*	*DS-TB*	*Median: $0*	*DS-TB*	Median: $1.59		
	DR-TB	*Median: $63.63*	*DR-TB*	*Median: $ 11.14*	*DR-TB*	*Median: $0*	*DR-TB*	Median: $12.73		
	Total	*Median: $17.50*	*Total*	*Median: $6.36*	*Total*	*Median: $0*	*Total*	Median: $1.59		
De Siqueria Filha, 2018 [25]			*TB/HIV*	*Mean - $12.90*			*TB/HIV*	*Mean - $6.07*		
			LTBI/HIV	*Mean - $2.98*			*LTBI/HIV*	Mean - $10.47		
Ellaban, 2021 [26]			Median (IQR): $5.6 (1.3-12.5)				Median (IQR): $0.0 (0.0-3.8)			
Gurung, 2019 [33]	ACF	Median: $3.69	ACF	Median: $3.58			ACF	NA		
	PCF	Median: $10.53	PCF	Median: $5.86			PCF	Median: $0		
	Total	Median: $5.86	Total	Median: $4.02			Total	Median: $0		
Gurung, 2021 [32]	*ACF*	Mean (95% CI): $6.8 (3.7–9.9)								
		Median (IQR): $1.4 (0–5.8)								
	PCF	Mean (95% CI): $18.4 (11.9–24.8)								
		Median (IQR): $5.3								

		(1.8–14.1)									
	Total	Mean (95% CI): $12.7 (9.0–16.4)									
		Median (IQR): $3.0 (0.4–10.8)									
Lu, 2020[35]	*Residents*	*Mean: $167.78*								*Residents*	*Mean: $139.09*
	Migrants	*Mean: $79.44*								*Migrants*	*Mean: $64.75*
Mauch, 2013[(1) 36]			*Ghana*	*Mean: $0.59*	*Ghana*	*Mean: $0.29*	*Ghana*	*Mean: $0.88*			
				Median (IQR): $0.15 (0 – 0.59)		*Median (IQR): $0 (0-0)*		*Median (IQR): $0.15 (0 – 0.59)*			
			Vietnam	*Mean: $1.35*	*Vietnam*	*Mean: $7.18*	*Vietnam*	*Mean: $6.06*			
				Median (IQR): $0.45 (0.27 – 0.79)		*Median (IQR): $6.51 (1.98 – 13.20)*		*Median (IQR): $0.67 (0.27 – 6.60)*			
			Dominican Republic	*Mean: $0.40*	*Dominican Republic*	*Mean: $0*	*Dominican Republic*	*Mean: $0.40*			
				Median (IQR): $ 0.16 (0.12 – 0.56)		*Median (IQR): $0 (0-0)*		*Median (IQR): $0.12 (0 – 0.28)*			
Mauch, 2013[(2) 38]			New	Median: $1.53	New	Median: $0	New	Median: $1.53			
			Retreatment	Median: $1.26	Retreatment	Median: $0	Retreatment	Median: $1.26			
			MDR-TB	Median: $1.26	MDR-TB	Median: $0	MDR-TB	Median: $0.90			
McAllister, 2020[39]			*CHC*	*Median (IQR): $3.55*			*CHC*	*Median (IQR): $1.26*			
			Public Hospital	*Median (IQR): $6.41*			*Public Hospital*	*Median (IQR): $2.02*			
			Private Hospital	*Median (IQR): $4.12*			*Private Hospital*	*Median (IQR): $2.03*			

			Private Practice	*Median (IQR): $5.19*			*Private Practice*	*Median (IQR): $1.01*			
Morishita, 2016[40]			*ACF*	Mean (SD): $ 0.97			*ACF*	Mean (SD): $ 0.20			
				Median (IQR): $ 0.61				Median (IQR): $ 0.00			
			PCF	Mean (SD): $ 3.68			*PCF*	Mean (SD): $ 1.07			
				Median (IQR): $ 0.92				Median (IQR): $ 0.00			
Muttamba, 2020[43]			DS-TB	Mean (95% CI): $ 0.84	DS-TB	Mean (95% CI): $ 0.14	DS-TB	Mean (95% CI): $ 0.44	DS-TB	Mean (95% CI): $ 75.68	
			MDR-TB	Mean (95% CI): $ 2.59	MDR-TB	Mean (95% CI): $ 0.00	MDR-TB	Mean (95% CI): $ 0.28	MDR-TB	Mean (95% CI): $ 505.73	
			Total	Mean (95% CI): $ 0.86	Total	Mean (95% CI): $ 0.14	Total	Mean (95% CI): $ 0.44	Total	Mean (95% CI): $ 90.09	
Nhung, 2018[44]	*DS-TB*	Mean (95% CI): $ 175.71									
	MDR-TB	Mean (95% CI): $ 724.81									
	Total	Mean (95% CI): $219.64									
Pedrazzoli, 2018[45]	*DS-TB*	*Median (IQR): $* 0.88									
	MDR-TB	*Median (IQR): $* 0.88									
	Total	*Median (IQR): $*									

		0.88										
Ramma, 2015[48]			*Inpatient*	*Mean (SD): $2.50*				*Inpatient*	Mean (SD): $5.95		*Inpatient*	Mean (SD): $ 3.21
				Median: $0					Median (IQR): $ 0.71			Median (IQR): $0
			Outpatient	*Mean (SD): $1.70*				*Outpatient*	Mean (SD): $ 23.25		*Outpatient*	Mean (SD): $ 0.99
				Median (IQR): $0					Median (IQR): 19.85			Median: $0
Stracker, 2019[51]			*TB+*	*Mean:* $45.72							*TB+*	*Mean: $33.47*
			Xpert-	*Mean:* $2.45							*Xpert -*	*Mean: $11.43*
Timire, 2021[53]			*DS-TB*	Median (IQR): $4.08		*DS-TB*	Median (IQR): $ 14.69	*DS-TB*	Median (IQR): $1.63			
			DR-TB	Median (IQR): $4.08		*DR-TB*	Median (IQR): $ 7.35	*DR-TB*	Median (IQR): $0			
			Total	Median (IQR): $4.08		*Total*	Median (IQR): $ 14.69	*Total*	Median (IQR): $0			
Ukwaja, 2013 (1)[56]			Mean (SD): $7.94		Mean (SD): $0.00	Mean (SD): $2.12				*Card/User Fees*	Mean (SD): $3.17	
Viney, 2019[59]	*Mean (SD):* $9.32											
Walcott, 2020[60]	Mean (SD): $3.60		Mean (SD): $2.00			Mean (SD): $1.20				Phone Call	Mean (SD): $0.10	
											Median (IQR): $0	
	Mean (SD): $3.60		Median (IQR): $0.80			Median (IQR): $0				Caregiver	Mean (SD): $0.40	
											Median (IQR): $0	

Abbreviations: TB – Tuberculosis, DS-TB – Drug sensitive TB, MDR-TB – Multi-drug resistant TB, DR-TB – Drug resistant TB, RS-TB – Rifampicin sensitive TB, RMR-TB – Rifampicin mono-resistant TB, HIV – Human Immunodeficiency Virus, LTBI – Latent TB Infection, CHC – Community health centre, ACF – Active case finding, PCF – Passive case finding, SD – Standard deviation, IQR – Interquartile range, CI – Confidence Interval

Table S5 – Breakdown of the indirect costs incurred by patients during the pre-diagnostic phase of TB care

	Total	*Loss of Income*		*Time/Productivity Loss*	*Caregiver/Guardian Costs*	*Other*
Assebe, 2020[18]		*Outpatient*	Mean (SD) - $11 (28)			
			Median (IQR) - $0 (0-5)			
		Inpatient	Mean (SD) - $0 (0)			

					Median (IQR) - $0 (0)					
			Total		Mean (SD) - $11 (26)					
					Median (IQR) - $0 (0-3)					
Chandra, 2021 (1) [21]	Public	Median (IQR): $38.5(16.8-140.3)								
	Private	Median (IQR): $70.1(16.6-192.4)								
	Total	Median (IQR): $43.6 (16.8-150.8)								
Chandra, 2021 (2) [22]	Median (IQR): $0 (0-15)								Administrative Burden	Median (IQR): $0 (0)
	Mean (SD): $ 32 (76)									Mean (SD): $0 (0)
Collins, 2018[24]	MDR-TB	Median: $0								
De Siqueria Filha, 2018[25]	TB/HIV	Mean - $158.50	TB/HIV		Mean - $116.44	TB/HIV	Mean - $42.06			
	LTBI/HIV	Mean - $2.91	LTBI/HIV		Mean - $0	LTBI/HIV	Mean - $2.91			
Ellaban, 2021[26]	Median (IQR): $0.0 (0.0-75.0)									
Fuady, 2018[29]	TB	Median: $0.34	TB	Patient	Median: $0					
	MDR-TB	Median: $1.38		Guardian	Median: $0					
	TB	Median: $0.34	MDR-TB	Patient	Median: $0					
				Guardian	Median: $0					
Fuady, 2020[27]	Mean: $2.06									
Getahun, 2016[30]	Mean: $16.67									
	Median: $13.19									
Gurung, 2019[33]	ACF	Median: $68.92	ACF		Median: $55.78	ACF	Median: $4.78			
	PCF	Median: $50.00	PCF		Median: $33.32	PCF	Median: $14.54			
	Total	Median: $55.46	Total		Median: $44.06	Total	Median: $8.47			
Gurung, 2021[32]	ACF	Mean (95% CI) - $7.5 (5.6–9.5)								
		Median (IQR) -								

		$4.3 (1.9–8.7)							
	PCF	*Mean (95% CI) - $15.3 (11.9–18.6)*							
		Median (IQR) - $10.0 (5.6–18.0)							
	Total	*Mean (95% CI) - $11.5 (9.4–13.5)*							
		Median (IQR) - $6.7 (3.3–13.6)							
Lu, 2020[35]			*Residents*		*Mean: $610.64*		*Residents*	*Mean: $23.68*	
			Migrants		*Mean: $310.27*		*Migrants*	*Mean: $14.69*	
Mauch, 2013[(1) 36]	*Ghana*	*Mean; $55.78*	*Ghana*		*Mean; $55.78*				
		Median (IQR): $24.89 (6.30 – 49.78)			*Median (IQR): $24.89 (6.30 – 49.78)*				
	Vietnam	*Mean: $186.30*	*Vietnam*		*Mean: $186.30*				
		Median (IQR): $161.84 (107.29 – 230.97)			Median (IQR): $161.84 (107.29 – 230.97)				
	Dominican Republic	*Mean: $211.12*	*Dominican Republic*		*Mean: $211.12*				
		Median (IQR): $133.78 (55.24 – 238.24)			*Median (IQR): $133.78 (55.24 – 238.24)*				
Mauch, 2013 [(2) 38]	New	*Median: $654.98*	New		*Median: $654.98*				
	Retreatment	*Median: $199.18*	Retreatment		*Median: $199.18*				
	MDR-TB	*Median: $2836.59*	MDR-TB		*Median: $2836.59*				
Mauch, 2011[37]	*Median: $69.16*								
Morishita, 2016[40]	*ACF*	Mean (SD): $ 9.48	*Sick Leave*	*ACF*	Mean (SD): $ 8.67		*ACF*	Mean (SD): $ 0.56	

					Median (IQR): $ 0.00				
		Median (IQR): $ 0.00		*PCF*	Mean (SD): $ 19.63			Median (IQR): $ 0.20	
					Median (IQR): $ 0.00				
	PCF	Mean (SD): $ 30.13	*Care Seeking*	*ACF*	Mean (SD): $ 0.82		*PCF*	Mean (SD): $3.26	
					Median (IQR): $ 0.00				
		Median (IQR): $ 0.71		*PCF*	Mean (SD): $ 10.50			Median (IQR): $ 0.56	
					Median (IQR): $ 0.00				
Muniyandi, 2020[42]	*Mean (SD): $153.61 (304.00)*								
	Median (IQR): $0.00 (0.00 – 1709.74)								
Muttamba, 2020[43]			DS-TB	Mean (95% CI): $ 0.68					
			MDR-TB	Mean (95% CI): $ 0.61					
			Total	Mean (95% CI): $ 0.68					
Pedrazzoli, 2021[46]	*Insured*	*Mean: $* 1.43							
		Median (IQR): $ 0.49							
	Uninsured	*Mean: $* 3.34							
		Median (IQR): $ 0.67							
Ramma, 2015[48]	*Inpatient*	Mean (SD): $ 114.79	*Seeking Care*	*Inpatient*	*Mean (SD): $* 5.15		*Inpatient Outpatient*	*Mean (SD): $* 3.17 *Median (IQR): $* 0.99	
					Median (IQR): $ 0.43				
				Outpatient	*Mean (SD): $* 3.92			*Mean (SD): $* 13.33	

						Median (IQR): $ 1.37				Median (IQR): $ 0.00	
	Outpatient		Mean (SD): $ 29.87	Hospitalization	Inpatient	Mean (SD): $ 106.42			Inpatient Outpatient	Mean (SD): $ 3.17	
						Median (IQR): $ 70.41				Median (IQR): $ 0.99	
					Outpatient	Mean (SD): $ 12.62				Mean (SD): $ 13.33	
						Median (IQR): $ 3.17					
Ukwaja, 2013 (1)[56]	Mean (SD): $271.46			Mean (SD): $270.40			Value of time	Mean (SD): $1.06			
Van der Hof, 2016[58]	Ethiopia	DS-TB	Median (IQR): $0.00								
		MDR-TB	Median (IQR): $0.00								
	Indonesia	DS-TB	Median (IQR): $1.29								
		MDR-TB	Median (IQR): $0.97								
	Kazakhstan	DS-TB	Median (IQR): $1.07								
		MDR-TB	-								
Walcott, 2020[60]							Patients (n=49)	Mean (SD): $15.62			
								Median (IQR): $6.81			
							All	Mean (SD): $7.61			
								Median (IQR): $0			

Abbreviations: TB – Tuberculosis, DS-TB – Drug sensitive TB, MDR-TB – Multi-drug resistant TB, DR-TB – Drug resistant TB, RS-TB – Rifampicin sensitive TB, RMR-TB – Rifampicin mono-resistant TB, HIV – Human Immunodeficiency Virus, LTBI – Latent TB Infection, ACF – Active case finding, PCF – Passive case finding, SD – Standard deviation, IQR – Interquartile range, CI – Confidence Interval

Table S6 – Breakdown of the direct medical costs incurred by patients during the post-diagnostic phase of TB care

		Total	Consultation		Medication	Diagnostic Imaging		Follow-up Tests		Hospitalization			Other
Aung, 2021[19]	MDR-TB	Median (min-max): $199.19											
	DS-TB	Median (min-max): $72.89											
	Total	Median (min-max): $72.89											
Chandra, 2021 [(2)] [22]		Median (IQR): $0			Median (IQR): $0	Median (IQR): $0		Median (IQR): $0		Median (IQR): $0			
		Mean (SD): $1.70 (10.60)			Mean (SD): $1.20 (10.40)	Mean (SD): $0 (0)		Mean (SD): $0.50 (2.30)		Mean (SD): $0 (0)			
Chittamany, 2020 [23]	DS-TB	Median (IQR): $42.95		DS-TB	Median (IQR): $0 (0 – 49.31)		DS-TB	Median (IQR): $0 (0 – 4.77)	DS-TB	Median (IQR): $20.68 (20.68 – 47.72)	DOT	DS-TB	Median (IQR): $0 (0-0)
	DR-TB	Median (IQR): $334.06		DR-TB	Median (IQR): $209.00 (109.79 – 3102.01)		DR-TB	Median (IQR): $0 (0 – 3.18)	MDR-TB	Median (IQR): $330.88	DOT	DR-TB	Median (IQR): $0 (0-0)

	Total	*Median (IQR): $46.13*			*Total*	*Median (IQR): $0 (0 – 49.31)*		*Total*	*Median (IQR): $0 (0 – 4.77)*	*Total*	*Median (IQR): $20.68 (20.68 – 47.72)*	*Total*	*Median (IQR): $0 (0-0)*
Collins, 2018[24]*								*Addis Ababa (MDR)*	*Median (IQM): $228.73*	*Addis Ababa (MDR)*	*Median (IQM): $1.25*		
								Gonder (MDR)	*Median (IQM): $146.23*	*Gonder (MDR)*	*Median (IQM): $11.25*		
De Siqeruia Filha, 2018[25]	*TB/HIV*	*Mean: $32.80*	*TB/HIV*	*Mean: $24.90*	*TB/HIV*	*Mean: $6.48*		*TB/HIV*	*Mean: $1.42*				
	LTBI/HIV	*Mean: $22.05*	*LTBI/HIV*	*Mean: $0.17*	*LTBI/HIV*	*Mean: $9.57*		*LTBI/HIV*	*Mean: $12.31*				
Ellaban, 2021[26]	*First two months of treatment*	*Median (IQR): $0.00 (0.00 – 0.00)*											
	Second two months of treatment	*Median (IQR): $0.00 (0.00 – 0.00)*											

	Third two months of treatment	*Median (IQR): $0.00 (0.00 – 0.00)*															
Fuady, 2018[29]	*DS-TB*	*Median (IQR): $0.00*	*DS-TB*	*Median (IQR): $0.00*					*DS-TB*		*Median (IQR): $0.00 (0-0)*	*DS-TB*		*Median (IQR): $0.00 (0-0)*	*Adverse events*	*DS-TB*	*Median (IQR): $0.00 (0-0)*
	MDR-TB	*Median (IQR): $5.16*	*MDR-TB*	*Median (IQR): $0.00 (0-0)*					*MDR-TB*		*Median (IQR): $0.00 (0.00)*	*MDR-TB*		*Median (IQR): $2.75*		*MDR-TB*	*Median (IQR): $0.00 (0-0)*
Getahun, 2016[30]				*Mean (SD): $27.28*					*Unscheduled Additional Follow-up*		*Mean (SD): $9.73*			*Mean (SD): $76.94*			
				Median (R): $26.76							*Median (R): $6.64*			*Median (R): $51.56*			
Gospodarevskaya, 2014† 31					*Tanzania*	*First two months of treatment*	*Mean: $3.28*		*Tanzania*	*First two months of treatment*	-	*Tanzania*	*First two months of treatment*	*Mean: $5.28*			
						Most recent two months of	*Mean: $1.90*			*Most recent two months of*	*Mean: $0.29*		*Most recent two months of*	*Mean: $0.00*			
						Total treatment	*Mean: $7.07*			*Total treatment*	*Mean: $0.58*		*Total treatment*	*Mean: $5.28*			

				Bangladesh	First two months of	Mean: $3.06		Bangladesh	First two months of	-	Bangladesh	First two months of	Mean: $18.88	
					Most recent two months of	Mean: $2.16			Most recent two months of	Mean: $2.40		Most recent two months of	Mean: $0.00	
					Total treatment	Mean: $7.37			Total treatment	Mean: $4.80		Total treatment	Mean: $18.88	
Gurung, 2019[33]	ACF	-		ACF		-								
	PCF	Median (IQR): $0.00		PCF		Median (IQR): $0.00								
	Total	-		Total		-								
Gurung, 2021[32]	ACF	Mean (95% CI): $19.50 (13.50 – 25.50)												
		Median (IQR): $10.80 (6.30 – 20.70)												

	PCF	*Mean (95% CI): $21.10 (14.90 – 27.40)*												
		Median (IQR): $ 12.20 (7.20 – 21.20)												
	Total	*Mean 95% CI): $20.30 (16.00 – 24.60)*												
		Median (IQR): $11.80 (6.60 – 20.70)												
Kirubi, 2021[34]	*Median (IQR): $10.86*													
Lu, 2020[35]	*Residents*	*Mean: $3,321.78*		*Residents*	*Mean: $2,185.94*	*Residents*	*Mean: $867.54*					*Medical Supplies*	*Residents*	*Mean: $268.30*
	Migrants	*Mean: $1,938.93*		*Migrants*	*Mean: $1,321.70*	*Migrants*	*Mean: $540.79*						*Migrants*	*Mean: $36.90*
Mauch, 2013[(1) 36]				*Ghana*	*Mean: $7.29*			*Ghana*	*Mean: $0.15*	*Ghana*	*Mean: $6.15*	*DOTS*	*Ghana*	*Mean: $3.95*
					Median (IQR): $0.29				*Median (IQR): $0.00*		*Median (IQR): $2.34*			*Median (IQR): $0.00*
				Vietnam	*Mean: $0.74*			*Vietnam*	*Mean: $1.12*	*Vietnam*	*Mean: $26.49*		*Vietnam*	*Mean: $4.04*
					Median (IQR): $0.13				*Median (IQR): $0.67*		*Median (IQR): $9.88*			*Median (IQR): $1.80*
				Dom inica	*Mean: $3.52*			*Dom inica n Rep*	*Mean: $3.62*	*Dom inica n Rep ublic*	*Mean: $18.88*		*Dom inica*	*Mean: $1.00*

					Median (IQR): $0.80				*Median (IQR): $1.61*		*Median (IQR): $0.00*			*Median (IQR): $0.80*
Mauch, 2013[(2) 38]				*New*	*Median: $5.59*			*New*	*Median: $14.97*	*New*	*Median: $55.00*	*DOTS*	*New*	*Median: $20.92*
				Retreatment	*Median: $11.27*			*Retreatment*	*Median: $29.48*	*Retreatment*	*Median: $13.34*		*Retreatment*	*Median: $25.79*
				MDR	*Median: $12.53*			*MDR*	*Median: $9.38*	*MDR*	*Median: $50.04*		*MDR*	*Median: $52.48*
Mauch, 2011[37]												*DOTS*		*Median: $0.00*
McAllister, 2020[39]		*CHC*	*Median (IQR): $1.83*	*CHC*	-	*CHC*	*Median (IQR): $13.85*	*CHC*	*Median (IQR): $4.05*	*CHC*	*Median (IQR): $32.94*			
		Public Hospital	*Median (IQR): $7.60*	*Public Hospital*	*Median (IQR): $4.61*	*Public Hospital*	*Median (IQR): $8.61*	*Public Hospital*	*Median (IQR): $5.83*	*Public Hospital*	*Median (IQR): $50.66*			
		Private Hospital	*Median (IQR): $9.12*	*Private Hospital*	*Median (IQR): $15.20*	*Private Hospital*	*Median (IQR): $5.83*	*Private Hospital*	*Median (IQR): $6.70*	*Private Hospital*	*Median (IQR): $278.66*			

				Private Practice	*Median (IQR): $17.10*	*Private Practice*	*Median (IQR): $48.14*	*Private Practice*	*Median (IQR): $10.13*	*Private Practice*	*Median (IQR): $14.19*	*Private Practice*	-	
Morishita, 2016[40]												*ACF*	*Mean (SD): $0.00*	
												ACF	*Median (IQR): $0.00*	
												PCF	*Mean (SD): $1.38*	
												PCF	*Median (IQR): $0.00*	
Mudzengi, 2017[41]	*Study Clinic*	*TB/HIV*	*Mean (SD): $0.00 (0.00)*											
	Study Clinic	*TB*	*Mean (SD): $0.00 (0.00)*											
	Study Clinic	*HIV*	*Mean (SD): $0.00 (0.00)*											
	Other Facilities	*TB/HIV*	*Mean (SD): $* 0.82											

		TB	*Mean (SD): $0.03*							
		HIV	*Mean (SD): $0.42*							
Muniyandi, 2020[42]							*Mean (SD): $0.06 (0.50)*	*Hospitalization*	*Mean (SD): $34.90 (146.53)*	
									Median (IQR): $0.00 (0.00 – 1824.35)	
							Median (Range): $0.00 (0.00 – 7.22)	*Escort*	*Mean (SD): $3.81 (15.36)*	
									Median (IQR): $0.00 (0.00 – 140.33)	
								Visitors	*Mean (SD): $0.56 (3.89)*	
									Median (IQR): $0.00 (0.00 – 60.14)	

Muttamba, 2020[43]	*MDR-TB*	*Mean (95% CI): $31.51 (5.01 – 58.06)*							
	DS-TB	*Mean (95% CI): $6.49 (3.68 – 9.29)*							
	Total	*Mean (95% CI): $7.41 (4.48 – 10.37)*							
Nhung, 2018[44]	*MDR-TB*	*Mean (95% CI): $2,793.83*							
	DS-TB	*Mean (95% CI): $412.92*							
	Total	*Mean (95% CI): $601.81*							
Pedrazzoli, 2018[45]	*MDR-TB*	*Median (IQR): $12.37*							
	DS-TB	*Median (IQR); $22.49*							

	Total	Median (IQR): $21.27										
Pedrazzoli, 2021[46]	Uninsured	Mean (SD): $40.42										
		Median (IQR): $25.22										
	Insured	Mean (SD): $43.15										
		Median (IQR): $25.22										
Prasanna, 2018[47]			Study population	Median (IQR): $0.00	Study population	Median (IQR): $0.00	Study population	Median (IQR): $0.00		Study population	Median (IQR): $0.00	
			Those who incurred costs	Median (IQR): $3.70	Those who incurred costs	Median (IQR): $12.82	Those who incurred costs	Median (IQR): $13.81		Those who incurred costs	Median (IQR): $61.53	
Ramma, 2015[48]			Inpatient	Mean (SD): $0.66								
				Median (IQR): $0.00								
			Outpatient	Mean (SD): $0.52								
				Median (IQR): $0.00								
			Inte	Mean (SD): $0.80								

				Median (IQR): $0.00											
			Continuation Phase	Mean (SD): $0.66											
				Median (IQR): $0.00											
Rupani, 2020[*49]	*Private Provider*	*Median (IQR): $30.00 (10-76)*	*Private Provider*	*Median (IQR) $3.00 (0 – 7)*	*Private Provider*	*Median (IQR): $14.00 (5-55)*	*Private Provider*	*Median (IQR): $4.00 (0-7)*	*Private Provider*	*Median (IQR): $4.00 (0-7)*	*Private Provider*	*Median (IQR) : $0 (0-0)*	*Prescribed Nutrition*	*Private Provider*	*Median (IQR): $0.00 (0-0)*
	Public Provider	*Median (IQR): $0.00 (0-0)*	*Public Provider*	*Median (IQR): $0.00 (0 – 0)*	*Public Provider*	*Median (IQR): $0.00 (0-0)*	*Public Provider*	*Median (IQR): $0.00 (0-0)*	*Public Provider*	*Median (IQR); $0.00 (0-0)*	*Public Provider*	*Median (IQR) : $0.00 (0-0)*		*Public Provider*	*Median (IQR): $0.00 (0-0)*
	Total	*Median (IQR): $0.00 (0-0)*	*Total*	*Median (IQR): $0.00 (0-0)*	*Total*	*Median (IQR): $0.00 (0-0)*	*Total*	*Median (IQR): $0.00 (0-0)*	*Total*	*Median (IQR): $0.00 (0-0)*	*Total*	*Median (IQR) : $0.00 (0-0)*		*Total*	*Median (IQR): $0.00 (0-0)*
Shin, 2020[50]			*Inpatient (Initial)*	*Mean (SD):* $0.07	*Inpatient (Initial)*	*Mean (SD): $0.00*									
			Inpatient (Recurrent)	*Mean (SD):* $0.27	*Inpatient (Recurrent)*	*Mean (SD):* $1.13									
			Outpatient (HIV)	*Mean (SD):* $0.90	*Outpatient (HIV)*	*Mean (SD):* $0.31									

			Outpatient (TB)	-	*Outpatient (TB)*	-					
Sweeney, 2018[52]	*Mean: $17.70*		*Mean: $4.79*		*Mean: $2.91*		*Mean: $0.00*	*Mean: $0.36*	*Mean: $0.51*	*Traditional Healer*	*Mean: $5.67*
										DOT	*Mean: $0.00*
Timire, 2021[53]	*DS-TB*	*Median (IQR): $72.29*									
	DR-TB	*Median (IQR: $168.99*									
	Total	*Median (IQR): $74.45*									
*Tomeny, 2020**[54]	DS-TB	Mean: $2.45									
	MDR-TB	Mean: $2.19									
*Trajman, 2016**[55]	*Minimum Wage*	*Mean (SD): $26.83 (34.35)*									
	Reported Income	*Mean (SD): $34.35 (51.69)*									

Ukwaja, 2013[(1) 56]		*Mean: $0.53*				*Mean: $3.17*	
Viney, 2019[59]	*Mean (95% CI): $293.09*						
Wang,2020[61]	*Direct*: *Mean: $7,850.66* *Median (IQR): $6,900.75* *OOP medi*: *Mean: $4,914.93* *Median (IQR): $4,147.59*						
*Yang, 2020**[62]	*Hospitalized* RS-TB: Mean (SD): $ 3,714.23; Median (IQR): $ 2,521.78 RMR-TB: Mean (SD): $ 15,000.89; Median (IQR): $ 7,644.25 MDR-TB: Mean (SD): $ 17,139.85; Median (IQR): $ 14,093.21 *Non-Hospitalized* RS-TB: Mean (SD): $ 1,247.24; Median (IQR): $ 919.38 RMR-TB: Mean (SD): $ 1,744.25; Median (IQR): $ 1,352.92 MDR-TB: Mean (SD): $ 1,517.11; Median (IQR): $ 617.24						

Abbreviations: TB – Tuberculosis, DS-TB – Drug sensitive TB, MDR-TB – Multi-drug resistant TB, SSM – Sputum smear microscopy, LJ – Löwenstein Jensen solid culture, LPA – Line probe assay, DR-TB – Drug resistant TB, RS-TB – Rifampicin sensitive TB, RMR-TB – Rifampicin mono-resistant TB, HIV – Human Immunodeficiency Virus, LTBI – Latent TB Infection, CHC -Community health centres, ACF – Active case finding, PCF – Passive case finding, SES – Socioeconomic status, DOT – Directly observed therapy, SD – Standard deviation, IQR – Interquartile range, CI – Confidence Interval

**Costs reported are a combination of pre- and post-diagnostic costs*

Table S7 – Breakdown of the direct non-medical costs incurred by patients during the post-diagnostic phase of TB care

Study			Total	Transportation		Accommodation		Food		Nutritional Supplements	Other
Aung, 2021[19]				MDR-TB	Median (min-max): $118.81	MDR-TB	Median (min-max): $24.63	MDR-TB	Median (min-max): $626.98		
				DS-TB	Median (min-max): $25.98	DS-TB	Median (min-max): $1.53	DS-TB	Median (min-max): $92.56		
				Total	Median (min-max): $24.63	Total	Median (min-max): $1.53	Total	Median (min-max): $101.04		
Bogdanova, 2019[20]	Culture Algorithm	BacTAlert (SSM+)	Mean: $0.24								
		LJ (SSM+)	Mean: $0.24								
		LJ (SSM-)	Mean: $0.27								

Study												
	LPA Algorithm – LPA (SSM+)	Mean: $0.24										
	LPA Algorithm – LPA+ Bactec MGIT (SSM-	Mean: $0.27										
	LPA Algorithm – LPA+LJ(SS M-)	Mean: $0.27										
Chandra, 2021[(2)22]	*Median (IQR): $13.00(1.4-63)*		*Median (IQR): 40.6 (0-2.50)*		*Median (IQR): $0*		*Food during travel*	*Median (IQR): $0*				
								Mean (SD): $0.15 (1.10)				
	Mean (SD): $41 (56)		Mean (SD): $5 (5.20)		Mean (SD): $0 (0)		*Special diet*	*Median (IQR): $0 (0-35)*				
								Mean (SD): $27.00 (49)				
Chittamany, 2020[23]	*DS-TB*	*Median (IQR): $520.18*	*DS-TB*	*Median (IQR): $52.50*	*DS-TB*	*Median (IQR): $0 (0-0)*	*DS-TB*	*Median (IQR): $0*	*DS-TB*	*Median (IQR): $364.29*	*DS-TB*	*Median (IQR): $0*
	DR-TB	*Median (IQR): $423.15*	*DR-TB*	*Median (IQR): $135.22*	*DR-TB*	*Median (IQR): $0 (0-0)*	*DR-TB*	*Median (IQR): $39.77*	*DR-TB*	*Median (IQR): $256.11*	*DR-TB*	*Median (IQR): $15.91*
	Total	*Median (IQR): $520.18*	*Total*	*Median (IQR): $52.50*	*Total*	*Median (IQR): $0 (0-0)*	*Total*	*Median (IQR): $ 1.59*	*Total*	*Median (IQR):$354.74*	*Total*	*Median (IQR): $0*
Collins, 2018[24]			*MDR-TB* – *Addis Ababa*	*Median (IQM): $143.74*			*MDR-TB* – *Addis Ababa*	*Median (IQM): $489.95*				
			Gonder	*Median (IQM): $11.25*			*Gonder*	*Median (IQM): $66.24*				

De Siqueria Filha, 2018[25]	*TB/HIV*	*Mean: $45.60*	*TB/HIV*	*Mean: $22.99*		*TB/HIV*	*Mean: $ 22.61*					
	LTBI/HIV	*Mean: $31.66*	*LTBI/HIV*	*Mean: $1.63*		*LTBI/HIV*	*Mean: $1.63*					
Ellaban 2021[26]			*First two months of treatment (intensive phase)*	*Median (IQR): $5.00 (2.60 – 9.40)*		*First two months of treatment (intensive phase)*	*Median (IQR): $0.00 (0.00 – 1.60)*					
			Second two months of treatment	*Median (IQR): $3.80 (1.90 – 5.60)*		*Second two months of treatment*	*Median (IQR): $0.00 (0.00 - 0.00)*					
			Third two months of treatment	*Median (IQR): $1.90 (1.30 – 3.80)*		*Third two months of treatment*	*Median (IQR): $0.00 (0.00 – 0.00)*					
Fuady, 2018[29]	*DS-TB*	*Median (IQR): $11.36*	*DS-TB*	*Median (IQR): $2.41*		*DS-TB*	*Median (IQR): $0.00*	*DS-TB*	*Median (IQR): $4.47 (0.00 – 23.06)*			
	MDR-TB	*Median (IQR): $294.56*	*MDR-TB*	*Median (IQR): $138.68*		*MDR-TB*	*Median (IQR): $92.57*	*MDR-TB*	*Median (IQR): $61.59 (1.38 – 119.41)*			
Getahun, 2016[30]			Intensive Phase	Mean (SD): $6.27		Intensive Phase	Mean (SD): $13.73				Additional Food	Mean (SD): $72.36
				Median (R): $4.90			Median (R): $12.27					
			Continuation Phase	Mean (SD): $2.28		Continuation Phase	Mean (SD): $5.00					
				Median (R): $1.78			Median (R): $4.46					Median (R): $97.00
			Total	Mean (SD): $8.55		Total	Mean (SD): $11.27					
				Median (R): $6.69			Median (R): $8.91					
Gospodarevskaya, 2014[31]								*Tanzania*	First two months of treatment	Mean: $2.89		
									Most recent two months of	Mean: $1.65		

									treatment		
									Total treatment costs	Mean: $6.19	
								Bangladesh	First two months of treatment	Mean: $20.80	
									Most recent two months of treatment	Mean: $14.09	
									Total treatment cost	Mean: $48.97	
Gurung, 2019[33]	*ACF*	*Median (IQR): $0.00*	*ACF*	*Median (IQR): $0.00*		*ACF*	*Median (IQR): $0.00*	*ACF*	*Median (IQR): $14.76*		
	PCF	*Median (IQR): $1.41*	*PCF*	*Median (IQR): $0.43*		*PCF*	*Median (IQR): $0.00*	*PCF*	*Median (IQR): $16.82*		
	Total	*Median (IQR): $0.00*	*Total*	*Median (IQR): $0.00*		*Total*	*Median (IQR): $0.00*	*Total*	*Median (IQR): $16.17*		
Gurung, 2021[32]	*ACF*	*Mean (95% CI): $7.60 (5.10 – 10.20)*									
		Median (IQR) $1.90 (0.30 – 9.40)									
	PCF	*Mean (95% CI): $9.50 (6.80 – 12.10)*									
		Median (IQR): $3.40 (0.70 – 13.20)									
	Total	*Mean (95%*									

		CI): $8.60 (6.70 – 10.40)							
		Median (IQR): $2.70 (0.70 – 10.80)							
Kirubi, 2021[34]	Median (IQR): $170.85								
Lu, 2020[35]	Residents	Mean: $230.53							
	Migrants	Mean: $113.31							
Mauch, 2013(1) [36]						Ghana	Mean: $2.49		
							Median (IQR): $1.61		
						Vietnam	Mean: $4.94		
							Median (IQR): $2.69		
						Dominican Republic	Mean: $4.22		
							Median (IQR): $1.61		
Mauch, 2013(2) [38]						New	Median: $17.49		
						Retreatment	Median: $18.12		
						MDR	Median: $22.54		
McAllister, 2020[39]			CHC	Median (IQR): $5.47		CHC	Median (IQR): $2.58		
			Public Hospital	Median (IQR): $15.45		Public Hospital	Median (IQR): $6.41		

		Private Hospital		*Median (IQR): $8.31*		*Private Hospital*	*Median (IQR): $6.59*		
		Private Practice		*Median (IQR): $10.64*		*Private Practice*	*Median (IQR): $2.31*		
Morishita, 2016[40]		*DOT*	*ACF*	*Mean (SD): $4.84*		*ACF*	*Mean (SD): $33.50*		
				Median (IQR): $0.00					
			PCF	*Mean (SD): $15.35*					
				Median (IQR): $0.00			*Median (IQR): $22.94*		
		Drug pick-up	*ACF*	*Mean (SD): $9.58*					
				Median (IQR): $7.65					
			PCF	*Mean (SD): $8.57*		*PCF*	*Mean (SD): $47.36*		
				Median (IQR): $6.12					
		Follow-up examination	*ACF*	*Mean (SD): $0.46*					
				Median (IQR): $0.00			*Median (IQR): $67.55*		

			PCF	*Mean (SD): $0.41*						
				Median (IQR): $0.00						
Mudzengi, 2017[41]		*Study Clinic*	*TB/HIV*	*Mean (SD): $* 1.98		*Hospital*	*TB/HIV*	*Mean (SD): $* 0.13		
			TB	*Mean (SD): $* 0.81			*TB*	*Mean (SD): $0.00*		
			HIV	*Mean (SD): $* 0.60			*HIV*	*Mean (SD): $* 0.02		
		Other Facilities	*TB/HIV*	*Mean (SD): $* 0.30		*Special Diet*	*TB/HIV*	*Mean (SD): $* 6.32		
			TB	*Mean (SD): $* 0.02			*TB*	*Mean (SD): $* 3.88		
			HIV	*Mean (SD): $* 0.12			*HIV*	*Mean (SD): $* 4.69		
Muniyandi, 2020[42]		*Mean (SD): $1.16 (1.92)*				*Mean (SD): $0.30 (0.98)*				
		Median (IQR): $0.00 (0.00 – 16.04)				*Median (IQR): $0.00 (0.00 – 12.03)*				

Muttamba, 2020[43]			MDR-TB	Mean (95% CI): $408.03 (358.78 – 457.68)	MDR-TB	Mean (95% CI): $0.16	MDR-TB	Mean (95% CI): $199.41	MDR-TB	Mean (95% CI): $505.73	
			DS-TB	Mean (95% CI): $17.58	DS-TB	Mean (95% CI): $0.56	DS-TB	Mean (95% CI): $12.25	DS-TB	Mean (95% CI): $75.68	
			Total	Mean (95% CI): $31.99	Total	Mean (95% CI): $0.56	Total	Mean (95% CI): $19.18	Total	Mean (95% CI): $219.36	
Nhung, 2018[44]	MDR-TB	Mean (95% CI): $8,649.44	MDR-TB	Mean (95% CI): $1,730.77	MDR-TB	Mean (95% CI); $188.89	MDR-TB	Mean (95% CI): $4,647.59			
	DS-TB	Mean (95% CI): $1,629.73	DS-TB	Mean (95% CI): $158.14	DS-TB	Mean (95% CI): $20.65	DS-TB	Mean (95% CI); $1,010.35			
	Total	Mean (95% CI): $2,196.41	Total	Mean (95% CI): $285.53	Total	Mean (95% CI): $34.26	Total	Mean (95% CI): $1300.27			
Pedrazzoli, 2018[45]	MDR-TB	Median (IQR): $387.86	MDR-TB	Median (IQR): $8.24	MDR-TB	Median (IQR): $0.00	MDR-TB	Median (IQR): $69.26	MDR-TB	Median (IQR): $144.05	
	DS-TB	Median (IQR): $146.39	DS-TB	Median (IQR): $5.56	DS-TB	Median (IQR): $0.00	DS-TB	Median (IQR): $20.79	DS-TB	Median 9IQR): $30.39	
	Total	Median (IQR): $157.81	Total	Median (IQR): $5.56	Total	Median (IQR): $0.00	Total	Median (IQR): $23.76	Total	Median (IQR): $39.81	
Pedrazzoli, 2021[46]	Uninsured	Mean (SD): $137.97									
		Median (IQR): $45.89									

	Insured	Mean (SD): $133.11											
		Median (IQR): $46.19											
Prasanna, 2018[47]			Study population	Median (IQR): $6.66	Study population	Median (IQR): $0.00	Study population	Median (IQR): $0.00	Study population	Median (IQR): $18.37	Comorbidities	Study population	Median (IQR): $0.00
			Those who incurring costs	Median (IQR): $8.14	Those who incurring costs	Median (IQR): $110.11	Those who incurring costs	Median (IQR): $8.14	Those who incurring costs	Median (IQR): $22.07		Those who incurring costs	Median (IQR): $17.39
Ramma, 2015[48]			Inpatients	Mean (SD): $2.50					Inpatients	Mean (SD): $5.95	Miscellaneous	Inpatients	Mean (SD): $3.21
				Median (IQR): $0.00						Median (IQR): $0.71			Median (IQR): $0.00
			Outpatients	Mean (SD): $1.70					Outpatients	Mean (SD): $23.25		Outpatients	Mean (SD): $0.99
				Median (IQR): $0.00						Median (IQR): $19.85			Median (IQR): $0.00
			Intensive Phase	Mean (SD): $0.99					Intensive Phase	Mean (SD): $7.70		Intensive Phase	Mean (SD): $4.35
				Median (IQR): $0.00						Median (IQR): $1.98			Median (IQR): $0.00
			Continuation Phase	Mean (SD): $4.96					Continuation Phase	Mean (SD): $20.79		Continuation Phase	Mean (SD): $1.37
				Median (IQR): $0.00						Median (IQR): $16.54			Median (IQR): $0.00

Rupani, 2020[49]	*Private Provider*	*Median (IQR): $4.00 (2-5)*	*DOT*	*Private Provider*	*Median (IQR): $0.00 (0-0)*	*Private Provider*	*Medina (IQR): $0.00 (0-0)*	*Private Provider*	*Median (IQR): $0.00 (0-0)*				
				Public Provider	*Median (IQR): $0.00 (0-0)*								
	Public Provider	*Median (IQR): $3.00 (2-4)*		*Total*	*Median (IQR): $0.00 (0-0)*	*Public Provider*	*Median (IQR): $0.00 (0-0)*	*Public Provider*	*Median (IQR): $0.00 (0-0)*				
			Travel to attend health facility	*Private Provider*	*Median (IQR): $4.00 (2-5)*								
	Total	*Median (IQr): $3.00 (2-4)*		*Public Provider*	*Median (IQR): $3.00 (2-4)*	*Total*	*Median (IQR): $0.00 (0-0)*	*Total*	*Median (IQR): 0.00 (0-0)*				
				Total	*Median (IQR): $3.00 (2 – 4)*								
Shin, 2020[50]			*Inpatient (Initial)*	Mean (SD): $3.19		*Inpatient (Initial)*	-	*Inpatient (Initial)*	Mean (SD): $6.55		*Childcare*	*Inpatient (Initial)*	*Mean (SD):* $2.03
			Inpatient (Recurrent)	Mean (SD): $2.06		*Inpatient (Recurrent)*	-	*Inpatient (Recurrent)*	Mean (SD): $10.18			*Inpatient (Recurrent)*	*Mean (SD):* $3.68
			Outpatient (HIV)	*Mean (SD):* $0.25		*Outpatient (HIV)*	Mean (SD): $0.61	*Outpatient (HIV)*	Mean (SD): $0.40			*Outpatient (HIV)*	*Mean (SD):* $0.29
			Outpatient (TB)	Mean (SD): $0.26		*Outpatient (TB)*	Mean (SD): $0.39	*Outpatient (TB)*	Mean (SD): $0.51			*Outpatient (TB)*	*Mean (SD):* $0.18
Stracker, 2019[51]											*Non-transport OOP costs*	*TB+*	*Mean: $8.98*
												Xpert-	*Mean: $0.82*

Sweeney, 2018[52]*	*Mean: $23.18*											
Timire, 2021[53]		*DS-TB*	*Median (IQR): $26.12*	*DS-TB*	*Median (IQR) $0.00 (0-0)*	*DS-TB*	*Median (IQR): $20.41*	*DS-TB*	*Median (IQR): $293.89*			
		DR-TB	*Median (IQR): $124.09*	*DR-TB*	*Median (IQR): $0.00 (0-0)*	*DR-TB*	*Median (IQR): $81.64*	*DR-TB*	*Median (IQR): $783.72*			
		Total	*Median (IQR): $26.12*	*Total*	*Median (IQR): $0.00 (0-0_*	*Total*	*Median (IQR): $20.41*	*Total*	*Median (IQR): $293.89*			
Tomeny, 2020[54]*		DS-TB	Mean: $0.78	DS-TB	*Mean:* $0.04	DS-TB	*Mean:* $0.07	DS-TB	*Mean:* $3.64			
		MDR-TB	Mean: $17.23	MDR-TB	*Mean:* $1.30	MDR-TB	*Mean:* $2.60	MDR-TB	*Mean:* $12.77			
*Trajman, 2016**		Minimum Wage	Mean (SD): $2.62			Minimum Wage	Mean (SD): $0.65	Minimum Wage	Mean (SD): $26.83	*Non-Transport & Food Services*	*Minimum Wage*	*Mean (SD):* $0.98
		Reported Income	Mean (SD): $1.64			Reported Income	Mean (SD): $0.65	Reported Income	Mean (SD): $34.35		*Reported Income*	*Mean (SD):* $0.16
Ukwaja, 2013[(1)56]		*Mean: $14.82*				*Mean: $2.65*						
Viney, 2019[59]	*Mean (95% CI): $1,889.77*	*Mean (95% CI): $511.52*		*Mean (95% CI): $19.95*		*Mean (95% CI): $1358.29*						

Wang, 2020[61]	*Mean: $505.48*					
	Median (IQR): $460.40					

Abbreviations: TB – Tuberculosis, DS-TB – Drug sensitive TB, MDR-TB – Multi-drug resistant TB, SSM – Sputum smear microscopy, LJ – Löwenstein Jensen solid culture, LPA – Line probe assay, DR-TB – Drug resistant TB, RS-TB – Rifampicin sensitive TB, RMR-TB – Rifampicin mono-resistant TB, HIV – Human Immunodeficiency Virus, LTBI – Latent TB Infection, CHC – Community health centre, ACF – Active case finding, PCF – Passive case finding, SES – Socioeconomic status, DOT – Directly observed therapy, SD – Standard deviation, IQR – Interquartile range, CI – Confidence Interval

**Costs reported are a combination of pre- and post-diagnostic costs*

Table S8 – Breakdown of the indirect costs incurred by patients during the post-diagnostic phase of TB care

	Total	*Loss of Income*		*Time/Productivity Loss*	*Caregiver/Guardian Costs*		*Other*
Assebe, 2020[18]		*Outpatient*	Mean (SD) - $11.82 (27.94)				
			Median (IQR) - $0.00 (0-4.30)				
		Inpatient	Mean (SD) - $13.23 (33.31)				
			Median (IQR) - $0.00				
		Total	Mean (SD) - $10.75 (27.94)				
			Median (IQR) - $0.00 (0-3.22)				
Aung, 2021[19]					*MDR-TB*	*Median (min-max): $506.36*	
					DS-TB	*Median (min-max): $0*	
					Total	*Median (min-max): $0*	
Chandra, 2021[(2)22]	*Median (IQR): $0 (0 – 105)*						
	Mean (SD): $114 (230)						

Chittamany, 2020[23]	*DS-TB*	*Median (IQR): $50.90*							
	DR-TB	*Median (IQR): $2,106.19*							
	Total	*Median (IQR): $90.67*							
De Siqueria Filha, 2018[25]	*TB/HIV*	*Mean: $212.80*		*TB/HIV*	*Mean: $143.41*	*TB/HIV*	*Mean: $69.38*		
	LTBI/HIV	*Mean: $12.45*		*LTBI/HIV*	*Mean: $0*	*LTBI/HIV*	*Mean: $12.45*		
Ellaban, 2021[26]	*First two months of treatment (intensive phase)*	*Median (IQR_: $0.00 (0.00 – 93.80)*							
	Second two months of treatment	*Median (IQR): $0.00 (0.00 – 75.0)*							
	Third two months of treatment	*Median (IQR): $0.00 (0.00 - 62.50)*							
Fuady, 2018[29]	*DS-TB*	*Median (IQR): $2.75 (0.00 – 154.16)*	*Patient*	*DS-TB*	*Median (IQR): $0.69 (0.00 – 154.16)*				
				MDR-TB	*Median (IQR): $462.48 (0.69-886.77)*				
			Guardian	*DS-TB*	*Median (IQR): $0.00 (0-0)*				
				MDR-TB	*Median (IQR): $0.00 (0-0)*				
	MDR-TB	*Median (IQR): $462.48 (0.69-886.77)*	*Total*	*DS-TB*	*Median (IQR): $40.26*				
				MDR-TB	*Median (IQR): $949.74*				

Getahun, 2016[30]	Mean (SD): $63.21		Mean (SD): $47.81						Mean (SD): $1.74			Hospital Stay	Mean (SD): $19.08
	Median (R): $51.97		Median (R): $35.54						Median (R): $1.12				Median (R): $14.91
Gospodarevskaya, 2014[31]			Tanzania	Patients	First two months of treatment	Mean: $6.38			Tanzania	First two months of treatment	Mean: $1.58		
					Most recent two months of treatment	Mean: $4.61							
					Total treatment	Mean: $15.61				Most recent two months of treatment	Mean: $1.72		
				Caregivers	First two months of treatment	Mean: $0.66							
					Most recent two months of treatment	Mean: $0.45							
					Total treatment	Mean: $1.56				Total treatment	Mean: $5.02		
			Bangladesh	Patients	First two months of treatment	Mean: $12.41			Bangladesh	First two months of treatment	Mean: $2.16		
					Most recent two months of treatment	Mean: $9.65							
					Total treatment	Mean: $31.71				Most recent two months of treatment	Mean: $1.14		
				Caregivers	First two months of treatment	Mean; $0.36							
					Most recent two months of treatment	Mean: $0.18							
					Total treatment	Mean: $0.72				Total treatment	Mean: $4.44		
Gurung, 2019[33]	ACF	Median (IQR): $59.58	ACF			Median (IQR): $19.64	ACF	Median (IQR): $32.45					
	PCF	Median (IQR): $64.68	PCF			Median (IQR): $10.42	PCF	Median (IQR): $33.64					
	Total	Median (IQR): $59.80	Total			Median (IQR): $18.56	Total	Median (IQR): $32.45					
Gurung, 2021[32]	ACF	Mean (95% CI): $38.70 (33.20 – 44.10)											
		Median (IQR): $29.60 (21.20 – 50.10)											
	PCF	Mean (95% CI): $44.10 (33.40 – 54.80)											

		Median (IQR): $27.90 (17.00 – 51.50)								
	Total	*Mean (95% CI): $41.40 (35.40 – 47.30)*								
		Median (IQR): $29.10 (19.50 – 50.20)								
Kirubi, 2021[34]	*Median (IQR): $35.55*		*Median (IQR): $28.64*							
Lu, 2020[35]			*Residents*		*Mean: $1270.44*		*Care-seeking*	*Residents*	*Mean: $71.65*	
			Migrants		*Mean: $715.56*			*Migrants*	*Mean: $32.68*	
Mauch, 2013(1) [36]	*Ghana*	*Mean: $1.76*								
		Median (IQR): $0.00								
	Vietnam	*Mean: $5.84*								
		Median (IQR): $1.57								
	Dominican Republic	*Mean: $13.86*								
		Median (IQR): $11.25								
Mauch, 2013(2) *[38]	New	*Median: $654.98*					New		*Median: $105.50*	
	Retreatment	*Median: $199.18*					Retreatment		*Median: $65.82*	
	MDR-TB	*Median: $2,836.59*					MDR-TB		*Median: $158.70*	
McAllister, 2020[39]	*CHC*	*Median (IQR): $102.69*	*CHC*		*Median (IQR): $108.93*					
	Public Hospital	*Median (IQR): $169.81*	*Public Hospital*		*Median (IQR): $179.36*					
	Private Hospital	*Median (IQR): $233.39*	*Private Hospital*		*Median (IQR): $133.25*					
	Private Practice	*Median (IQR): $198.81*	*Private Practice*		*Median (IQR): $70.93*					
Morishita, 2016[40]			*Patient*	*ACF*	*Mean (SD): $67.55*					
					Median (IQR): $0.00					
				PCF	*Mean (SD): $98.70*					
					Median (IQR): $0.00					
			G	*ACF*	*Mean (SD): $28.60*					

					Median (IQR): $0.00					
				PCF	Mean (SD): $14.02					
					Median (IQR): $0.00					
Mudzengi, 2017[41]	TB/HIV	Mean (SD): $ 25.17	Job Loss	TB/HIV	Mean (SD): $ 7.41		Study Clinic	TB/HIV	Mean (SD): $ 0.54	
				TB	Mean (SD): $ 8.55			TB	Mean (SD): $ 0.11	
	TB	Mean (SD): $ 28.12		HIV	Mean (SD): $ 1.44			HIV	Mean (SD): $ 1.88	
			Care Seeking	TB/HIV	Mean (SD): $ 14.64		Other Facilities	TB/HIV	Mean (SD): $ 0.45	
	HIV	Mean (SD): $ 10.64		TB	Mean (SD): $ 16.64			TB	Mean (SD): $ 0.02	
				HIV	Mean (SD): $ 6.64			HIV	Mean (SD): $ 0.11	
Muniyandi, 2020[42]	Mean (SD): $320.68 (677.17)		Mean (SD): $272.73 (576.89)				Mean (SD): $41.88 (354.65)		Hospitalization Escort	Mean (SD): $5.11 (40.04)
	Median (IQR): $0.00 (0.00 – 6114.57)		Median (IQR): $0.00 (0.00 – 4323.95)				Median (IQR): $0.00 (0.00.-5412.90)			Median (IQR): $0.00 (0.00 – 701.67)
Muttamba, 2020[43]	MDR-TB	Mean (95% CI): $488.11					MDR-TB	Mean (95% CI): $46.05		
	DS-TB	Mean (95% CI): $46.05					DS-TB	Mean (95% CI): $10.09		
	Total	Mean (95% CI): $62.47					Total	Mean (95% CI): $11.17		
Nhung, 2018*[44]	MDR-TB	Mean (95% CI); $6,044.51	MDR-TB		Mean (95%					

					CI); $6044.51					
	DS-TB	*Mean (95% CI): $2,231.55*	*DS-TB*		*Mean (95% CI): $2231.55*					
	Total	*Mean (95% CI): $2,534.65*	*Total*		*Mean (95% CI): $2534.65*					
Pedrazzoli, 2018[45]			*MDR-TB*		Median (IQR): $0.00			*MDR-TB*	Median (IQR): $0.00	
			DS-TB		Median (IQR): $0.00			*DS-TB*	Median (IQR): $0.00	
			Total		Median (IQR): $0.00			*Total*	Median (IQR): $0.00	
Pedrazzoli, 2021[46]			*Uninsured*		*Mean (SD): $93.90*					
					Median (IQR): $0.00					
			Insured		*Mean (SD): $97.55*					
					Median (IQR): $0.00					
Prasanna, 2018[47]	*Study Population*	Median (IQR): $ 61.90	*Income Change*	*Study Population*	Median (IQR): $ 0.00	*Study Population*	Median (IQR): $ 80.51	*Study Population*	Median (IQR): $ 0.00	
				Those who incurred	Median (IQR): $ 82.61					
	Those who incurred costs	Median (IQR): $ 164.36	*Job Loss*	*Study Population*	Median (IQR): $ 0.00	*Those who incurred costs*	Median (IQR): $ 84.34	*Those who incurred costs*	Median (IQR): $ 0.00	
				Those who incurred	Median (IQR): $ 412.93					

Ramma, 2015[48]	*Inpatients*	*Mean (SD): $114.79*			*Seeking Care*	*Inpatients*	*Mean (SD): $5.15* *Median (IQR): $0.43*	*Inpatients*	*Mean (SD): $3.17*			
						Outpatients	*Mean (SD): $3.92* *Median (IQR): $1.37*		*Median (IQR): $0.99*			
	Outpatients	*Mean (SD): $29.86*				*Intensive Phase*	*Mean (SD): $3.64* *Median (IQR): $0.00*	*Outpatients*	*Mean (SD); $13.33*			
						Continuation Phase	*Mean (SD): $1.94* *Median (IQR): $0.61*		*Median (IQR): $0.00*			
	Intensive Phase	*Mean (SD); $91.44*			*Hospitalization*	*Inpatients*	*Mean (SD): $106.42* *Median (IQR): $70.41*	*Intensive Phase*	*Mean (SD): $5.95*			
						Outpatients	*Mean (SD): $12.61* *Median (IQR): $0.00*		*Median (IQR): $0.85*			
	Continuation Phase	*Mean (SD): $60.01*				*Intensive Phase*	*Mean (SD): $81.85* *Median (IQR): $54.63*	*Continuation Phase*	*Mean (SD): $15.55*			
						Continuation Phase	*Mean (SD): $42.53* *Median (IQR): $0.00*		*Median (IQR): $0.00*			
Rupani, 2020[49]	*Private Provider*	*Median (IQR): $20.00 (3-76)*	*Private Provider*	*Median (IQR): $8.00 (0-21)*				*Private Provider*	*Median (IQR): $0.00 (0-19)*	*Household income loss*	*Private Provider*	*Median (IQR): $0.00*

										(0-27)
	Public Provider	*Median (IQR): $4.00 (3-10)*	*Public Provider*	*Median (IQR): $3.00 (0-6)*		*Public Provider*	*Median (IQR): $0.00 (0-3)*		*Public Provider*	*Median (IQR): $0.00 (0-0)*
	Total	*Median (IQR): $6.00 (3-13)*	*Total*	*Median (IQR): $3.00 (0-6)*		*Total*	*Median (IQR): $0.00 (0-3)*		*Total*	*Median (IQR): $0.00 (0-0)*
Shin, 2020[50]	Inpatient (Initial)	Mean (SD): $21.34	Inpatient (Initial)	Mean (SD): $14.46		Inpatient (Initial)	*Mean (SD):* $10.97			
	Inpatient (Recurrent)	Mean (SD): $66.71	Inpatient (Recurrent)	Mean (SD): $56.69		Inpatient (Recurrent)	*Mean (SD):* $13.47			
	Outpatient (HIV)	*Mean (SD):* $1.26	Outpatient (HIV)	Mean (SD): $1.26		Outpatient (HIV)	-			
	Outpatient (TB)	*Mean (SD):* $1.43	Outpatient (TB)	Mean (SD): $1.43		Outpatient (TB)	-			
Stracker, 2019[51]			*TB+*	*Mean: $186.40*		*TB+*	*Mean: $8.98*			
			Xpert-	*Mean: $2.45*		*Xpert-*	*Mean: $1.63*			
*Sweeney, 2018**[52]	*Approach #1: Current income (prompted ranges)*	*Mean (SD):* $21.12								
	Approach #2: Current income (detailed)	*Mean (SD):* $27.59								
	Approach #3: Permanent income (MCA)	*Mean (SD):* $47.36								
	Approach #4: National mean income	*Mean (SD):* $72.08								
	Approach #5: Self-reported income loss	*Mean (SD):* $54.45								

Timire, 2021[53]*	*DS-TB*		*Median (IQR): $195.93*								
	DR-TB		*Median (IQR): $979.66*								
	Total		*Median (IQR): $244.92*								
Tomeny, 2020[54]*	DS-TB		*Mean:* $4.94								
	MDR-TB		*Mean:* $51.46								
Trajman, 2016[55]*	All	*Minim*	Mean (SD): $103.38			*Minimum Wage*	*Mean (SD):* $6.87	*Minimum Wage*	*Mean (SD);* $6.54		
		SES In	Mean (SD): $103.38								
		Incom	*Mean (SD):* $108.62			*SES Income per*	*Mean (SD):* $5.89	*SES Income per Capita*	*Mean (SD):* $7.20		
		Repo	Mean (SD): $116.80								
	Patients Only	*Minim*	*Mean (SD):* $101.42			*Income per Activity*	*Mean (SD):* $9.81	*Income per Activity*	*Mean (SD):* $8.83		
		SES In	*Mean (SD):* $102.40								
		Incom	Mean (SD): $105.67			*Reported Income*	*Mean (SD):* $8.18	*Reported Income*	*Mean (SD):* $1.64		
		Repo	Mean (SD) $115.82								
Ukwaja, 2013[(1)56]	*Mean: $42.86*				*Mean: $42.33*			*Median: $33.87*		<u>*Value of time for drug collections*</u>	*Mean: $0.80*
Ukwaja, 2013[(2)57]										*DOT supporter costs*	*Mean: $3.70*
Van der Hof, 2016[58]			DS-TB	MDR-TB							
	Ethiopia	Intensive Phase	*Median (IQR): $0.00*	*Median (IQR): $275.02*							
		Continuation Phase	*Median (IQR): $0.00*	*Median (IQR): $91.26*							
	Indonesia	Intensive Phase	*Median (IQR): $3.24*	*Median (IQR): $101.90*							

		Continuation Phase	*Median (IQR): $2.91*	*Median (IQR): $82.17*					
	Kazakhstan	Intensive Phase	*Median (IQR): $143.96*	*Median (IQR): $547.71*					
		Continuation Phase	*Median (IQR): $37.06*	*Median (IQR): $80.89*					
Viney, 2019[59]	*Mean (95% CI): $1,392.81*								
Wang, 2020[61]	*Mean: $2,579.84*								
	Median (IQR): $1,575.69								

Abbreviations: TB – Tuberculosis, DS-TB – Drug sensitive TB, DR-TB – Drug resistant TB, MDR-TB – Multidrug resistant TB, RS-TB – Rifampicin sensitive TB, RMR-TB – Rifampicin mono-resistant TB, HIV – Human Immunodeficiency Virus, LTBI – Latent TB Infection, ACF – Active case finding, PCF – Passive case finding, SES – Socioeconomic status, DOT – Directly observed therapy, SD – Standard deviation, IQR – Interquartile range, CI – Confidence Interval

**Costs reported are a combination of pre- and post-diagnostic costs*