Cost-effectiveness study on the use of novel drug-resistant tuberculosis diagnostics and tuberculosis preventive treatment to END tuberculosis.

By

Suvesh Shrestha

Thesis submitted to the University of Ottawa in partial fulfillment of the requirements of the degree of Doctor of Philosophy in Epidemiology

School of Epidemiology and Public Health

Faculty of Medicine

University of Ottawa

Supervisors

Primary Supervisor

Dr. Alice Ann Zwerling, *University of Ottawa*

Thesis Advisory Committee

Dr. Hawre Jalal, *University of Ottawa*

Dr. Gonzalo Alvarez, *University of Ottawa*

Dr. Kevin Schwartzman, *McGill University*

Table of Contents

ABSTRACT ..... **VI**

ACKNOWLEDGMENTS ..... **VIII**

LIST OF TABLES ..... **X**

LIST OF ABBREVIATIONS ..... **XIV**

CHAPTER 1: BACKGROUND **1**

1.1 Introduction 1
1.2 Tuberculosis Disease 1
1.2.1 Pathogenesis and Transmission of Tuberculosis *1*
1.2.2 Drug-Resistant Tuberculosis (DR-TB) and diagnosis of DR-TB *2*
1.2.3 TB Infection and Treatment *5*
1.3 Global Epidemiology of TB 8
1.3.1 Burden and Trends in TB Epidemiology *8*
1.3.2 Burden and Trends in DR-TB Epidemiology *9*
1.3.3 Epidemiology of TB Infection *11*
1.4 The WHO End TB Strategy and the role of novel diagnostic and preventive treatment 12
1.4.1 WHO End TB strategy: Pillars and Targets *12*
1.4.3 Addressing social determinant and the SDGs to End TB *14*
1.4.4 Global progress toward End TB targets *15*
1.4.5 Role of tNGS and TB Preventive Treatment: Aligning with Strategy and HLM *17*
1.5 Rationale for Economic Evaluation in TB 20
1.5.1 Global funding scenario and economic burden of TB *20*
1.5.2 Importance of economic evaluation for efficient investment *21*
1.5.3: Gap in economic evidence around implementation of tNGS and TPT with person-centered care *22*
1.6 Rationale for This Thesis 24
1.6.1 Manuscript 1: Evaluate the cost-effectiveness of using tNGS for the diagnosis of DR-TB in low and middle-income countries with a high burden of TB *25*
1.6.2 Manuscript 2: Estimate real-world cost of TPT Delivery Across Five Sub-Saharan African Countries with high TB and HIV *25*
1.6.3 Manuscript 3: Evaluate the cost-effectiveness of TPT provided with SDM and EAS in Sub-Saharan Africa *25*
1.6.4 Overall Thesis Contribution *26*
1.7 References: 27

CHAPTER 2 ..... **37**

2.1 Preface 38

2.2 Abstract 40
2.3 Research in Context 42
2.4 Introduction: 43
2.5 Methods: 45
2.5.1Study design: *45*
2.5.2 Model structure, intervention, and comparator: *45*
2.5.3 Statistical analysis: *49*
2.5.4 Sensitivity and scenario analysis: *49*
2.5.5 Ethics: *50*
2.5.6 Role of funding source: *50*
2.6 Results: 50
2.6.1 Cost-effectiveness of tNGS vs. Universal pDST for DST among persons with RR: *50*
2.6.2 Cost-effectiveness of tNGS vs. in-country DST practice for DST among persons with RR: *50*
2.6.3 Cost-effectiveness of tNGS as an initial test for TB drug resistance: *51*
2.6.4 Sensitivity analysis: *51*
2.6.5 Scenario analysis: *52*
2.7 Discussion: 53
2.8 Contributors: 57
2.9 Data sharing statement: 57
2.10 Declaration of interests: 58
2.11 Acknowledgements 58
2.12 References 59
2.13 Supplement 78

CHAPTER 3 85

3.1 Preface 86
3.2 Abstract 88
3.3 Background 90
3.4 Methods 91
3.4.1 Study Design *91*
3.4.2 Calculating cost per individual on different TPT regimens: *92*
3.4.3 Cost data collection and cost calculation by component: *93*
3.4.4 Ethical Considerations *94*
3.5 Results 95
3.5.1 TPT drugs cost across countr *95*
3.5.2 Cost of TPT activities and components, excluding drugs *95*
3.5.3 Total cost per-patient treated with TB preventive treatment: *96*
3.5.4 Key drivers of per-patient TPT cost by regimen and country: *96*
3.6 Discussion: 97
3.7 Acknowledgement: 101

3.8 Reference: 101
3.9. Supplemental appendix 110
3.9.1Supplemental methods: *111*
3.9.2. Supplemental results *122*
CHAPTER 4: 128
4.1: Preface 129
4.2 Abstract: 131
4.3 Background: 133
4.4 Methods: 136
4.4.1 Study Design and Setting *136*
4.4.2 Modelling *137*
4.4.3 Time Horizon and Perspective *138*
4.4.4 Model parameters: *138*
4.4.5 Assumption: *139*
4.4.6 Analysis *140*
4.4.7 Uncertainty, sensitivity and scenario analysis *141*
4.5 Results: 142
4.5.1 Incremental Cost-Effectiveness of TPT Implementation Strategies *142*
4.5.2 TB cases averted and deaths averted *143*
4.5.3 Probabilistic sensitivity analysis: *143*
4.5.4 Deterministic sensitivity analysis: *144*
4.5.5 Scenario analysis results: *144*
4.6 Discussion: 146
4.7 Acknowledgement: 150
4.8 References: 151
4.9 Supplemental 169
CHAPTER 5: GENERAL DISCUSSION 179
5.1 Integrated studies summaries 179
5.2 Policy implications 182
5.3 Cross-cutting limitations: 184
5.4 Priorities for Future Research and Global Strategic Implications 185
5.4.1 Bridging the Implementation and Scalability Gap *185*
5.4.2 Equity Considerations and the Societal Perspective *185*
5.4.3 Real-World Effectiveness and Long-Term Impact *186*
5.4.4 Generalizability to Other High-Burden Settings *186*
5.5 Overall conclusion 187
5.6 Reference 187

Abstract

Background

Tuberculosis (TB) remains a major global health challenge, particularly in high-burden settings and among people with HIV. Achieving the World Health Organization (WHO) End TB Strategy requires improved detection of drug-resistant TB (DR-TB) and effective scale-up of tuberculosis preventive treatment (TPT). However, economic evidence to guide the adoption of novel diagnostic technologies and optimized TPT delivery strategies remains limited. This thesis aimed to generate policy-relevant economic evidence to inform TB diagnostic and prevention strategies across diverse high-burden settings.

Methods

Three complementary studies were conducted. First, a stochastic decision-analytic model was developed to evaluate the cost-effectiveness of targeted next-generation sequencing (tNGS) for DR-TB detection in India, South Africa, and Georgia, compared with existing drug susceptibility testing (DST) strategies. Second, a multi-country micro-costing study estimated health system costs of TPT delivery across high-burden settings using standardized bottom-up and top-down costing approaches. Third, a hybrid decision-analytic model integrating a decision tree and Markov framework evaluated the cost-effectiveness of four TPT delivery strategies among people with HIV: (1) standard of care, (2) universal 3HP, (3) TPT with shared decision-making , and (4) TPT with shared decision making plus enhanced adherence support (as a scenario analysis). Outcomes were expressed as incremental cost per disability-adjusted life year (DALY) averted, with uncertainty assessed through deterministic, probabilistic, and scenario analyses.

Results

Across the three studies, the findings provide economic evidence for strengthening TB control across the care cascade. For the detection of DR-TB, the economic value of diagnostic innovation tNGS varied across settings, reflecting differences in existing drug susceptibility testing practices and test costs, highlighting the importance of local context when considering the adoption of new diagnostic technologies to enable appropriate treatment selection and reduce the risk of ongoing transmission and further development of drug resistance. For TB prevention, understanding true TPT delivery costs is essential, and the micro-costing analysis showed that drugs and human resources were the primary cost drivers, providing national programs with realistic, regimen-specific estimates for informed budgeting and resource allocation. Finally, for maximizing preventive treatment impact, combining shorter regimens with patient-centred support delivered the greatest health gains. The strategy providing TPT with shared decision making and enhanced adherence support was cost-effective at $235 per DALY averted, demonstrating that investing in adherence support is both clinically and economically justified. Together, these findings show that effective TB control requires aligning diagnostic investments with local infrastructure, using comprehensive cost data to guide resource allocation, and pairing effective preventive treatment with patient support to ensure treatment completion.

Conclusions

This thesis includes several key pieces of economic evidence, which, taken together, will inform strategic investment decisions across the TB care cascade, from prevention, through detection and treatment. These findings provide actionable evidence to guide national TB programs and global policy efforts toward TB elimination while using resources to ensure the most value for money.

Acknowledgments

I would like to express my deepest and most sincere gratitude to my supervisor, **Dr. Alice Zwerling**, for her exceptional guidance, mentorship, and unwavering support throughout my doctoral journey. Her intellectual rigour, thoughtful feedback, and commitment to excellence have profoundly shaped this work and my development as a researcher. I am especially grateful for the opportunities she provided me to contribute to meaningful global health research and to present our work in international forums. These experiences have been invaluable to my academic growth and professional development.

I am also sincerely thankful to my Thesis Advisory Committee members for their insightful comments, constructive critiques, and continuous encouragement. Their expertise and thoughtful guidance strengthened both this thesis and my overall research perspective. I deeply appreciate the time and care they invested in supporting my progress.

My sincere thanks to my PhD friends and collaborators, particularly Abdulhameed, for the camaraderie, intellectual support, and shared moments that made this journey enriching. Your contributions strengthened this work in countless ways.

To my beloved wife Videsha, thank you for your patience, sacrifice, and constant belief in me. Your support carried me through the most challenging moments of this journey. To my two wonderful children, Aayan and Aahana, you are my greatest source of motivation and joy. This achievement is as much yours as it is mine.

I am profoundly grateful to my father, Bharat and mother, Sulochana, for their unconditional love, prayers, and lifelong encouragement. Their values, resilience, and faith laid the foundation upon which all my achievements stand. To my brother, Saurav, thank you for your steady support and for always standing by me.

This journey has been possible because of the collective support, guidance, and love of all those mentioned above. I am deeply thankful.

List of tables

Chapter 1	
Table 1.1: WHO End TB strategy milestones and targets for 2020-2025	12
Chapter 2	
Table 2.1: Key Model Parameter estimate, ranges for sensitivity analysis and data sources	71
Table 2.2: CEA result of using tNGS for DST	74
Table 2.3: Scenario analysis tNGS compared to pDST and in country DST practice among RR individuals	75
Supplementary table 2.1: Additional scenario analysis tNGS compared to in-country DST practice	83
Chapter 3	
Table 3.1: Cost of TPT delivery activities by country, disaggregated by cost components (human resources, consumables, equipment, and overheads)	105
Table 3.2: Cost per-patient treated with different TPT regimens by country (US$, 2024)	108
Supplemental Table 3.1. Framework for calculating cost per individual receiving tuberculosis preventive treatment (TPT): Activities and calculation by country.	111
Supplemental Table 3.2: Drug costs of different TPT regimens by country	122
Supplemental Table 3.3: Share of total per-patient cost by component for each TPT regimen, by country	123
Supplemental Table 3.4: CHEERS checklist for economic studies	126
Chapter 4	
Table 4.1: Epidemiological parameters for the cost-effectiveness analysis of TB preventive treatment among PWH in Eswatini	163
Table 4.2: ICER per DALYs averted with 95% UR	166
Table 4.3. . Lifetime TB cases and deaths per 1,000 people living with HIV under alternative Strategies	166
Table 4.4. Scenario analysis result when TPT is provided with SDM and EAS	168
Supplemental Table 4.1: Description of TPT strategies	169

Supplemental Table 4.2: ICER per DALYs averted in sequential analysis	170
Supplemental Table 4.3: Scenario Analysis Results: ICER per DALY Averted Under Alternative Assumptions on EAS Effectiveness and SDM Regimen Availability	174
Supplemental Table 4.4: CHEERS checklist for economic studies	176

List of figures

Chapter 1	
Figure 1.1: Estimated TB incidence rate at the country level, 2024	9
Figure 1.2: The WHO End TB Strategy:	13
Figure1.3: End TB strategy target and latest status of progress	15
Figure 1.4: 2023 UN high-level meeting on TB, its target and progress	16
Figure 1.5: Projected TB incidence reduction under the WHO End TB strategy: Required Vs Current trend 2015-2035	19
Chapter 2	
Figure 2.1 Simplified model decision structure. Two strategies were compared: DST with tNGS vs pDST as a test for DST among person with RR:	65
Figure 2.2a: Incremental cost-effectiveness scatterplot comparing tNGS versus South Africa's in-country DST as a test for DST among person with RR.	66
Figure 2.2b: Incremental cost-effectiveness scatterplot comparing tNGS versus Georgia's in-country DST as a test for DST among person with RR.	66
Figure 2.2c: Incremental cost-effectiveness scatterplot comparing tNGS versus India's in-country DST as a test for DST among person with RR.	67
Figure 2.3: Incremental cost-effectiveness scatterplot comparing tNGS as an initial test for TB drug resistance in patients with bacteriologically confirmed TB compared to use of mWRDs followed by pDST.	67
Figure 2.4a: One way sensitivity analyses tornado diagram on incremental cost effectiveness ratio (ICER) of using tNGS as a replacement of South Africa's DST practice as a test for DST among person with RR	68

Figure 2.4b: One way sensitivity analyses tornado diagram on incremental cost effectiveness ratio (ICER) of using tNGS as a replacement of Georgia's DST practice as a test for DST among person with RR.	69
Figure 2.4c: One way sensitivity analyses tornado diagram on incremental cost effectiveness ratio (ICER) of using tNGS as a replacement of India's DST practice as a test for DST among person with RR.	70
Figure 2.5: One way sensitivity analyses tornado diagram on incremental cost effectiveness ratio (ICER) of using tNGS as initial test for DR diagnosis.	71
Supplement Figure 2.1: Simplified model decision structure. Two strategies were compared: DST with tNGS vs South Africa and Georgia's in country DST practice as a subsequent test for DST following detection of RR.	78
Supplement Figure 2.2: Simplified model decision structure. Two strategies were compared: DST with tNGS vs India's in country DST practice as a subsequent test for DST following detection of RR.	79
Supplement Figure 2.3: Simplified model decision structure. Two strategies were compared: DST with tNGS vs mWRDs followed by pDST among individuals with bac. confirmed TB.	80
Supplement Figure 2.4a: One way sensitivity analyses tornado diagram on incremental cost effectiveness ratio (ICER) of using tNGS as a replacement of pDST in South Africa as a subsequent test for DST following detection of RR.	81
Supplement Figure 2.4b: One way sensitivity analyses tornado diagram on incremental cost effectiveness ratio (ICER) of using tNGS as a replacement of pDST in Georgia as a subsequent test for DST following detection of RR.	82
Supplement Figure 2.4c: One way sensitivity analyses tornado diagram on incremental cost effectiveness ratio (ICER) of using tNGS as a replacement of pDST in India as a subsequent test for DST following detection of RR.	83
Chapter 3	
Figure 3.1. Median human resource time (in minutes) spent on tuberculosis preventive treatment (TPT) activities in Eswatini, Lesotho, Malawi, Uganda and Tanzania.	107

Figure 3.2. Median human resource cost (in US$) for tuberculosis preventive treatment (TPT) activities in Eswatini, Lesotho, Malawi, Uganda and Tanzania.	108
Figure 3.3. Share of total per-patient cost by component for each TPT regimen, by country.	109
Supplemental Figure 3.1. Cost estimation approach for tuberculosis (TB) activities by cost component, data source, and method.	114
Supplemental Figure 3.2: Summary of time data collected using three data collection tools	124
Supplemental Figure 3.3: Panels A–E show country-specific costs for five TPT service activities:	125
Supplemental Figure 3.4: Cost ranges for TPT regimens across five countries	126
Chapter 4	
Figure 4.1. Hybrid decision-analytic model structure for tuberculosis preventive treatment (TPT) strategies among people with HIV (PWH):	162
Figure 4.2: Cost-effectiveness acceptability curve of different TPT strategies	167
Figure 4.3: Two-way deterministic sensitivity analysis of EAS cost and completion gain	167
Supplemental Figure 4.1a: Incremental cost-effectiveness scattered plot for 3HP provided to all age group.	171
Supplemental Figure 4.1b: Incremental cost-effectiveness scattered plot for TPT provided with SDM.	171
Supplemental Figure 4.2a. One-way sensitivity analysis of the ICER for Strategy 2 versus standard of care.	172
Supplemental Figure 4.2b. One-way sensitivity analysis of the ICER for Strategy 3 versus standard of care.	173
Supplemental Figure 4.3: Cost-effectiveness acceptability curve with addition of hypothetical scenario analysis strategy 4 (TPT with SDM and EAS):	174

List of abbreviations

Abbreviation	Full term
AMR	Antimicrobial resistance
ART	Antiretroviral treatment
BDQ	Bedaquiline
BIA	Budget impact analysis
BPaL	Bedaquiline, pretomanid, and linezolid
BPaLM	Bedaquiline, pretomanid, linezolid, and moxifloxacin
BSL-3	Biosafety level 3
CEA	Cost-effectiveness analysis
DALY	Disability-adjusted life year
DALYs	Disability-adjusted life years
DR	Drug resistant
DR-TB	Drug-resistant tuberculosis
DSD	Differentiated service delivery
DST	Drug susceptibility testing
EAS	Enhanced adherence support
FQ	Fluoroquinolone
GDP	Gross domestic product
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GS	Genoscreen
HIV	Human immunodeficiency virus
HP	Rifapentine plus isoniazid
HR	Isoniazid plus rifampicin
Hr-TB	Isoniazid-resistant tuberculosis
ICER	Incremental cost-effectiveness ratio
INH	Isoniazid
LMIC	Low- and middle-income countries
LPA	Line probe assay
TBI	Tuberculosis infection
LTFU	Loss to follow-up
LZD	Linezolid
MDR	Multidrug resistant
MDR-TB	Multidrug-resistant tuberculosis
M. tuberculosis (Mtb)	*Mycobacterium tuberculosis*
mWRDs	WHO-recommended molecular diagnostics
NMB	Net monetary benefit

pDST	Phenotypic drug susceptibility testing
PICO	Population, Intervention, Comparison, Outcome
PLHIV	People living with HIV
PZA	Pyrazinamide
QALY	Quality-adjusted life year
RIF	Rifampicin
RR	Rifampicin resistant
RR-TB	Rifampicin-resistant tuberculosis
SDG	Sustainable Development Goal
SDM	Shared decision-making
SSA	Sub-Saharan Africa
TB	Tuberculosis
tNGS	Targeted next-generation sequencing
TPT	Tuberculosis preventive treatment
UN	United Nations
UNHLM	United Nations High-Level Meeting
UR	Uncertainty range
WHO	World Health Organization
WTP	Willingness to pay
XDR	Extensively drug resistant
XDR-TB	Extensively drug-resistant tuberculosis
6H	Six months of isoniazid

Chapter 1: Background

1.1 Introduction

Tuberculosis (TB) remains one of the most significant public health challenges globally despite being preventable and curable. The burden of TB is still substantial globally, where in 2024 an estimated 10.7 million people fell ill with TB, and 1.23 million people died from the disease, making it one of the top causes of death worldwide and the leading cause of death from a single infectious agent. (1) WHO have set an ambitious target to end the TB epidemic by 2035, which includes reducing TB deaths by 95%, TB incidence by 90%, and eliminating catastrophic costs for TB-affected households compared to 2015 levels. (2) To achieve these targets, an urgent concentrated action is required, on ensuring everyone with TB has access to high-quality diagnostic and preventive treatment. (3) As the diagnostic and preventive treatment are most needed for ending TB, they provide rationales for the economic evaluation presented in this thesis.

This chapter provides the background for the thesis, beginning with an overview of TB disease, including its pathogenesis and transmission, as well as drug-resistant TB (DR-TB) and TB infection (TBI). This is followed by the epidemiology of TB, DR-TB and TBI. The chapter finally outlines the WHO End TB Strategy and concludes by putting the three manuscripts of this thesis together and explaining how they contribute to ending TB.

1.2 Tuberculosis Disease

1.2.1 Pathogenesis and Transmission of Tuberculosis

Tuberculosis (TB) is one of the oldest diseases known to humankind (4), which is a communicable and airborne infection caused by bacillus *Mycobacterium tuberculosis (M.tuberculosis)*. (5)

Pulmonary TB is the common type of TB globally, but TB can affect almost any part of the body to cause extra-pulmonary TB. The transmission of TB occurs through the inhalation of infectious droplet nuclei, which contain viable bacilli. Following exposure to *M. tuberculosis*, individuals may clear the organism, develop TBI, or progress to active disease. (6) The early stages of infection involve bacterial uptake by alveolar macrophages followed by evasion of host immune responses and formation of granulomas. (7) In most immunocompetent individuals, the host immune system contains the bacilli but does not eliminate them, leading to TB infection.(8) The clinical spectrum of TB ranges from latent TB infection with no symptoms to active tuberculosis disease. (9) TB infection represents a state in which individuals harbour viable bacilli with no evidence of clinically manifest TB disease. (10) People with TB infection have no signs or symptoms of TB disease and are also not infectious, but they are at risk of developing TB disease and becoming infectious. Approximately 5–10% of individuals with TB infection will develop active disease during their lifetime, usually within the first 5 years after initial infection. (10,11) The risk of progressing to TB disease is significantly higher in certain populations, including young children, older adults, and individuals with Human Immunodeficiency virus (HIV), diabetes, malnutrition, or other immunosuppressive conditions. HIV coinfection dramatically increases both the risk of progression and the severity of disease. Globally, people with HIV are about 18 times more likely to develop TB disease than those without HIV infection. (10)

1.2.2 Drug-Resistant Tuberculosis (DR-TB) and diagnosis of DR-TB

DR-TB remains one of the most formidable obstacles to ending the TB epidemic. (12) WHO defines DR-TB as TB disease caused by a strain of *M.tuberculosis* complex that is resistant to any TB medicines. The extent of resistance against key anti-TB drug regimens classifies DR-TB. One

of the most important of these drugs is rifampicin (Rif), a bactericidal and sterilizing drug that allows shortening of treatment duration. (13) Multidrug-resistant TB (MDR-TB) is defined as TB disease caused by a strain of *M. tuberculosis* complex that is resistant to both Rif and isoniazid (Inh). In Rifampin-Resistant TB (RR-TB), the *M. tuberculosis* complex is resistant to rifampin and is treated with similar regimens to those with MDR-TB, regardless of INH resistance. (12,13) When there is resistance to INH but susceptibility to Rif, then it is called rifampicin-susceptible, isoniazid-resistant TB (Hr-TB). Similarly, pre-extensively drug-resistant TB (pre-XDR-TB) is considered when a strain of *M. tuberculosis* complex that is resistant to rifampicin (with or without resistance to isoniazid), and that is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin). When a strain of *M. tuberculosis* complex is resistant to rifampicin (with or without resistance to isoniazid), and that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin), and to at least one other "Group A" drug (bedaquiline or linezolid), then it is called extensively drug-resistant TB (XDR-TB). (12)

DR TB occurs through two main mechanisms: either through acquired resistance or directly through transmitted resistance. (14,15) Primary or transmitted resistance occurs when resistant strains are transmitted to a new host, and it is the main reason for RR/MDR incidence in high DR-TB burden countries. (13,16) Acquired or secondary resistance occurs through the acquisition of drug resistance mutations to one or more drugs believed to be linked with inadequate drug treatment of drug-susceptible strains, either caused by poor regimen selection, nonadherence or subtherapeutic drug concentration. (15,16)

Bacteriological confirmation is necessary to diagnose DR-TB and determine the appropriate treatment regimen formally. Detection of drug resistance requires bacteriological confirmation of TB and testing for drug resistance using rapid molecular tests, culture methods or sequencing technologies. Currently, WHO recommends molecular WHO-recommended Diagnostics (mWRDs) with the capacity to detect RR as an initial test for diagnosis of TB drug-resistance, followed by Line Probe Assay (LPA), phenotypic and genotypic drug susceptibility testing (DST) for detection of additional drug-resistance. (17) The molecular test used for initial diagnosis can provide rapid test results, but it can only detect rif. resistance caused by the most common mutations in the Rifampicin Resistance Determining Region (RRDR) of rpoB; while rare, Mtb strains with rif. Resistance-conferring mutations located outside the RRDR would be missed by this test. (18) Furthermore, this will only help to make the diagnosis of RR/MDR TB and further test needs to be done to identify the drug susceptibility of additional TB drugs used in the treatment of drug-resistant TB.

The current standard of care for DST for TB is being conducted using culture-based methods, which rely on either a liquid or solid culture. Unfortunately, this requires Biosafety Level 3 (BS3) laboratories; specialized reagents as well as cold-chain requirements; and may take 6-8 weeks for results, leading to delays and negative impacts on patient outcomes. (19) Phenotypic DST (pDST) is also not widely available for newer drugs. (20)

An alternative DST method includes LPAs, a family of DNA strip-based tests that detect mutations associated with drug resistance. The LPAs come in two forms: one for resistance to first-line drugs (INH and RIF) and another for fluoroquinolones and second-line injectable drugs. (18) The

advantages of LPAs are that they are highly effective at diagnosing tuberculosis, rifampicin resistance, isoniazid resistance, and MDR-TB; and they can detect samples within only a few hours. (17) This assay performs well on smear-positive samples, but poorly on smear-negative and scanty samples, and can serve as a rapid diagnostic tool, particularly in isoniazid mono-resistance cases of tuberculosis. (21) LPAs are quite laboratory and staff-intensive, requiring complex laboratory infrastructure and expensive equipment that is normally only available in reference laboratories. The sensitivity and specificity of LPA also vary according to the mutation prevalence in the area, as LPA target coverage is limited to the main mutations. (22)

There are novel diagnostics, such as targeted next-generation sequencing (tNGS), that offer the possibility of comprehensive resistance profiling in timeframes compatible with clinical decision-making. tNGS can detect resistance for first-line and second-line drugs, guide regimen selection, and reduce delays to effective therapy. (23) We identified that there have been no economic evaluations done on the use of tNGS for the diagnosis of DRTB while doing systematic review on cost and cost-effectiveness of tNGS. As economic evaluations of these tools are critical to inform decisions about national adoption and scale-up, chapter 2 of my thesis has looked into the cost-effectiveness of using tNG for the diagnosis of DRTB in high TB burden, low and middle-income countries

1.2.3 TB Infection and Treatment

Once infected with Mtb, most of the time, the adaptive immunity effectively contains the pathogen. (24) Successful infection depends on several factors, such as the proximity and duration of contact with TB disease individuals and the immune function of the host. (25) The state where active

bacteria not detectable, and the infected individual remains completely asymptomatic, then this state is referred to as TB infection. (26) The latency period duration varies, where a healthy individual can harbour TB infection for a lifetime, with reactivation occurring in a small fraction (5%-10%) often within the first 2 to 5 years following infection. (10,27)

There are various comorbidities and risk factors which are associated with increased risk of developing TB disease. Among them, People living with human immunodeficiency virus (PLHIV) are one of the most vulnerable risk groups. Those with HIV and latent TB co-infection have more than a 10-18 fold increased risk of developing TB disease, with an annual risk of 5-10% of developing TB. (28,29) As there is a chance of reactivation of TB infection into TB disease, TB infection is therefore a major reservoir for the incidence of TB disease, and TB preventive treatment (TPT) plays an important role in stopping this process. (27)

The main aim of TPT is to prevent progression to TB disease. WHO currently recommends TPT, which can reduce the TB reactivation rate by up to 60% to 90%. (10) WHO currently recommends 6 or 9 months of daily isoniazid (6H or 9H), or a 3-month regimen of weekly rifapentine plus isoniazid (3HP) or a 3-month regimen of daily isoniazid plus rifampicin (3HR) as the TPT option regardless of HIV status. WHO also recommends a 1-month regimen of daily rifapentine plus isoniazid (1HP) or a 4-month regimen of daily rifampicin (4R) as an alternative TPT regimen. (10) WHO strongly recommends TPT to PLHIV of all ages, all household contacts of people with TB disease (regardless of HIV status) and other people who are at risk, like those who are initiating anti-tumour-necrosis factor treatment, receiving dialysis, preparing for an organ or hematological transplant or who have silicosis. (10,30)

Despite clinical advantages of TPT, including a short-course rifapentine-based TPT regimen, adherence and implementation challenges persist.(31) Adherence remains a significant barrier to the effectiveness of TPT among PLHIV. Even when TPT is initiated, a considerable proportion of patients fail to complete the full course. (32–35)

One of the main reasons for this adherence challenge is that treatment and prevention programs in TB have been driven by a "one-size-fits-all" approach, which stands in conflict with the person-centred approach of TB care and does not reflect the needs of different groups.(36) To address these challenges, global health programs, especially in HIV care, have introduced the concept of Differentiated Service Delivery (DSD). (37) DSD is a person-centred approach that adapts how care is provided based on the needs and preferences of different groups, to improve access and uptake of care, reduce patient burden and costs, and use health system resources more efficiently, while maintaining high-quality care. (38,39) However, its application to TPT is still emerging. (40)DSD can include enhanced adherence support, such as bidirectional messaging and shared decision-making (SDM) between providers and patients. (24) Enhanced adherence support (EAS) interventions, including mobile short message services and voice call reminders, have demonstrated benefits for anti-retroviral treatment (ART) adherence. (41) Yet, evidence of their effect on TPT adherence and completion in PLHIV is scarce. (42) SDM is a core element of person-centred care where providers and patients jointly choose a regimen that aligns with clinical needs, preferences and daily realities. (43) The WHO People-Centred TB Care Framework emphasizes SDM as essential for improving treatment acceptability and completion. (44) Recent discrete choice experiment evidence among people living with HIV in Uganda shows that

preferences for TPT regimens vary widely, particularly regarding pill burden, dosing frequency, duration, and ART compatibility (Aschmann et al., 2024). This highlights the need for SDM to ensure individuals receive a regimen they are willing and able to complete. (45) Costing study and along with the cost-effectiveness of TPT in chapters 3 and 4 of this thesis, are critical to inform decisions national TB program and global policy makers on implementing different person centered cared at national and global level.

1.3 Global Epidemiology of TB

1.3.1 Burden and Trends in TB Epidemiology

Despite a decline in the TB incidence by 1.7% in 2024 compared to previous years, TB remains a major cause of both morbidity and mortality worldwide, with 10.7 million people falling ill with TB and 1.23 million dying from it. The net reduction in TB incidence was 12% from 2015 to 2024, falling short of the End TB strategy's milestones of a 50% reduction by 2025 and an 80% reduction by 2030. (1) The burden of TB is unevenly distributed across regions, with most TB cases seen in South-East Asia, the Western Pacific and Africa, which accounts for almost 85% of total TB cases globally. (1)

Among the ten million TB cases estimated by WHO, 5.8% were among PLHIV, with the highest proportion of cases occurring in the WHO African region. In 2024, among 1.23 million deaths caused by TB, 150,000 (19%) of these were in PLHIV. (1)

The burden of TB is particularly high in sub-Saharan Africa (SSA), where HIV co-infection amplifies risk and mortality. (46,47) Even though SSA only represent 14% of the global

population, it accounted for 24% of all incident cases in 2023 and 33% of deaths. (48) Eighteen of the 30 high-TB-burden countries are located in SSA, where the incidence rate exceeds 300-500 cases per 100,000 population, as shown in Fig. 1.1 sourced from the WHO Global TB report. (1) Out of these 18 countries, 16 countries also appear on the WHO high TB/HIV burden list, which highlights the strong overlap between the TB and HIV epidemic in the region and also underscores the role of HIV in driving TB incidence and mortality across SSA. (1)

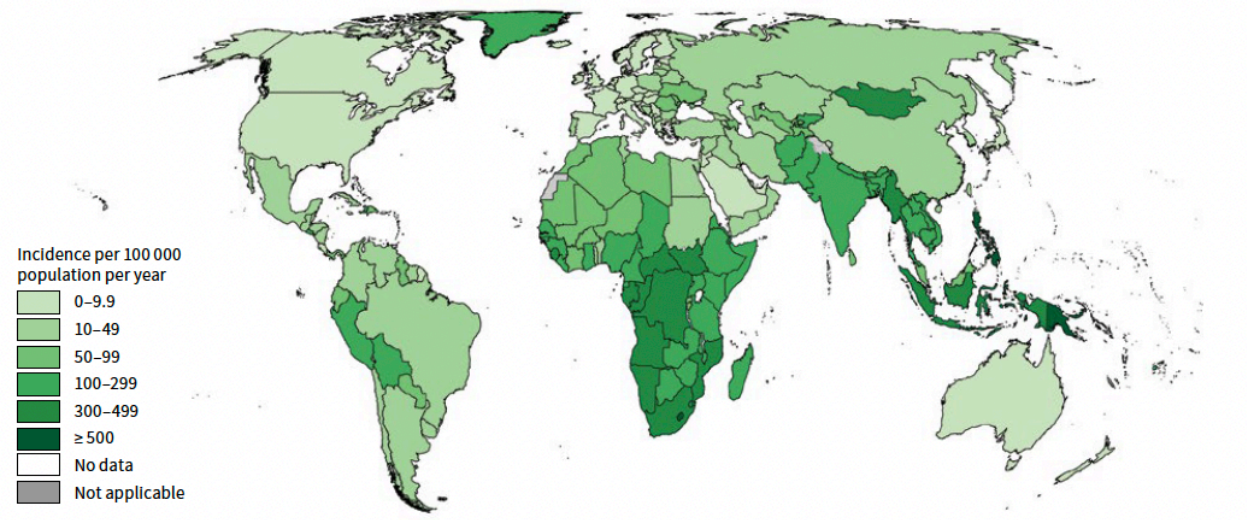


Figure 1.1: Estimated TB incidence rate at the country level, 2024
(Source: WHO Global TB report 2025)

1.3.2 Burden and Trends in DR-TB Epidemiology

As DR-TB continues to be a public health threat, with an estimated 390,000 people developing RR/MDR TB in 2024. (1) DR-TB is also recognized as one of the leading causes of death associated with antimicrobial resistance (AMR) globally. RR/MDR continues to cause a substantial number of deaths each year and remains one of the most significant contributors to the global AMR burden. In settings like SSA and certain parts of Asia, the mortality caused by DR TB exceeds that of most individual AMR pathogen drug combinations. (49) The proportion of RR/MDR among new cases was 3.2% and among previously treated cases was 16%. The burden

of MDR/RR-TB varies substantially between regions and across countries. The WHO estimates that India, China, the Philippines and the Russian Federation account for more than half of the global number of people estimated to have developed RR/MDR TB in 2024. (1) A modest progress was seen in the coverage of DST globally in 2024, where 83% of people diagnosed with bacteriologically confirmed TB cases were tested for RR, up from 62% in the pre-pandemic year of 2019. (1) This improvement is largely attributed to the expansion of mWRDs, which have the capacity to detect RR but do not detect resistance to other drugs used in TB treatment. (50) WHO have recommended new drug regimens that consist of bedaquiline, clofazimine, linezolid, pretomanid, and delamanid which are being used globally. (12,51) These regimens also have shorter duration for treating RR/MDR TB, Pre-XDR and XDR TB with better outcome compared to old regimens. (52) Therefore, it is of critical importance to have DST of these new drugs for the effective management and control of DR-TB.

There has been a decline of 7% among people with RR/MDR TB who were enrolled on treatment in 2024 compared to the previous year. Those 164,545 RR/MDR TB individuals also represent only 42% of estimated cases, indicating more than half of the individuals with DR-TB remain either undiagnosed or unlinked to appropriate care. (1) The main reason for this gap is incomplete coverage of DST, where many people with TB are not bacteriologically confirmed, and even among those, only a proportion undergo testing for RR. Even among those with established RR, most individuals do not receive DST for other first and second-line TB drugs, which results in delayed or suboptimal treatment with a treatment success rate of around 71% among those treated for RR/MDR TB. (1,52) Fluoroquinolone is an essential second-line drug to treat DR-TB, but its resistance is a major challenge, with resistance among RR/MDR TB being approximately 20%.

(53) There is also an emerging concern about bedaquiline and linezolid resistance (54), which highlights the need for a test which can provide universal DST of both first and second-line TB drugs without delay for a person with bacteriologically confirmed TB. (55) As discussed in section 1.2.2, current DST methods have several limitations, including DST for many new and repurposed drugs. In this context, tNGS offers an opportunity to transform DR-TB diagnosis by providing a comprehensive resistance profile that can guide effective treatment selection, which is important particularly in countries where DR-TB burden is high and DST capacity is constrained. tNGS represents a transformative approach to DR-TB diagnosis, bridging the gap between rapid molecular tests and comprehensive pDST. The technique combines multiplex PCR amplification with next-generation sequencing to simultaneously identify resistance-associated mutations across multiple genomic regions directly from clinical specimens. This enables concurrent susceptibility profiling for up to 16 anti-TB drugs including critical newer agents like bedaquiline, linezolid, and pretomanid in a fraction of the time required for culture-based methods.(56)

1.3.3 Epidemiology of TB Infection

TB infection represents the reservoir from which future TB disease cases arise, and therefore remains central to TB control. (27) It is estimated that roughly 23% of the global population have been infected with TB, which acts as a reservoir of 1.9 billion individuals. Around 80% of TB infection is prevalent in the WHO South-East Asia, Western-Pacific and Africa regions. (57,58) Sub-Saharan Africa has one of the highest burdens of TB infection in the world, with its prevalence as high as 49% in Uganda and 55.2% in South Africa. (59)

A 1% rise in TB infection prevalence is linked to an increase of 5.23 per 100,000 in TB incidence and 1.41 per 100,000 in TB mortality. (58) The risk of progression from TB infection to TB disease is elevated in SSA due to the high HIV epidemic in the region, which remains one of the dominant drivers of reactivation. Out of 18 high TB burden countries in the region, 16 are also classified by the WHO as high TB and HIV burden countries.(1) Because of this, there was an increase in incident TB cases in SSA by 25.6% and prevalence by 44.2% between 1990 and 2021. (60)

1.4 The WHO End TB Strategy and the role of novel diagnostic and preventive treatment

1.4.1 WHO End TB strategy: Pillars and Targets

In 2014, the WHO and United Nations member states committed to ending TB by 2035, by adopting the WHO End TB Strategy, which aligned with Sustainable Development Goals (SDGs). (61) The strategy set bold targets in TB incidence and mortality relative to 2015 baseline levels. The strategy aims for a 50% reduction in TB incidence and 75% reduction in TB deaths by 2025. An 80 % incidence reduction and 90% mortality reduction by 2030, and 90% incidence reduction and 95% mortality reduction by 2035 (Table 1.1).

Table 1.1: WHO End TB strategy milestones and targets for 2020-2025

Indicator	Milestones		Targets	
			SDG	End TB
	2020	2025	2030	2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20%	50%	80%	90%
TB-affected families facing catastrophic costs due to TB (%)	0%	0%	0%	0%

These targets are to be achieved through three core pillars (Figure 1.2):(2,62)

Pillar 1-Integrated patient-centred care and prevention, which emphasizes early detection, universal DST, treatment of all, access to preventive treatment and putting patients at the heart of service delivery.

Pillar 2- Bold policies and a supportive system, which calls for strong government commitment, multisectoral collaboration, and social protection to remove barriers to TB cases.

Pillar 3-Intensifies research and innovation, prioritizes the development and uptake of new tools (diagnostics, drugs, vaccines) to break the trajectory of the TB epidemic and achieve the target.

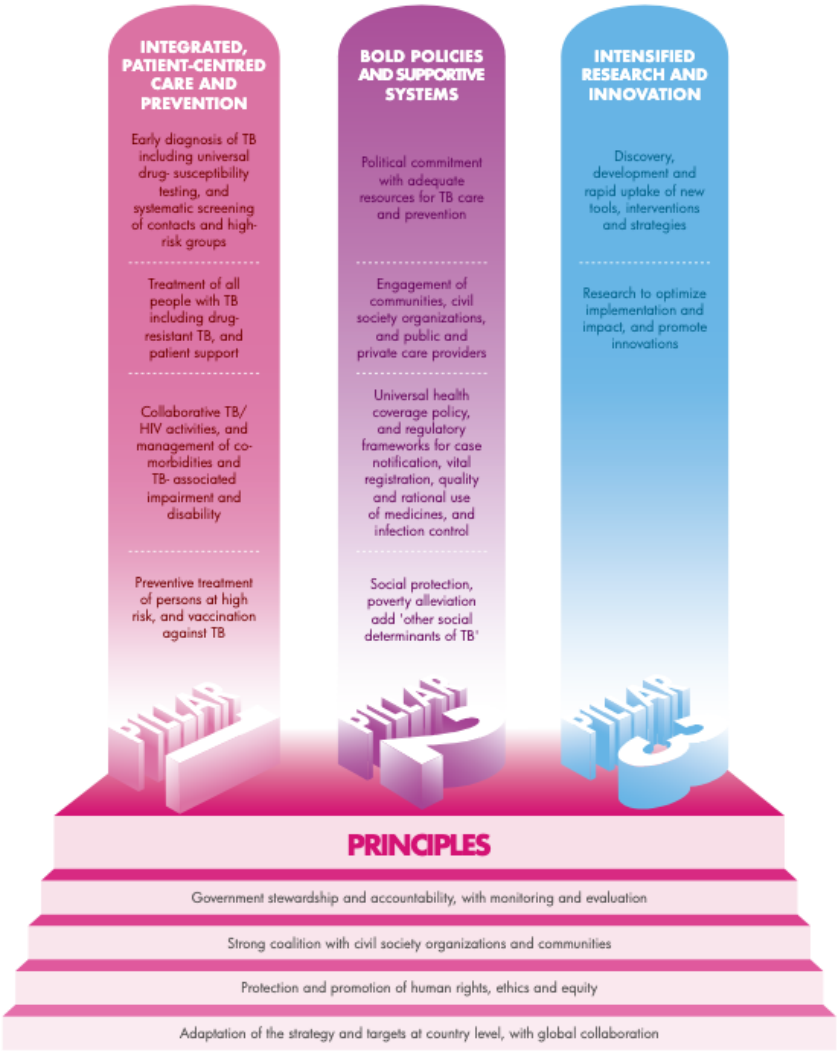


Figure 1.2: The WHO End TB Strategy:

It is structured around three core pillars, supported by four foundational principles that emphasize government accountability, community engagement, equity, and global collaboration. This framework guides global efforts to end TB as a public health threat by 2035. (Source: WHO End TB Strategy (62)).

To achieve the End TB goals and ensure political commitment, there was a United Nations High-Level meeting on TB (UNHLM) held in 2018 and in 2023, which included the commitments and targets. The targets were for the coverage of rapid diagnostic testing, TB treatment, TPT, health and social benefits for people with TB, funding, TB research and availability of TB vaccine. The commitment was also made in terms of addressing the crisis of DR-TB by working towards achieving universal, equitable and affordable access to WHO-recommended diagnostic and DST. (63). The global target set in 2023 by 2027 included 100% coverage of rapid diagnostic test, 90% of people with TB to be diagnosed and treated, and provide TPT to up to 45 million people globally in the 5 years 2023–2027: up to 30 million household contacts of people with TB and up to 15 million people living with HIV. (1)

1.4.3 Addressing social determinant and the SDGs to End TB

The global strategy to eliminate TB cannot rely solely on biomedical interventions; it requires a concerted effort to address the social determinants of health (SDOH) that sustain the epidemic. This multisectoral necessity is included within the United Nations Sustainable Development Goals (SDGs), where eliminating the TB epidemic by 2030 is established under SDG Target 3.3.(64) However, achieving this health target is fundamentally interdependent with progress across several non-medical SDGs. Specifically, TB transmission is directly mitigated by actions targeting SDG 1 (No Poverty) through expanded social protection, SDG 2 (Zero Hunger) by eradicating undernutrition, a primary driver of host susceptibility, and SDG 11 (Sustainable Cities and Communities) through the mitigation of overcrowded, poorly ventilated housing.(65,66)

Consequently, the WHO End TB Strategy positions structural development frameworks as core requirements to reduce global TB incidence and shield vulnerable populations from catastrophic health-related costs.

1.4.4 Global progress toward End TB targets

As per WHO, the global progress towards the end TB milestones and targets is mostly off track, where TB incidence and mortality are declining slowly to meet the 2025 milestones globally and in most parts of the world. As of 2024, the global TB incidence had declined by only about 12% since 2015, which is far short of the 50% reduction milestone set for 2025. Similarly, the TB mortality had decreased by approximately 29% which is also behind the 75% target. The goal of eliminating catastrophic costs also remains unmet, with nearly 50% of households still facing financial hardship (Figure 1.3). (1)

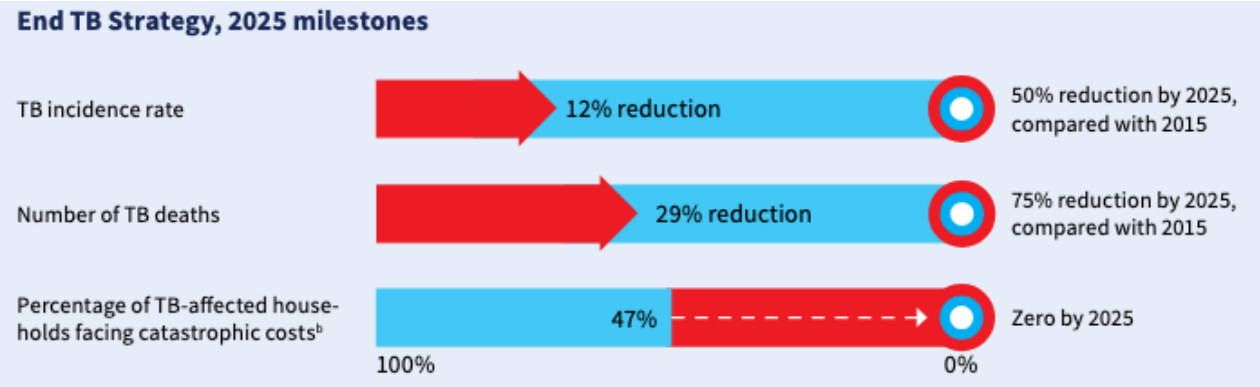


Figure1.3: End TB strategy target and latest status of progress
(Source: Global TB report, 2025)

A similar finding was observed when looking against the 2023 UNHLM targets, where global efforts remain insufficient to meet the 2027 goals, particularly in TB diagnosis and preventive treatment. (Figure 1.4). (1) As of 2023, only 54% of the people diagnosed with TB were using

mWRDs, which is far from the 100% target. Similarly, the coverage of TPT lags behind the commitments, where only 58% of PLHIV and 25% of the household contacts received TPT compared to 90% target set for both groups. There is a huge shortfall in the funding for access to TB prevention, diagnosis, treatment and care compared to the target which has further constrained the implementation of TB program. TB care received only US$ 5.9 billion in 2023 against a goal of US$ 22 billion annually by 2027, and TB research funding remains less than one-quarter of the US$ 5 billion target. (1) These funding shortfalls not only threaten the achievement of diagnostic and prevention goals but also highlight the urgency of identifying value-for-money interventions where using cost-effectiveness analyses are essential to guide national programs and global donors in prioritizing novel diagnostic and preventive treatment that can accelerate progress toward the End TB targets.(67)

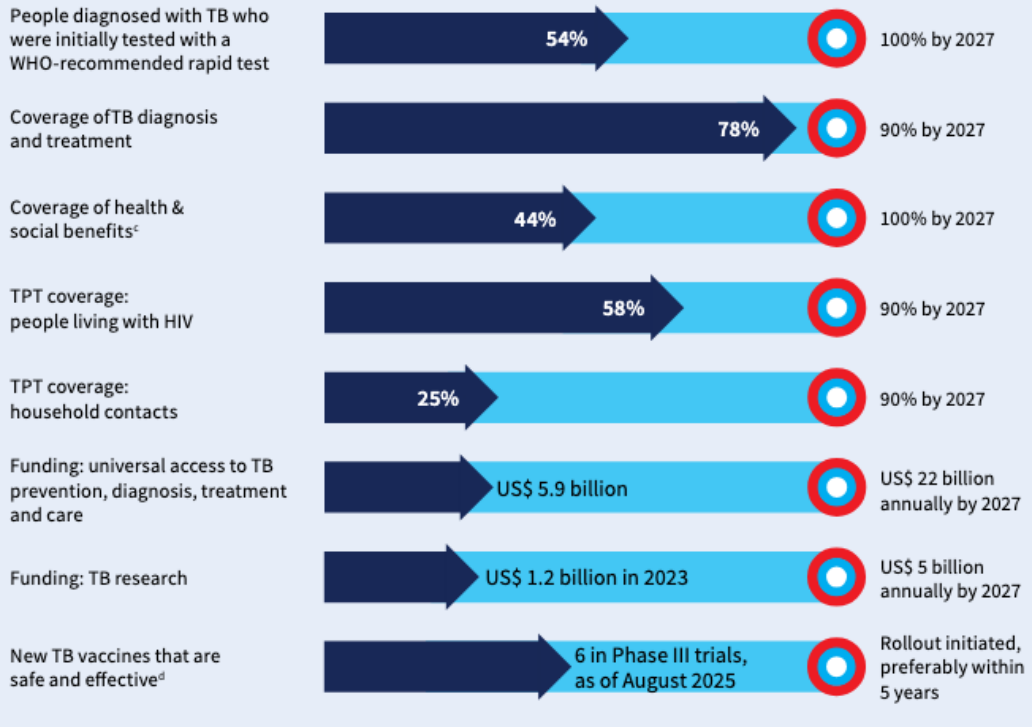


Figure 1.4: 2023 UN high-level meeting on TB, its target and progress
(Source: Global TB report, 2025)

The gap between End TB targets and current progress highlights the need for interventions that can accelerate both the detection of drug-resistant TB and the prevention of future disease through effective treatment of latent infection.

1.4.5 Role of tNGS and TB Preventive Treatment: Aligning with Strategy and HLM

Despite clear global commitments to end TB, the progress towards END TB targets continued to be constrained due to bottlenecks across the TB care and prevention cascades. Previous sections have highlighted constraints on incomplete DST beyond rifampicin, leading to delayed diagnosis and persistent shortfalls in TPT initiation and completion among eligible populations. These constraints have directly challenged the goal of the WHO End TB strategy and UNHLM, which emphasize universal access to comprehensive diagnosis, timely treatment and large-scale preventive therapy.

Among the range of interventions required to achieve the global targets, tNGS for the diagnosis and DST together with TPT are especially well aligned with the End TB strategy and 2023 UNHLM priorities. These interventions directly support core policy objectives, including rapid testing, access to care and prevention of future TB disease through treatment of TB infection. Implementing novel diagnostics like tNGS alongside TPT regimens like 3HP delivered with adherence support are necessary strategies for accelerating progress and bending the curve of the TB epidemic.

tNGS and End TB strategy:

tNGS provides an in-depth analysis of specific genome sequences and would be able to detect a large variety of pathogens and DR genes in the clinical setting and guiding the appropriate selection of antimicrobial drugs. (68) tNGS can provide rapid DST of drugs used to treat both DS

and DR-TB by amplifying multiple regions of the *M tuberculosis* genome and can predict drug resistance to many tuberculosis drugs simultaneously.(69) This technology has the potential to revolutionize TB diagnosis and aligns strongly with the End TB strategy Pillar 1, which includes early diagnosis with universal DST. (62) It also supports Pillar 3, which is research and innovation, where introducing tNGS can be an innovative strategy to end the DR-TB epidemic. As DR-TB had been a significant obstacle to reaching the End TB mortality and incidence goal, by enabling faster identification of DR-TB, tNGS can help reduce DR-TB transmission, improve cure rate and lower TB mortality. Therefore, tNGS can be a powerful tool to improve TB care and control.

TPT and End TB strategy

Expanding preventive therapy for people at high risk of developing TB is a core component of Pillar 1 (integrated prevention) and is supported by Pillar 2 (policy commitment to expand access). With roughly a quarter of the world's population being infected with TB infection, to end TB is not enough to treat TB disease, but also needs to prevent new cases by treating latent infection. The End TB strategy also mentions use of safer and more effective treatment for latent TB infection by 2025 to reduce new TB incidence. (70) The uptake of TPT has been slow, because of which in 2023 UNHLM have also made TPT scale-up a top priority by setting an ambitious goal of reaching 90% of those at risk with preventive treatment by 2027. (1) TPT is one of the most important elements to achieving the steep reduction in the incidence envisioned in the End TB strategy. A modelling study has shown that to decrease the incidence of TB to the level envisioned by the End TB strategy, TB efforts should expand beyond the TB treatment cascade to a comprehensive strategy incorporating TB prevention as well. This modeling analysis in the context of WHO South-East Asian region, which is one of the high TB burden regions, it is estimated that full uptake

of WHO WHO-recommended TPT among the eligible population could reduce TB incidence in 2030 by an additional 8.3% relative to baseline. (71) TPT is therefore a critical component of the multi-pronged approach, like better diagnostic treatment and a hopeful vaccine to reach the End TB target (Figure 1.5).

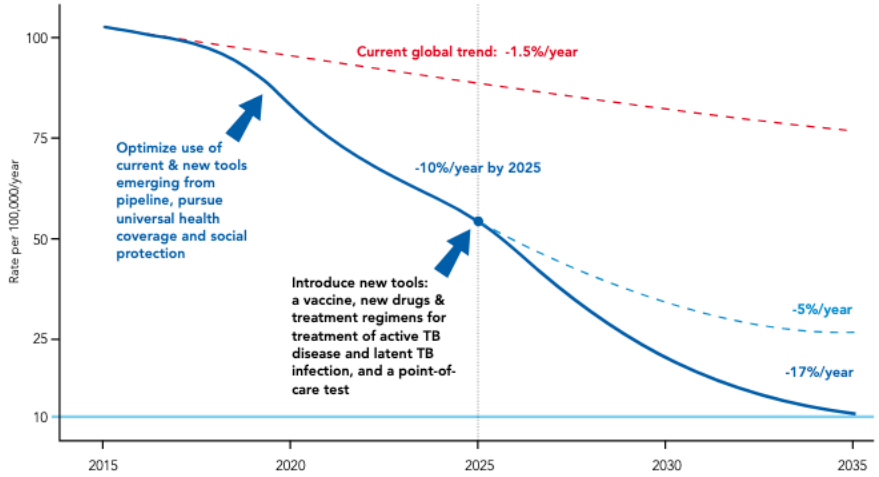


Figure 1.5: Projected TB incidence reduction under the WHO End TB strategy: Required Vs Current trend 2015-2035
(Source: WHO End TB Strategy)

In conclusion, tNGS and TPT are vital complementary tools in the fight to end TB, which embodies the core pillars of the End TB strategy, and the priorities set in the 2023 UN High-Level meeting. tNGS can accelerate and improve DR TB diagnosis, which aligns with the universal DST and innovation agenda of the End TB strategy. TPT, on the other hand, attacked the epidemic source by preventing future cases and supports the prevention target and the goal of steep TB incidence decline.

Although novel diagnostics and tuberculosis preventive treatment are central to achieving End TB targets, their large-scale implementation requires substantial investment, underscoring the importance of economic evaluation to inform efficient and sustainable decision-making.

1.5 Rationale for Economic Evaluation in TB

1.5.1 Global funding scenario and economic burden of TB

Ending TB requires adequate funding for TB prevention, diagnostics, and treatment and should be sustained over many years. Contrary to this, funding for TB remains inadequate at both global and country levels compared to the scale of the TB epidemics. Despite renewed commitments of mobilizing US$22 billion annually by 2027 in the 2023 UNHLM, only US$5.9 billion was available for 2023, which is barely a quarter of the target (Figure 4). (1) This shortfall has been further impacted by recent U.S. foreign aid cuts, which have threatened essential TB service delivery, including diagnostics, treatment and research initiatives which are critical to end TB. (72) As international donor funding remains crucial in many countries for the TB program, such a reduction risks slowing or even reversing progress towards the End TB strategy target. (72,73) Low and middle-income countries (LMICs) bear 99% of the global TB burden and dominate TB financial needs. Trends in recent years have shown that the TB funding in LMICs has been stagnant and remains short of what is needed. In 2024, the total funding available in LMICs was US$5.9 billion, which is just 27% of the global target of US$22 billion annually. The funding for the TB program is split between domestic and external funding. In 2024, international donor funding accounted for 54% of the funding available in 26 high-TB-burden countries. However, international donor support has remained flat at US$1.1-1.2 billion per year since 2015. TB not only imposes a substantial economic burden on the health system but also on the affected individuals and their families. Several studies have shown that despite many countries offering free TB treatment, patients still incur high catastrophic costs. (74,75) The WHO reported that about 50% of TB affected households and 82% of DR-TB-affected households have experienced catastrophic cost (out-of-pocket expenses and income loss exceeding 20% of annual household

income) during the course of illness and treatment. In this context of uncertainty, any new investment, either for diagnostics or prevention, requires careful economic justification to ensure optimal resource allocation.

1.5.2 Importance of economic evaluation for efficient investment

Economic evaluation is being used increasingly to inform health policies. To ensure the best value for money spent in healthcare, economic considerations are gaining increasing prominence among governments worldwide. (76) Economic evaluation in health care can assess a health intervention's value for money, which will support optimal allocation of limited resources available for health care, which is also true for the TB program.(77) In the face of limited resources and an immense TB burden, economic evaluation like cost-effective analysis (CEA) is critical to guide efficient investment and prioritize high-impact interventions.

CEA is a systematic way to compare interventions (e.g. diagnostic tools, treatment or preventive strategies) in terms of their health outcomes and cost, helping to identify the options that yield the greatest health benefit per dollar spent. (78) Primary outcome captured in cost-utility analysis are benefit incurred by the intervention, which can be in terms of quality-adjusted life year (QALY) or disability-adjusted life year (DALY). QALYs is a measure that incorporates impact on both quantity and quality of life and is a traditional metric of evaluating CEA in a resource-rich setting. (79) DALYs, on the other hand, are the sum of years of life lost due to premature mortality and years lived with disability. (80) DALYs is also a preferred metric for use in resource-limited settings and is also being recommended by WHO to be used as a part of CEA. (81)

CEA had played a pivotal role in informing TB policy and decisions and in guiding WHO recommendations for TB diagnostics and treatment. WHO uses the GRADE (Grading of

Recommendations Assessment, Development and Evaluation) approach to assess the certainty of evidence and develop policy recommendations. Within GRADE's evidence-to-decision (EtD) framework, cost and cost-effectiveness are one of the core criteria considered alongside clinical effectiveness, equity, acceptability, and feasibility. (82,83) This emphasis on cost-effectiveness is evident in recent WHO guidelines on TB diagnosis and treatment, which recommend the use of molecular mWRDs for initial TB testing, and endorse novel, shorter all-oral regimens (such as BPaL and BPaLM) for drug-resistant TB, both supported by formal economic evaluations reviewed as part of the WHO GRADE-based guideline process. (12,84) In summary, applying health economic evaluations in TB policy helps ensure that limited resources are allocated efficiently, guiding the adoption of interventions, whether it is novel diagnostics like tNGS or preventive treatment with enhanced adherence support that provides the greatest health benefit for the investment.

1.5.3: Gap in economic evidence around implementation of tNGS and TPT with person-centered care

While the use of economic evidence in TB control has grown, there remains a critical gap in the literature for tNGS and TPT that needs to be addressed to inform future policy and research.

- **Gap in economic evidence around use of tNGS for DST:** Before undertaking this study, we conducted a systematic review on the economic evaluation of using tNGS to diagnose DR-TB. Our search, conducted on Aug 14, 2024, included databases such as PubMed, EMBASE, and SCOPUS, without restrictions on publication year, age group, country, income level, comparator group, HIV status, or other comorbidities. The search revealed

no CEA specifically focused on the use of tNGS for the diagnosis of DR-TB. Hence, this study is the first CEA on tNGS for the detection of DR TB in low and middle-income countries.

- **Scarcity of real-world cost data for implementing TPT in SSA**: Although TB preventive therapy is strongly recommended and multiple cost-effectiveness analyses indicate it is beneficial, there is a notable lack of empirical cost and programmatic data on large-scale TPT implementation in high-burden, low-resource settings. Cost analyses are crucial in this context, providing detailed insights into the financial resources required to implement and sustain TPT programs at scale. Existing studies, such as those from the Value TB project, have provided valuable frameworks for estimating the costs of tuberculosis care and prevention, including cost categories like diagnostics, treatment, and program management. These analyses help guide resource allocation decisions but often focus on general TB services.(85) In particular, these resources do not fully address the specific costs associated with scaling up newer TPT regimens, particularly in sub-Saharan Africa, where the burden of TB and HIV is greatest. While studies like the CaP-TB initiative (86) have examined the costs of child-focused TPT programs across several African countries, and others (87–90) have assessed the cost-effectiveness of specific regimens like 6H, 3HP and 1HP, comprehensive cost data for implementing these regimens at scale are still lacking. This gap poses challenges for national TB programs, donors, and stakeholders, who need precise cost estimates to optimize TPT delivery and ensure financial sustainability. In sub-Saharan Africa, where health systems are often under-resourced, and the economic burden

of TB and HIV is substantial, understanding these costs is essential for avoiding additional strain on existing systems.(91)

- **Absence of CEA studies evaluating TPT combined with shared decision making and enhanced adherence support:** As explained in section 1.2.3, incorporating DSD principles like EAS and SDM into TPT programmes can offer a practical strategy to overcome adherence barriers and improve outcomes for PLHIV and reduce TB incidence. However, implementing these approaches requires additional resources for training, support, and delivery adaptations. The cost-effectiveness of TPT programs incorporating EAS and/or SDM has not yet been established, particularly in high-burden, resource-limited settings. Existing CEAs of 3HP in sub-Saharan Africa show it can be cost-effective, but most omit comprehensive programme and patient costs, and do not incorporate DSD principles like EAS or SDM, reducing real-world policy relevance. (87,89,92,93)

Addressing these evidence gaps is essential for informing national and global TB policies, providing the foundation for the research objectives of this thesis.

1.6 Rationale for This Thesis

This thesis addresses critical evidence gaps in the economic evaluation of TB diagnostics and preventive treatment interventions, contributing directly to the goals of the WHO End TB Strategy. It brings together three complementary studies that evaluate tNGS for DR-TB diagnosis, TPT implementation in sub-Saharan Africa, and enhanced adherence support models for TPT, using health economic methodologies.

1.6.1 Manuscript 1: Evaluate the cost-effectiveness of using tNGS for the diagnosis of DR-TB in low and middle-income countries with a high burden of TB

To our knowledge, this study is the first to conduct a cost-effectiveness analysis of tNGS for the detection of DR-TB in LMICs. It provides essential economic evidence that has informed the WHO in making recommendations regarding the adoption of this novel diagnostic tool. This study highlights the potential of tNGS to improve patient outcomes and offers valuable insights into its cost-effectiveness in diverse healthcare settings.

1.6.2 Manuscript 2: Estimate real-world cost of TPT Delivery Across Five Sub-Saharan African Countries with high TB and HIV

Despite global policy support, the scale-up of TPT has been constrained by a lack of reliable cost data. This multi-country study fills a major gap by generating empirical implementation cost estimates across five high-TB burden sub-Saharan African countries. The findings inform programmatic planning and budget forecasting for national TB programs and global partners aiming to expand preventive treatment.

1.6.3 Manuscript 3: Evaluate the cost-effectiveness of TPT provided with SDM and EAS in Sub-Saharan Africa

TPT initiation and adherence remains the weakest link in TPT delivery, with high drop-off rates undermining effectiveness. This study evaluates a person-centred intervention combining shared decision-making and enhanced adherence support. It is the first economic evaluation of such a model for TPT, providing critical data on its potential health and economic value in improving completion rates and long-term impact.

1.6.4 Overall Thesis Contribution

This thesis provides a structural rationale for TB control rooted in health economics. In high-burden, resource-limited settings, the lack of affordable diagnostics and rigid treatment delivery systems acts as an institutional barrier, trapping vulnerable populations in cycles of delay and default. By evaluating the cost-effectiveness of tNGS and different TPT delivery methods, this research provides the economic evidence needed to optimise resource allocation, supporting SDG Target 3.3, health equity (SDG 10), and protection from catastrophic costs (SDG 1).Together, these three studies provide a cohesive and timely evaluation of innovative diagnostic and preventive strategies aligned with the End TB Strategy. They offer evidence to guide investment, implementation, and scale-up decisions in resource-constrained, high-burden settings. Each study applies rigorous and consistent economic evaluation methods which includes cost-effectiveness analysis with Markov modelling, and real-world costing ensuring comparability and practical relevance for global and national TB policy.

1.7 References:

1. 2025 tuberculosis Global report.
2. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new end TB strategy. The Lancet. 2015. doi:10.1016/S0140-6736(15)60570-0
3. Floyd K, Glaziou P, Houben RMGJ, Sumner T, White RG, Raviglione M. Global tuberculosis targets and milestones set for 2016–2035: definition and rationale. The International Journal of Tuberculosis and Lung Disease. 2018 Jul 1;22(7):723. doi:10.5588/IJTLD.17.0835 PubMed PMID: 29914597.
4. Bos KI, Harkins KM, Herbig A, Coscolla M, Weber N, Comas I, et al. Pre-Columbian mycobacterial genomes reveal seals as a source of New World human tuberculosis. Nature. 2014;514(7253). doi:10.1038/nature13591
5. Pallett S, Houston A. Tuberculosis.
6. Flynn JL, Chan J. Tuberculosis: Latency and Reactivation. Infect Immun. 2001;69(7):4195. doi:10.1128/IAI.69.7.4195-4201.2001 PubMed PMID: 11401954.
7. Lin PL, Flynn JL. Understanding Latent Tuberculosis: A Moving Target. J Immunol. 2010 Jul 1;185(1):15. doi:10.4049/JIMMUNOL.0903856 PubMed PMID: 20562268.
8. Heemskerk D, Caws M, Marais B, Farrar J. Pathogenesis [Internet]. 2015 [cited 2025 Nov 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK344406/
9. Pai M, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC, et al. Tuberculosis. Nat Rev Dis Primers. 2016 Oct 27;2. doi:10.1038/NRDP.2016.76 PubMed PMID: 27784885.
10. WHO. WHO consolidated guidelines on tuberculosis. Module 1: Prevention. Infection prevention and control. WHO. 2022.
11. Vynnycky E, Fine PEM. Lifetime risks, incubation period, and serial interval of tuberculosis. Am J Epidemiol. 2000;152(3). doi:10.1093/aje/152.3.247
12. Who. WHO consolidated guidelines on tuberculosis. Module 4: Treatment and care.
13. Farhat M, Cox H, Ghanem M, Denkinger CM, Rodrigues C, Abd MS, et al. Drug-resistant tuberculosis: a persistent global health concern. Nature Reviews Microbiology |. 2024;22:617–35. doi:10.1038/s41579-024-01025-1
14. Liebenberg D, Gordhan BG, Kana BD. Drug resistant tuberculosis: Implications for transmission, diagnosis, and disease management. Front Cell Infect Microbiol. 2022 Sep 23;12:943545. doi:10.3389/FCIMB.2022.943545 PubMed PMID: 36211964.

15. Kempker RR, Kipiani M, Mirtskhulava V, Tukvadze N, Magee MJ, Blumberg HM. Acquired Drug Resistance in Mycobacterium tuberculosis and Poor Outcomes among Patients with Multidrug-Resistant Tuberculosis. Emerg Infect Dis. 2015;21(6):992. doi:10.3201/EID2106.141873 PubMed PMID: 25993036.
16. Dookie N, Rambaran S, Padayatchi N, Mahomed S, Naidoo K. Evolution of drug resistance in Mycobacterium tuberculosis: a review on the molecular determinants of resistance and implications for personalized care. J Antimicrob Chemother. 2018 May 1;73(5):1138–51. doi:10.1093/JAC/DKX506 PubMed PMID: 29360989.
17. World Health Organization (WHO). Operational handbook on tuberculosis Module 3 Diagnosis Updated 2021. Module 3: Diagnosis Rapid diagnotsics for tuberculosis diagnosis. 2021.
18. Koch A, Cox H, Mizrahi V. Drug-resistant tuberculosis: challenges and opportunities for diagnosis and treatment. Curr Opin Pharmacol. 2018 Oct 1;42:7–15. doi:10.1016/j.coph.2018.05.013 PubMed PMID: 29885623.
19. Hepple P, Novoa-Cain J, Cheruiyot C, Richter E, Ritmeijer K. Implementation of liquid culture for tuberculosis diagnosis in a remote setting: Lessons learned. International Journal of Tuberculosis and Lung Disease. 2011;15(3).
20. Tiberi S, Utjesanovic N, Galvin J, Centis R, D'Ambrosio L, van den Boom M, et al. Drug resistant TB – latest developments in epidemiology, diagnostics and management. International Journal of Infectious Diseases. 2022. doi:10.1016/j.ijid.2022.03.026
21. Ninan MM, Gowri M, Christopher DJ, Rupali P, Michael JS. The diagnostic utility of line probe assays for multidrug-resistant tuberculosis. Pathog Glob Health. 2016;110(4–5). doi:10.1080/20477724.2016.1214350
22. Nguyen TNA, Berre VA Le, Bañuls AL, Nguyen TVA. Molecular diagnosis of drug-resistant tuberculosis; A literature review. Front Microbiol. 2019;10(MAR). doi:10.3389/fmicb.2019.00794
23. Behjati S, Tarpey PS. What is next generation sequencing? Arch Dis Child Educ Pract Ed. 2013;98(6). doi:10.1136/archdischild-2013-304340
24. Liu Q, Que S, Qiu Y, Tang M, Liu S, Yang G, et al. Host Immune Response to Mycobacterium tuberculosis Infection: Implications for Vaccine Development [Internet]. 2025. doi:10.2147/JIR.S517034

25. Urbanowski ME, Ordonez AA, Ruiz-Bedoya CA, Jain SK, Bishai WR. Cavitary tuberculosis: the gateway of disease transmission. Lancet Infect Dis. 2020 Jun 1;20(6):e117–28. doi:10.1016/S1473-3099(20)30148-1 PubMed PMID: 32482293.
26. Haldar P. The Natural History of TB Latent Infection. Tuberculosis in Clinical Practice. 2021 Jan 1;1–14. doi:10.1007/978-3-030-75509-6_1/FIGURES/3
27. Kiazyk S, Ball TB. Latent tuberculosis infection: An overview. Can Commun Dis Rep. 2017;43(3). doi:10.14745/ccdr.v43i34a01
28. Selwyn PA, Hartel D, Lewis VA, Schoenbaum EE, Vermund SH, Klein RS, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med. 1989 Mar 2;320(9):545–50. doi:10.1056/NEJM198903023200901 PubMed PMID: 2915665.
29. Sadirova D, Grigoryan R, Parpieva N, Barotova V, Trubnikov A, Kalandarova L, et al. Incidence Rate and Risk Factors for Tuberculosis among People Living with HIV: A 2015–2017 Cohort from Tashkent, Uzbekistan. Int J Environ Res Public Health. 2021 Jun 1;18(11):5746. doi:10.3390/IJERPH18115746 PubMed PMID: 34071899.
30. Who. WHO operational handbook on tuberculosis Tuberculosis preventive treatment Second edition. 2020.
31. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16(11). doi:10.1016/S1473-3099(16)30216-X
32. Reddy MM, Thekkur P, Ramya N, Kamath PBT, Shastri SG, Kumar RBN, et al. To start or to complete?–Challenges in implementing tuberculosis preventive therapy among people living with HIV: a mixed-methods study from Karnataka, India. Glob Health Action. 2020;13(1). doi:10.1080/16549716.2019.1704540
33. Pathmanathan I, Ahmedov S, Pevzner E, Anyalechi G, Modi S, Kirking H, et al. TB preventive therapy for people living with HIV: Key considerations for scale-up in resource-limited settings. International Journal of Tuberculosis and Lung Disease. 2018. doi:10.5588/ijtld.17.0758
34. Gunde L, Wang A, Payne D, O'connor S, Kabaghe A, Kalata N, et al. Characteristics of TPT initiation and completion among people living with HIV. IJTLD Open. 2024;1(1). doi:10.5588/ijtldopen.23.0194

35. Bastos ML, Melnychuk L, Campbell JR, Oxlade O, Menzies D. The latent tuberculosis cascade-of-care among people living with HIV: A systematic review and meta-analysis. PLoS Med. 2021;18(9). doi:10.1371/journal.pmed.1003703
36. Makone A, Angami K, Bhattacharya D, Frick M, Castillo JG, Herrera R, et al. One size does not fit all: community views on choices for TB treatment and prevention. Public Health Action. 2023;13(3). doi:10.5588/pha.23.0034
37. Mavhu W, Willis N, Mufuka J, Bernays S, Tshuma M, Mangenah C, et al. Effect of a differentiated service delivery model on virological failure in adolescents with HIV in Zimbabwe (Zvandiri): a cluster-randomised controlled trial. Lancet Glob Health. 2020;8(2). doi:10.1016/S2214-109X(19)30526-1
38. Tran CH, Moore BK, Pathmanathan I, Lungu P, Shah NS, Oboho I, et al. Tuberculosis treatment within differentiated service delivery models in global HIV/TB programming. Journal of the International AIDS Society. 2021. doi:10.1002/jia2.25809
39. WHO. Updated recommendations on service delivery for the treatment and care of people living with HIV. World Health Organisation Guidelines. 2021.
40. Mugenyi L, Namuwenge PM, Ouma S, Bakashaba B, Nanfuka M, Zech J, et al. Isoniazid preventive therapy completion between July-September 2019: A comparison across HIV differentiated service delivery models in Uganda. PLoS One. 2024;19(1 January). doi:10.1371/journal.pone.0296239
41. Amankwaa I, Boateng D, Quansah DY, Akuoko CP, Evans C. Effectiveness of short message services and voice call interventions for antiretroviral therapy adherence and other outcomes: A systematic review and meta-analysis. PLoS One. 2018;13(9). doi:10.1371/journal.pone.0204091
42. Lester R, Park JJ, Bolten LM, Enjetti A, Johnston JC, Schwartzman K, et al. Mobile phone short message service for adherence support and care of patients with tuberculosis infection: Evidence and opportunity. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2019. doi:10.1016/j.jctube.2019.100108
43. Land V, Parry R, Seymour J. Communication practices that encourage and constrain shared decision making in health-care encounters: Systematic review of conversation analytic research. Health Expectations. 2017. doi:10.1111/hex.12557

44. People-centred framework for tuberculosis programme planning and prioritization User guide.
45. Aschmann HE, Musinguzi A, Kadota JL, Namale C, Kakeeto J, Nakimuli J, et al. Preferences of people living with HIV for features of tuberculosis preventive treatment regimens in Uganda: a discrete choice experiment. J Int AIDS Soc. 2024;27:26390. doi:10.1002/jia2.26390/full
46. 2024 Global tuberculosis report.
47. Shah GH, Ewetola R, Etheredge G, Maluantesa L, Waterfield K, Engetele E, et al. Risk factors for tb/hiv coinfection and consequences for patient outcomes: Evidence from 241 clinics in the Democratic republic of Congo. Int J Environ Res Public Health. 2021;18(10). doi:10.3390/ijerph18105165
48. Li S, Mensah E, Liu M, Pan L, Lu W, Zhou S, et al. The burden of tuberculosis and drug resistance in 22 Sub-Saharan African countries, 1990–2021: a GBD 2021 analysis and progress towards WHO 2035 targets with projections to 2050. Front Microbiol. 2025 Nov 17;16:1695592. doi:10.3389/FMICB.2025.1695592
49. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet. 2022 Feb 12;399(10325):629–55. doi:10.1016/S0140-6736(21)02724-0 PubMed PMID: 35065702.
50. Saktiawati AMI, Vasiliu A, Saluzzo F, Akkerman OW. Strategies to Enhance Diagnostic Capabilities for the New Drug-Resistant Tuberculosis (DR-TB) Drugs. Pathogens. 2024 Dec 1;13(12):1045. doi:10.3390/PATHOGENS13121045 PubMed PMID: 39770305.
51. World Health Organization. WHO Consolidated Guidelines on Tuberculosis. Module 4: Treatment - Drug-Resistant Tuberculosis Treatment, 2022 Update. WHO Press. 2022.
52. Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, Ngubane N, et al. Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis. New England Journal of Medicine. 2022 Sep 1;387(9):810–23. doi:10.1056/NEJMOA2119430;PAGEGROUP:STRING:PUBLICATION PubMed PMID: 36053506.

53. Jung S. Targeted Next-Generation Sequencing in Drug-Resistant Tuberculosis: WHO Guidance and Practical Implementation Priorities. Biomedicines. 2026 Jan 2;14(1):93. doi:10.3390/BIOMEDICINES14010093 PubMed PMID: 41595629.
54. Nehru VJ, Jose Vandakunnel M, Brammacharry U, Ramachandra V, Pradhabane G, Mani BR, et al. Risk assessment and transmission of fluoroquinolone resistance in drug-resistant pulmonary tuberculosis: a retrospective genomic epidemiology study. Scientific Reports 2024 14:1. 2024 Aug 24;14(1):19719-. doi:10.1038/s41598-024-70535-y PubMed PMID: 39181942.
55. Use of targeted next-generation sequencing to detect drug-resistant tuberculosis. 2023.
56. Naidoo K, Perumal R, Ngema SL, Shunmugam L, Somboro AM. Rapid Diagnosis of Drug-Resistant Tuberculosis–Opportunities and Challenges. Pathogens. 2023 Jan 1;13(1):27. doi:10.3390/PATHOGENS13010027 PubMed PMID: 38251335.
57. Houben RMGJ, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLoS Med. 2016 Oct 1;13(10). doi:10.1371/JOURNAL.PMED.1002152 PubMed PMID: 27780211.
58. Ding C, Hu M, Guo W, Hu W, Li X, Wang S, et al. Prevalence trends of latent tuberculosis infection at the global, regional, and country levels from 1990–2019. International Journal of Infectious Diseases. 2022 Sep 1;122:46–62. doi:10.1016/J.IJID.2022.05.029 PubMed PMID: 35577247.
59. Kapata N, Tembo J, Mwaba P, Nabyonga-Orem J, Ntoumi F, McHugh TD, et al. Undiagnosed burden of latent tuberculosis, active tuberculosis and tuberculosis-HIV co-infections in Africa—status quo, needs, priorities, and opportunities. IJID Regions. 2025 Mar 1;14:100585. doi:10.1016/J.IJREGI.2025.100585
60. Li S, Mensah E, Liu M, Pan L, Lu W, Zhou S, et al. The burden of tuberculosis and drug resistance in 22 Sub-Saharan African countries, 1990–2021: a GBD 2021 analysis and progress towards WHO 2035 targets with projections to 2050. Front Microbiol. 2025 Nov 17;16:1695592. doi:10.3389/FMICB.2025.1695592 PubMed PMID: 41334161.
61. World Health Organization. WHO | WHO End TB Strategy. World Health Organization. 2015.

62. World Health Organization. Implementing the End TB Strategy: The Essentials 2022 update. World Health Organization [Internet]. 2022 [cited 2025 Dec 6];30(4):373–8. Available from: https://visionzero.dc.gov/pages/2022-update
63. Zhang L, Liu Y. Interpretation of the Political Declaration of the Second High-level Meeting of the General Assembly of United Nations on the Fight Against Tuberculosis. Chinese Journal of Antituberculosis. 2023;45(12). doi:10.19982/j.issn.1000-6621.20230380
64. Votruba N, Thornicroft G. Sustainable development goals and mental health: learnings from the contribution of the FundaMentalSDG global initiative. Global Mental Health. 2016 Sep 9;3:e26. doi:10.1017/gmh.2016.20
65. Satyanarayana S, Satyanarayana S, Thekkur P, Thekkur P, Kumar AMV, Kumar AMV, et al. An Opportunity to END TB: Using the Sustainable Development Goals for Action on Socio-Economic Determinants of TB in High Burden Countries in WHO South-East Asia and the Western Pacific Regions. Trop Med Infect Dis. 2020 Jun 1;5(2):101. doi:10.3390/TROPICALMED5020101 PubMed PMID: 32570828.
66. Lönnroth K, Raviglione M. The WHO's new End TB Strategy in the post-2015 era of the Sustainable Development Goals. Trans R Soc Trop Med Hyg. 2016 Oct 7;110(3):148. doi:10.1093/TRSTMH/TRV108 PubMed PMID: 26884490.
67. Thomas R, Chalkidou K. Cost–effectiveness analysis [Internet]. 2016 [cited 2025 Dec 6]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK436886/
68. Liang A, Wu X, Zhu Y, Pan L, Wang A, Wu C, et al. Targeted next-generation sequencing (tNGS): An upcoming application for pathogen identification in clinical diagnosis. J Infect Public Health. 2025 Oct 1;18(10):102936. doi:10.1016/J.JIPH.2025.102936 PubMed PMID: 40857774.
69. Schwab TC, Perrig L, Göller PC, Guebely De la Hoz FF, Lahousse AP, Minder B, et al. Targeted next-generation sequencing to diagnose drug-resistant tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis. 2024 Oct 1;24(10):1162–76. doi:10.1016/S1473-3099(24)00263-9 PubMed PMID: 38795712.
70. Chen Z, Wang T, Du J, Sun L, Wang G, Ni R, et al. Decoding the WHO Global Tuberculosis Report 2024: A Critical Analysis of Global and Chinese Key Data. Zoonoses. 2025 Jan 7;5(1):999. doi:10.15212/ZOONOSES-2024-0061

71. Mandal S, Bhatia V, Sharma M, Mandal PP, Arinaminpathy N. The potential impact of preventive therapy against tuberculosis in the WHO South-East Asian Region: a modelling approach. BMC Medicine 2020 18:1. 2020 Jul 20;18(1):163-. doi:10.1186/S12916-020-01651-5 PubMed PMID: 32684164.
72. Mandal S, Nair S, Sahu S, Ditiu L, Pretorius C. A deadly equation: The global toll of US TB funding cuts. PLOS Global Public Health. 2025 Sep 1;5(9):e0004899. doi:10.1371/JOURNAL.PGPH.0004899 PubMed PMID: 40929049.
73. Floyd K, Fitzpatrick C, Pantoja A, Raviglione M. Domestic and donor financing for tuberculosis care and control in low-income and middle-income countries: an analysis of trends, 2002–11, and requirements to meet 2015 targets. Lancet Glob Health. 2013 Aug 1;1(2):e105–15. doi:10.1016/S2214-109X(13)70032-9 PubMed PMID: 25104145.
74. D'Silva OA, Lancione S, Ananthakrishnan O, Addae A, Shrestha S, Alsdurf H, et al. The catastrophic cost of TB care: Understanding costs incurred by individuals undergoing TB care in low-, middle-, and high-income settings - A systematic review. PLOS global public health. 2025 Apr 1;5(4). doi:10.1371/JOURNAL.PGPH.0004283 PubMed PMID: 40173113.
75. Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. Eur Respir J. 2014;43(6):1763. doi:10.1183/09031936.00193413 PubMed PMID: 24525439.
76. Chisholm D, Evans DB. Economic evaluation in health: Saving money or improving care? J Med Econ. 2007;10(3):325–37. doi:10.3111/13696990701605235;PAGE:STRING:ARTICLE/CHAPTER
77. Turner HC, Archer RA, Downey LE, Isaranuwatchai W, Chalkidou K, Jit M, et al. An Introduction to the Main Types of Economic Evaluations Used for Informing Priority Setting and Resource Allocation in Healthcare: Key Features, Uses, and Limitations. Front Public Health. 2021 Aug 25;9:722927. doi:10.3389/FPUBH.2021.722927/BIBTEX PubMed PMID: 34513790.
78. Bilinski A, Neumann P, Cohen J, Thorat T, McDaniel K, Salomon JA. When cost-effective interventions are unaffordable: Integrating cost-effectiveness and budget impact in priority setting for global health programs. PLoS Med. 2017 Oct 1;14(10):e1002397. doi:10.1371/JOURNAL.PMED.1002397 PubMed PMID: 28968399.

79. Rutstein SE, Price JT, Rosenberg NE, Rennie SM, Biddle AK, Miller WC. Hidden Costs: the ethics of cost-effectiveness analyses for health interventions in resource-limited settings. Glob Public Health. 2016 Oct 3;12(10):1269. doi:10.1080/17441692.2016.1178319 PubMed PMID: 27141969.
80. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012 Dec 15;380(9859):2197–223. doi:10.1016/S0140-6736(12)61689-4 PubMed PMID: 23245608.
81. Bertram MY, Lauer Id JA, Stenberg Id K, Tan T, Id TE, Askheim C, et al. Methods for the Economic Evaluation of Health Care Interventions for Priority Setting in the Health System: An Update From WHO CHOICE Politics and Power in Global Health: The Constituting Role of Conflicts Comment on "Navigating Between Stealth Advocacy …. Int J Health Policy Manag. 2021;10(11):117–9. doi:10.34172/ijhpm.2020.244
82. WHO handbook for guideline development, 2nd Edition [Internet]. [cited 2025 Dec 7]. Available from: https://www.who.int/publications/i/item/9789241548960
83. Li SA, Alexander PE, Reljic T, Cuker A, Nieuwlaat R, Wiercioch W, et al. Evidence to Decision framework provides a structured “roadmap” for making GRADE guidelines recommendations. J Clin Epidemiol. 2018 Dec 1;104:103. doi:10.1016/J.JCLINEPI.2018.09.007 PubMed PMID: 30253221.
84. Who. Module 3: Diagnosis WHO consolidated guidelines on tuberculosis.
85. Sweeney S, Laurence Y V., Cunnama L, Gomez GB, Garcia-Baena I, Bhide P, et al. Cost of TB services: approach and summary findings of a multi-country study (Value TB). International Journal of Tuberculosis and Lung Disease. 2022;26(11). doi:10.5588/ijtld.22.0096
86. Mafirakureva N, Mukherjee S, de Souza M, Kelly-Cirino C, Songane MJP, Cohn J, et al. Cost-effectiveness analysis of interventions to improve diagnosis and preventive therapy for paediatric tuberculosis in 9 sub-Saharan African countries: A modelling study. PLoS Med. 2023;20(9 September). doi:10.1371/journal.pmed.1004285
87. Ferguson O, Jo Y, Pennington J, Johnson K, Chaisson RE, Churchyard G, et al. Cost-effectiveness of one month of daily isoniazid and rifapentine versus three months of

weekly isoniazid and rifapentine for prevention of tuberculosis among people receiving antiretroviral therapy in Uganda [Internet]. 2020. doi:10.1002/jia2.25623/full

88. Kim HY, Hanrahan CF, Martinson N, Golub JE, Dowdy DW. Cost-effectiveness of universal isoniazid preventive therapy among HIV-infected pregnant women in South Africa. International Journal of Tuberculosis and Lung Disease. 2018 Dec 1;22(12):1435–42. doi:10.5588/ijtld.18.0370 PubMed PMID: 30606315.

89. Ryckman T, Weiser J, Gombe M, Turner K, Soni P, Tarlton D, et al. Impact and cost-effectiveness of short-course tuberculosis preventive treatment for household contacts and people with HIV in 29 high-incidence countries: a modelling analysis. Lancet Glob Health. 2023;11(8). doi:10.1016/S2214-109X(23)00251-6

90. Zhu J, Lyatuu G, Sudfeld CR, Kiravu A, Sando D, Machumi L, et al. Re-evaluating the health impact and cost-effectiveness of tuberculosis preventive treatment for modern HIV cohorts on antiretroviral therapy: a modelling analysis using data from Tanzania. Lancet Glob Health. 2022;10(11). doi:10.1016/S2214-109X(22)00372-2

91. Xue Y, Zhou J, Wang P, Lan JH, Lian WQ, Fan YY, et al. Burden of tuberculosis and its association with socio-economic development status in 204 countries and territories, 1990–2019. Front Med (Lausanne). 2022;9. doi:10.3389/fmed.2022.905245

92. Jo Y, Gomes I, Flack J, Salazar-Austin N, Churchyard G, Chaisson RE, et al. Cost-effectiveness of scaling up short course preventive therapy for tuberculosis among children across 12 countries. EClinicalMedicine. 2021;31. doi:10.1016/j.eclinm.2020.100707

93. Doan TN, Fox GJ, Meehan MT, Scott N, Ragonnet R, Viney K, et al. Cost-effectiveness of 3 months of weekly rifapentine and isoniazid compared with other standard treatment regimens for latent tuberculosis infection: A decision analysis study. Journal of Antimicrobial Chemotherapy. 2019;74(1). doi:10.1093/jac/dky403

Chapter 2

Cost-effectiveness of targeted Next-Generation Sequencing (tNGS) for detection of tuberculosis drug resistance in India, South Africa and Georgia: a modeling analysis

Suvesh Shrestha[1], Angelina Addae[1], Cecily Miller[2], Nazir Ismail[2,3], Alice Zwerling[1]

[1] School of Epidemiology and Public Health, University of Ottawa, Ottawa, Canada

[2] Global Tuberculosis Program, World Health Organization, Geneva, Switzerland

[3] Department of Clinical Microbiology and Infectious Diseases, Faculty of Health Sciences, Wits University, Johannesburg, South Africa

2.1 Preface

This chapter presents the manuscript titled "Cost-effectiveness of targeted next-generation sequencing (tNGS) for detection of tuberculosis drug resistance in India, South Africa and Georgia: a modelling analysis." It addresses the first research objective of this thesis: to do the economic evaluation of innovative diagnostic tools ie, tNGS, for drug-resistant TB diagnosis in high-burden settings, aligning with the WHO End TB Strategy.

This study is the first published cost-effectiveness evaluation of tNGS and was used as supporting economic evidence in the WHO Guideline Development Group's 2023 deliberations on DR-TB diagnostic recommendations. It uses country-specific modelling to estimate the cost-effectiveness of implementing tNGS in India, South Africa, and Georgia, in comparison to standard-of-care diagnostics.

Author Contributions: AZ and SS contributed to the conceptualization of the project, data curation, modelling, formal analysis, and manuscript writing. In addition, AZ also provided supervision of the overall project. CM and NI contributed to the conceptualization of the project and manuscript writing. AA contributed to data curation and analysis. The underlying data were verified by AZ and SKS. All authors read and approved the manuscript. AZ accepts full responsibility for the work and/or the conduct of the study, had access to the data, and the decision to publish.

Ethics Approval: Ethical approval was obtained from the University of Ottawa Research Ethics Boards (H-07-22-8325 - ANN1-8325). This analysis did not involve human subjects.

Publication Status: **Published** in The Lancet eClinicalMedicine on December 24, 2024.

Citation: Shrestha S, et al. Cost-effectiveness of targeted next-generation sequencing (tNGS) for detection of tuberculosis drug resistance in India, South Africa and Georgia: a modeling analysis. *eClinicalMedicine.* 2024;79:103003. https://doi.org/10.1016/j.eclinm.2024.103003

2.2 Abstract

Background: Targeted next-generation sequencing (tNGS) is promising alternative to phenotypic drug susceptibility testing (pDST) for detecting drug-resistant tuberculosis (DRTB). This study explored the potential cost-effectiveness of tNGS for the diagnosis of DR-TB across 3 settings: India, South Africa and Georgia.

Methods: To inform WHO guideline development group (GDG) on tNGS we developed a stochastic decision analysis model and assessed cost-effectiveness of tNGS for DST among rifampicin resistance individuals. We also assessed tNGS as initial test for TB drug resistance in bacteriologically confirmed TB. Diagnostic accuracy and cost data were sourced from a systematic review conducted for GDG, covering studies published until September 2022. The primary outcome was incremental cost (2021 US$) per disability-adjusted life year (DALY) averted.

Findings: tNGS when compared with in-country DST, tNGS proved cost-effective in South Africa (ICER:$15,619/DALY averted, WTP:$21,165) but not in Georgia (ICER:$18,375/ DALY averted, WTP:$15,069). In India, tNGS dominated in-country DST practice, providing greater health impact at lower cost. When comparing tNGS with universal pDST, tNGS was dominated by pDST in all three countries. In Georgia, using tNGS as initial test for TB drug-resistance compared to Xpert MTB/Rif followed by pDST appeared cost-effective. Scenario with 50% reduction in tNGS test kit costs made tNGS cost-effective across all three countries, while a high Bedaquiline resistance prevalence (30%) led to a worsening cost-effectiveness.

Interpretation: tNGS may be cost-effective in India, South Africa and Georgia when comprehensive DST is not routinely performed. Thus, existing DST practice and healthcare infrastructure should be considered before implementation and scale-up of tNGS.

Funding: Global Tuberculosis Program, World Health Organization (2022/1249364-0)

Keywords: Targeted next-generation sequencing (tNGS); Drug-resistant tuberculosis (DRTB); Cost-effectiveness analysis; Incremental cost-effectiveness ratio (ICER); Disability-adjusted life year (DALY)

2.3 Research in Context

Evidence before this study:

Before undertaking this study, we conducted a systematic review on the economic evaluation of using targeted next-generation sequencing (tNGS) to diagnose drug-resistant tuberculosis (DR-TB). Our search, conducted on Aug 14, 2024, included databases such as PubMed, EMBASE, and SCOPUS, without restrictions on publication year, age group, country, income level, comparator group, HIV status, or other comorbidities. The search revealed no prior cost-effectiveness analyses (CEA) specifically focused on the use of tNGS for the diagnosis of DR-TB.

Added value of this study:

This study is the first to conduct a cost-effectiveness analysis of tNGS for the detection of DR-TB in low- and middle-income countries (LMICs). It provides essential economic evidence that has informed the World Health Organization (WHO) in making recommendations regarding the adoption of this novel diagnostic tool. This study highlights the potential of tNGS to improve patient outcomes and offers valuable insights into its cost-effectiveness in diverse healthcare settings.

Implications of all the available evidence:

Our study suggests that tNGS can be a cost-effective tool for DR-TB diagnosis, particularly in settings where comprehensive drug susceptibility testing (DST) is not routinely performed. The findings underscore the importance of considering existing DST practices and healthcare infrastructure before implementing tNGS, especially in countries with varying levels of resource availability and TB burden. Future research should focus on further refining cost-effectiveness models and assessing the long-term impacts of integrating tNGS into TB control programs.

2.4 Introduction:

Drug-Resistant Tuberculosis (DR-TB) has become growing public health threat, with incidence increasing and only one third of people with multi-drug resistance (MDR)/Rifampicin resistant (RR) -TB diagnosed and enrolled in treatment annually.(1) DR-TB is more difficult to diagnose as it requires bacteriological confirmation with drug susceptibility testing (DST). As novel agents and treatment regimens are introduced, there is also an emerging concern about resistance to two newer DR-TB drugs i.e. bedaquiline (BDQ) and linezolid (LZD).(2,3)

To end the global DR-TB epidemic, universal DST which includes new and repurposed TB drugs should be accessible. While WHO-recommended rapid molecular diagnostics (mWRDs) can detect resistance to rifampicin, follow-up testing by low complexity automated nucleic acid amplification tests (LCaNAATs), Line Probe Assays (LPA) or culture is typically required for detection of additional drug-resistance.(4) Also, none of the mWRDs can detect resistance to new and repurposed drugs like bedaquiline, linezolid, delamanid and pretomanid.(5) Culture-based methods are current standard of care for DST but this requires Biosafety Level 3 (BS3) laboratories; specialized reagents, cold-chain requirements; and may take 6-8 weeks for results, leading to delays and negative impacts on patient outcomes. (6) Phenotypic DST (pDST) is also not widely available for newer drugs.(2) An alternative DST method includes LPAs but this assay performs poorly on smear-negative and scanty samples.(3,4,7) LPAs are also quite laboratory and staff intensive; requiring complex laboratory infrastructure and expensive equipment that is normally only available in reference laboratories.(8) The LCaNAATs although simpler and faster than LPAs, these have not reached wide scale adoption and are currently recommended for a limited number of drugs including fluoroquinolones and isoniazid but none of the new drugs.

One promising DST option is targeted Next Generation Sequencing (tNGS), which amplifies selected genes with next-generation sequencing technology to detect resistance to many drugs with a single test. (9) As tNGS can interrogate entire genes to identify specific mutations associated with resistance, it may provide improved accuracy compared with existing mWRDs.(10) The other advantages of tNGS include improved speed, and comprehensive coverage of many more potential mutations.(11) tNGS is valuable tool for the surveillance of DR-TB which allows the prediction of resistance to several anti-TB drugs including new and repurposed DR-TB drugs.(4,12)

Despite numerous advantages of tNGS, particularly in low and middle-income counties (LMICs) with a high burden of DR-TB, implementation of tNGS requires investment. TB programs globally continue to face inadequate funding, constraining available resources.(13) Hence, it's crucial to ensure that decision making is informed through critical economic evidence concerning tNGS technologies. This study aimed to generate economic evidence to aid the World Health Organization (WHO) guideline development group meeting (GDG) on formulating guidance on the use of tNGS for the detection resistance to anti-TB drugs. The primary aim of this study was to assess the potential cost-effectiveness of introducing the tNGS for the detection of DR-TB in South Africa, Georgia, and India.

This study assessed the cost-effectiveness of tNGS in three different contexts. First, we evaluated the cost-effectiveness of tNGS as a test for DST among persons with RR TB compared to phenotypic DST. Second, we analyzed the cost-effectiveness of using tNGS as a test for DST among persons with RR TB, comparing it to in-country DST practices: Xpert MTB/XDR and pDST in South Africa and Georgia, and LPA and pDST in India. Finally, we assessed the cost-

effectiveness of tNGS as an initial test for TB drug resistance in patients with bacteriologically confirmed TB, compared to the use of mWRDs followed by pDST in Georgia.

2.5 Methods:

2.5.1Study design:

We developed stochastic decision analysis model to assess the cost-effectiveness of introducing tNGS for the diagnosis of DR-TB for all three objectives. This study was done from healthcare system perspective and accounted for healthcare system costs to diagnose and treat TB. The primary outcome of this study was incremental cost-effectiveness ratio (ICER) calculated as the incremental cost in USD per disability-adjusted life years (DALYs) averted. The ICER was computed by comparing the difference in costs and DALYs averted between the tNGS strategy and the comparator.

2.5.2 Model structure, intervention, and comparator:

2.5.2.1 Model structure:

The decision analysis model employed a decision tree framework to simulate the diagnostic and treatment pathways for individuals with DR-TB. Each decision tree captured the sequence of testing, treatment decisions, and health outcomes, including true positive and false negative diagnostic results, treatment initiation based on DST outcomes, and final health outcomes such as survival and death. In our study, we used three different models to assess the cost effectiveness of tNGS. The first two models tracked individuals with RR when tNGS was used as test for DST among person with RR. First, model compared tNGS with universal DST (figure 2.1) and second model compared tNGS with in-country DST practice (supplement figure 2.1-2.2). In both models,

the probability of receiving test results depend on the indeterminant or contamination rate specific to tNGS and pDST, respectively. Within the model, DST was done only for group A DR-TB drugs (fluoroquinolone, bedaquiline and linezolid).(14) We treated those individuals with rifampicin resistance as MDR TB and did not specifically consider DST for INH. The prevalence rate of fluoroquinolone (FQ) resistance, bedaquiline (BDQ) resistance and linezolid (LZD) were specific to each country. (15–19) In the model we made an assumption that there was no resistance to other drugs outside Group A drugs used to treat DR TB largely due to limited or non-existent data regarding resistance to other DR-TB drugs. Once results were received, they either initiated or didn't initiate TB treatment ultimately resulting in either survival or death. Based on the DST results, treatment with Bedaquiline, Pretomanid, Linezolid and Moxifloxacin (BPALM), BPAL or an individualized regimen was initiated. (14) Since there was no clinical or programmatic data on effectiveness of individualised regimen guided by pDST or tNGS, we assumed that once individuals were diagnosed to have BDQ and/or LZD resistance, in addition to RR, the individualized treatment would include a minimum of four effective drugs. In every model, loss to follow-up in both intervention and comparator is the same so as not to unduly favour tNGS. Model comparing tNGS with in-country DST in India, since BDQ DST was not routinely performed among RR-TB patients, we assigned higher mortality to BDQ-resistant individuals in the in-country DST arm, as they would be initiated on regimens including BDQ, resulting in fewer than four effective drugs.

The third model tracked hypothetical cohort of bacteriologically confirmed TB individuals in the high DRTB burden setting of Georgia. They were offered either tNGS or Xpert MTB/RIF followed by pDST as an initial DST (supplement figure 3). Since tNGS can simultaneously detect resistance

to several drugs with a single test, in the tNGS arm DST of Rif, INH, FQ, BDQ and LZD was done simultaneously. In the comparator arm, we assumed that only those with rif. resistance in mWRDs were further subjected to DST for FQ, BDQ and LZD through pDST. It was assumed that DST of INH among RIF sensitive individuals in the comparator arm was not done.

2.5.2.2 Epidemiological, diagnostic and programmatic parameters:

We gathered epidemiological parameters - prevalence data, diagnostic accuracy data and health outcome data - that were essential for the model from various sources. A detailed list of those sources is included in Table 2.1. The estimate and ranges for the prevalence of DR-TB were derived from the 2021 WHO DR-TB surveillance sheet, published DR survey report (15,17), published literature, and in consultation with WHO experts. Parameters on treatment initiation, completion and outcomes were taken from published literature for BPaLM, BPaL and individualized treatment, WHO guidelines and the 2022 global TB report. (14,19–21) We used data from the systematic review on the diagnostic accuracy of tNGS done as a part of evidence generation for the WHO's GDG which covered the studies published until September of 2022 as well as the recently completed Foundation for Innovative New Diagnostics (FIND) multicenter clinical trial to assess the performance of culture-free, end-to-end tNGS solutions for diagnosis of DR-TB trial. The diagnostic accuracy of the comparator which included pDST, LPA and mWRDs was extracted from published literature. Utility data were sourced from the global burden of disease study.(22)

2.5.2.3 Cost parameters:

We only included costs incurred by the health care system (Table 2.1). Per unit test cost of tNGS were derived from a systematic review on the cost-effectiveness of tNGS and empirical costing done in consultation with manufacturers and FIND in preparation for the GDG meeting. The costs of the different treatment regimens for DRTB were extracted from a recently published cost-effectiveness study done by Sweeney et. al. on short oral treatment regimens in the countries selected of this study. (23) We assumed that the cost of individualized treatment will be same regardless of DST result. Per unit test costs of other diagnostics were taken from published literature and the Value TB studies which provide comprehensive cost information for various tuberculosis interventions.(24) All costs were converted to 2021 using inflation rates in the respective local currency and then converted to 2021 USD using US bureau of labour statistics.

2.5.2.4 Incremental cost-effectiveness:

This study measured outcomes in terms of total costs and DALYs, with the primary economic measure being incremental cost per DALY averted. When tNGS was used as a test for DST among person with RR, we analyzed the incremental cost per DALY averted of introducing tNGS, compared to universal pDST and in-country DST practice. When tNGS was used as an initial test for TB drugs resistance, we analyzed the incremental cost per DALYs averted of introducing tNGS compared to Xpert MTB/RIF followed by pDST. A willingness to pay (WTP) threshold of 3 times the countries' gross domestic product (GDP) per capita was employed as per World Bank report of 2021.(25) This WTP threshold of 3 times GDP per capita was based on WHO-CHOICE (26) recommendation and considering the significant health and economic benefits of effective DR-TB management.

2.5.3 Statistical analysis:

Uncertainty around included parameters and the impact of this uncertainty on model results were explicitly examined through probabilistic sensitivity analyses (PSA). The primary outcome of ICER were obtained from a Monte Carlo simulation with 10,000 replications with 95% uncertainty ranges reported as the 2.5^{th} and 97.5^{th} percentiles of corresponding distributions.

2.5.4 Sensitivity and scenario analysis:

One-way sensitivity analysis was conducted to understand the potential impact of key model inputs on the ICER. We evaluated each individual parameter value independently. Parameters that showed greater influence, such as per unit test cost, contamination rate, repeat test probability (considered a proxy for loss to follow-up (LTFU)) were presented in tornado diagrams. Two-way sensitivity analysis was carried out on unit costs of tNGS and LTFU and presented graphically.

To evaluate the impact of various scenarios on cost-effectiveness, additional scenario analyses were performed. One scenario assessed the cost-effectiveness of tNGS compared to phenotypic DST, where individualized treatment in pDST arm lacked four effective drugs due to its limitation to perform DST of certain other drugs used to treat DR TB, leading to higher mortality. Other scenario analyses focused on cost-effectiveness of using tNGS for DST among persons with RR TB compared to in-country DST practice. We explored scenario that accounted for the benefit of using tNGS for multiple disease. A volume-based analysis accounting for the benefit of patient volume was also explored in the scenario analysis. We also did a scenario analysis with reduced tNGS test kit costs, assuming a 50% reduction in test kit price. A scenario with increased tNGS costs due to 20% fewer samples was also included. We conducted a scenario analysis where there

was no LTFU in tNGS compared to 10% LFTU in pDST to give an advantage to tNGS for its faster turnaround time. We also conducted scenario analysis with increased BDQ resistant at 30%.

2.5.5 Ethics:

Ethical approval was obtained from the University of Ottawa Research Ethics Boards (H-07-22-8325 - ANN1-8325). This analysis did not involve human subjects.

2.5.6 Role of funding source:

The funder itself had no role in the design, conduct, analysis or in the decision to submit for publication.

2.6 Results:

2.6.1 Cost-effectiveness of tNGS vs. Universal pDST for DST among persons with RR:

The cost-effectiveness results for using tNGS as a test for DST after detection of RR, replacing pDST without considering differences in time to results and potential impact on loss to follow up is shown in Table 2.2. In this hypothetical context, the pDST approach resulted in fewer DALYs compared with tNGS and has lower costs across all three assessed countries. Under these conditions, pDST is considered dominant or preferred over tNGS.

2.6.2 Cost-effectiveness of tNGS vs. in-country DST practice for DST among persons with RR:

The incremental cost per DALYs averted of using tNGS as a test for DST after detection of RR, replacing in-country DST practice for South Africa and Georgia was $15,619 (95% UR: Dominated -$114,782) and $18,375 (95% UR: Dominated - $158,972) respectively (table 2.2). Using a WTP threshold at three times the country's GDP per capita, tNGS was cost effective in

South Africa and not in Georgia. In India, tNGS dominated pDST leading to cost-savings and health gains compared to India's existing standard of care relying on pDST and LPAs. For South Africa and India, almost 60% of model iterations fell below the respective WTP thresholds whereas for Georgia only 40% of iterations fall below the WTP threshold (figure 2.2 a-c).

2.6.3 Cost-effectiveness of tNGS as an initial test for TB drug resistance:

When tNGS was used as an initial test for TB drug resistance in the high DR TB setting of Georgia (table 2.2) it resulted in improved health gains leading to an ICER of $9,261 per DALY averted (95% UR: $5258-$32,040). At WTP threshold of 3 times the country's GDP using tNGS is cost-effective in high burden DR-TB setting of Georgia, with almost 70% of the iterations below the respective WTP threshold (figure 2.3).

2.6.4 Sensitivity analysis:

In univariable sensitivity analyses key epidemiological and cost parameters were varied across expected ranges to understand the influence of each parameter on model results. All variables having more than 10% change in model results were presented as a tornado diagram.

When tNGS was used as a test for DST among person with RR replacing pDST the most influencing parameter in the model for India and Georgia were the rate of probability of repeat testing among pDST and tNGS and per unit cost of tNGS. Conversely, for South Africa unit cost of tNGS and pDST exerted a greater effect on model outcome (supplement figure 2.4).

When tNGS was used as a test for DST among person with RR replacing in-country DST practice for South Africa and Georgia the rate of contamination of pDST, probability of repeat testing among pDST (proxy for LTFU) and per unit cost of tNGS exerted the greatest impact on ICER values (figure 2.4a-b). In India, the unit cost of tNGS, LPA and pDST were more influencing on model outcome (figure 2.4c). We have investigated these influencing parameters further in scenario analysis.

When tNGS was used as the initial test for TB drugs resistance detection in the high DR TB burden setting of Georgia the rate of indeterminant result of tNGS, probability of INH resistance and per unit cost of tNGS had the largest influence on ICER values (figure 2.5). Cost effectiveness threshold based on prevalence of INH resistance and tNGS indeterminate rate was also done which is shown in supplementary article.

2.6.5 Scenario analysis:

Table 2.3 shows the result of scenario analyses done to evaluate cost effectiveness of using tNGS. When tNTS was compared to pDST, the scenario where patients in the pDST arm were initiated on the least effective individualized treatment, compared to tNGS, pDST was no longer dominant over tNGS. In the scenario where tNGS was employed for multiple diseases, cost-effectiveness improved across all three countries, with ICER per DALY averted of $12,530 (95% UR: cost saving-$86,202) and $15,808 (95% UR: cost saving- $137,387) in South Africa and Georgia, respectively. In India, utilizing tNGS for multiple diseases dominated the in-country DST practice. In scenario where there was 50% reduction in tNGS test kit cost resulted in tNGS to be cost-effective in all 3 countries. In South Africa and Georgia, the ICER per DALY averted was $12,757

(95% UR: cost saving - $79,122) and $14,077 (95% UR: cost saving - $112,771) whereas in India tNGS dominated the in-country DST practice. We also looked in the scenario where there is 20% fewer samples per run of tNGS due to low volume of samples received, it resulted in increased ICER per DALY averted and resulted in tNGS being only cost-effective in South Africa (ICER: $17,763/DALY averted, WTP: $21,165) but not in Georgia (ICER: $20,130/ DALY averted, WTP: $15,069) and India (ICER: $7,520/ DALY averted, WTP: $6,771). In scenario where there is no LTFU in tNGS due to early turnaround time resulted in tNGS to be cost-effective in South Africa (ICER: $13,004/DALY averted, WTP: $21,165) and Georgia (ICER: $13,640/ DALY averted, WTP: $15,069) whereas in India tNGS dominated in-country DST practice. In scenario with high BDQ resistant the ICER per DALY averted was $16,144 and $22,889 for South Africa and Georgia respectively whereas in India tNGS dominated in-county DST practice. In supplemental table 2.1 we have additional scenario analysis result where the probability of death among untreated is 70%.

2.7 Discussion:

In this economic evaluation, we evaluated the cost-effectiveness of using tNGS for DST and detection of DR TB in the settings of South Africa, Georgia and India. When tNGS was compared with universal pDST, for DST among people with RR and assuming a similar probability of LTFU between tNGS and pDST, our findings indicated that tNGS was dominated by pDST. Therefore, in countries where pDST is well established without prohibitively high rates of LTFU, tNGS is less likely to be cost-effective. It should be noted that this is an idealistic comparator, as universal DST is not current practice is most countries particularly among low- and middle-income countries. Price of testing also influenced the overall cost-effectiveness and based on a 50% reduction which is expected upon market launch, tNGS would be cost-effective in all three settings.

When tNGS was compared as a replacement for current in-country DST practice, for DST among people with RR, tNGS was found to be cost-effective in South Africa. However, in Georgia, tNGS was not considered cost-effective according to WTP threshold of the country. In India, where the country is currently using LPA and pDST, tNGS dominated India's DST practice with lower costs and greater health gains. In India, BDQ pDST was conducted only among those who failed the BDQ regimen, and in South Africa, DST of BDQ and LZD is not being performed among FQ sensitive, though that is in the process of change. So, countries where universal DST of new and repurposed drugs is not being done routinely will benefit more from tNGS implementation. All three countries are currently using two DST methods after RIF. resistance. In South Africa and Georgia, they are using Xpert XDR followed by pDST and in India, they are using LPA and pDST. Therefore, countries with more complex and expensive existing DST algorithms (e.g. LPAs) are more likely to find tNGS cost-effective.

We found that tNGS was cost-effective as the initial test for DST after bacteriological confirmation of TB compared to mWRDs followed by pDST for those where RR is detected. Therefore, in countries with a high prevalence of DR TB and where DST of INH among those individuals with Rif. sensitive is not being done, implementing tNGS as the initial test for DST may be beneficial compared to mWRDs followed by pDST.

Different scenarios were looked at to assess the cost-effectiveness of using tNGS as a test for DST among person with RR replacing in-country DST practice. In the scenario where tNGS was compared to pDST, with pDST containing the least effective four drugs in the individualized

treatment regimen due to its limitations in conducting DST for all other drugs, pDST was no longer dominant. This result shows that tNGS is more effective compared to pDST in scenarios where pDST cannot test for a wider range of drugs, leading to less effective treatment regimens and higher mortality. In the scenario where tNGS is used with a multi-disease testing approach, cost-effectiveness improved in all three countries suggesting that tNGS used for TB and other diseases like SARS-CoV2, HIV and cancers, may be beneficial and improve cost-effectiveness. When LTFU decreased with tNGS compared to the in-country DST practice in scenario analysis, cost-effectiveness improved. This suggests that introducing tNGS in countries experiencing high LTFU rates due to delayed DST results is more likely to be cost-effective. It implies placement at decentralized sites or centralized testing with highly efficient sample referral to achieve faster turnaround times. However, testing in either situation is likely to require batching need to achieve efficiency and decrease test cost but may increase the turnaround time and which might increase the chance of LTFU among DR-TB individuals. If batching is implemented only factoring in improvement to turnaround time, it will increase unit test cost and will also decrease likelihood of being cost-effective which was seen in the scenario with tNGS running with 20% fewer samples and was only cost-effective in South Africa since WTP threshold is higher in South Africa compared to Georgia and India.

To our knowledge, this is the first economic analysis assessing the cost-effectiveness of using tNGS for the detection of DR TB in LMICs. There are few limitations in the study underpinned by the lack of patient important outcomes using tNGS for DST. The first limitation is that the model did not account for disease transmission and the long-term impact of using tNGS in TB incidence, which might have underrepresented the cost-effectiveness of tNGS. When

transmission-dynamic modelling was done using WGS DST by Mugwagwa et al. using WGS was initially associated with increase in annual cost but averting TB transmission and future TB cases subsequently resulted in cost savings and health benefits.(27) In the model impact of faster turnaround time was incorporated into the model through its effect on LTFU rates, We acknowledge that this approach may not fully capture the potential benefits of tNGS in reducing morbidity, and this is a limitation of our current model. tNGS can simultaneously detect resistance to several drugs with a single test. Yet, in the model, we only included DST of INH and RIF among the first-line drugs. Not including PZA and EMB in this model might have underrepresented the potential cost-effectiveness of tNGS. The cost-effectiveness result of tNGS for DST after rapid molecular test for RIF only looked at DST of three group A drugs i.e. FQ, BDQ and LZD. Not including other drugs used in the treatment of DR-TB in this model with tNGS can provide results that might have also lessened the potential cost-effectiveness of tNGS. In the cost-effective result for tNGS as initial diagnostic, only those with resistance to RIF from mWRD were further subjected to pDST in the comparator arm. So, this result may not be generalized to the countries where DST to INH is being done among all bacteriologically confirmed pulmonary TB. This study used utility data from the Global Burden of Disease study, which does not focus specifically on DR-TB and may have underestimated its unique morbidity profile and health-related burden.

Implementing tNGS as an initial test for drug resistance detection in patients with bacteriologically confirmed TB may be cost-effective in a country with a high prevalence of DR TB such as Georgia, and where DST of INH and Group A second-line drugs is not being performed universally. If the country is considering implementing tNGS after rapid molecular testing for RIF resistance, then the cost-effectiveness of tNGS depends on the existing DST practice of the country. In countries

where pDST is well established and provides universal DST of new and repurposed DR-TB drugs among individuals with RIF Resistance, implementing tNGS is less likely to be cost-effective. In contrast, in countries where universal DST of new and repurposed DR-TB drugs among RIF resistant individuals are not being done routinely, compared to their in-country DST practice implementing tNGS will be cost effective. In a scenario where tNGS can be used for multiple disease which will increase its utility and reduce cost implementing tNGS will be beneficial and cost-effective. Countries with high loss to follow up (LTFU) among RIF resistant individuals due to delayed follow-on DST results, the implementation of tNGS will more likely be cost-effective. In conclusion, implementing tNGS can be cost-effective depending on current DST practice and coverage. It is therefore important to consider the existing standard of care before implementation and scale-up of tNGS.

2.8 Contributors:

AZ and SS contributed to conceptualization of the project, data curation, modelling, formal analysis, and manuscript writing. In addition, AZ also provided supervision of overall project. CM and NI contributed to conceptualization of the project, and manuscript writing. AA contributed to data curation and analysis. The underlying data were verified by AZ and SKS. All authors read and approved the manuscript. AZ accepts full responsibility for the work and/or the conduct of the study, had access to the data, and decision to publish.

2.9 Data sharing statement:

The authors confirm that all parameters used in the cost-effectiveness analysis are available within the article and its supplementary materials. No new data were generated for this study.

2.10 Declaration of interests:

CM reports receiving funding from USAID to support the Global TB Programme staff at the WHO. All other authors declare no conflicts of interest.

2.11 Acknowledgements

We would like to acknowledge Dr. Florian Marx and Abigail De Villiers for their helpful feedback. This work was supported by funding from the Global TB Program, WHO.

2.12 References

1. Global tuberculosis report 2020. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.
2. Tiberi S, Utjesanovic N, Galvin J, Centis R, D'Ambrosio L, van den Boom M, et al. Drug resistant TB – latest developments in epidemiology, diagnostics and management. International Journal of Infectious Diseases. 2022;
3. Koch A, Cox H, Mizrahi V. Drug-resistant tuberculosis: challenges and opportunities for diagnosis and treatment. Vol. 42, Current Opinion in Pharmacology. 2018.
4. World Health Organization (WHO). Operational handbook on tuberculosis Module 3 Diagnosis Updated 2021. Module 3: Diagnosis Rapid diagnotsics for tuberculosis diagnosis. 2021.
5. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 3: diagnosis-rapid diagnostics for tuberculosis detection,2021 update. Vol. Module 3, World Health Organization. 2021.
6. Hepple P, Novoa-Cain J, Cheruiyot C, Richter E, Ritmeijer K. Implementation of liquid culture for tuberculosis diagnosis in a remote setting: Lessons learned. International Journal of Tuberculosis and Lung Disease. 2011;15(3).
7. Ninan MM, Gowri M, Christopher DJ, Rupali P, Michael JS. The diagnostic utility of line probe assays for multidrug-resistant tuberculosis. Pathog Glob Health. 2016;110(4–5).
8. Nguyen TNA, Berre VA Le, Bañuls AL, Nguyen TVA. Molecular diagnosis of drug-resistant tuberculosis; A literature review. Front Microbiol. 2019;10(MAR).
9. Behjati S, Tarpey PS. What is next generation sequencing? Arch Dis Child Educ Pract Ed. 2013;98(6).
10. Use of targeted next-generation sequencing to detect drug-resistant tuberculosis. 2023.
11. Mitchell SL, Simner PJ. Next-Generation Sequencing in Clinical Microbiology: Are We There Yet? Vol. 39, Clinics in Laboratory Medicine. 2019.
12. Zignol M, Cabibbe AM, Dean AS, Glaziou P, Alikhanova N, Ama C, et al. Genetic sequencing for surveillance of drug resistance in tuberculosis in highly endemic countries: a multi-country population-based surveillance study. Lancet Infect Dis. 2018;18(6).
13. Venkatesan P. Worrying lack of funding for tuberculosis. Lancet Infect Dis. 2022;22(3).

14. World Health Organization. WHO Consolidated Guidelines on Tuberculosis. Module 4: Treatment - Drug-Resistant Tuberculosis Treatment, 2022 Update. WHO Press. 2022.
15. Ismail NA, Mvusi L, Nanoo A, Dreyer A, Omar S V., Babatunde S, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018;18(7).
16. Kiria N, Avaliani Z, Chincharauli M, Mikiashvili L. Trends in tuberculosis notification and treatment in Georgia. In 2020.
17. Mishra G, Mulani J. First National Anti-Tuberculosis Drug Resistance Survey (NDRS) from India - An Eye Opener. J Infect (Grand Rapids). 2018;1(2).
18. WHO. WHO DR Surveillance sheet. 2021.
19. Global tuberculosis report 2022. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.
20. Nyang'wa BT, Berry C, Kazounis E, Motta I, Parpieva N, Tigay Z, et al. A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis. New England Journal of Medicine. 2022;387(25).
21. Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, Ngubane N, et al. Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis. New England Journal of Medicine. 2022;387(9).
22. Institute for Health Metrics and Evaluation (IHME). Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME). 2018.
23. Sweeney S, Berry C, Kazounis E, Motta I, Vassall A, Dodd M, et al. Cost-effectiveness of short, oral treatment regimens for rifampicin resistant tuberculosis. PLOS Global Public Health. 2022;2(12).
24. Sweeney S, Laurence Y V., Cunnama L, Gomez GB, Garcia-Baena I, Bhide P, et al. Cost of TB services: approach and summary findings of a multi-country study (Value TB). International Journal of Tuberculosis and Lung Disease. 2022;26(11).
25. The World Bank. GDP per Capita. 2021.
26. Making choices in health: who guide to cost-effectiveness analysis. Rev Esp Salud Publica. 2004;78(3).

27. Mugwagwa T, Abubakar I, White PJ. Using molecular testing and whole-genome sequencing for tuberculosis diagnosis in a low-burden setting: A cost-effectiveness analysis using transmission-dynamic modelling. Thorax. 2021;76(3).
28. He W, Liu C, Liu D, Ma A, Song Y, He P, et al. Prevalence of Mycobacterium tuberculosis resistant to bedaquiline and delamanid in China. J Glob Antimicrob Resist. 2021;26.
29. Monde N, Munyeme M, Chongwe G, Wensman JJ, Zulu M, Siziya S, et al. First and Second-Line Anti-Tuberculosis Drug-Resistance Patterns in Pulmonary Tuberculosis Patients in Zambia. Antibiotics. 2023;12(1).
30. Villellas C, Coeck N, Meehan CJ, Lounis N, De Jong B, Rigouts L, et al. Unexpected high prevalence of resistance-associated Rv0678 variants in MDR-TB patients without documented prior use of clofazimine or bedaquiline. Journal of Antimicrobial Chemotherapy. 2017;72(3).
31. Xu J, Wang B, Hu M, Huo F, Guo S, Jing W, et al. Primary clofazimine and bedaquiline resistance among isolates from patients with multidrug-resistant tuberculosis. Antimicrob Agents Chemother. 2017;61(6).
32. Zheng H, He W, Jiao W, Xia H, Sun L, Wang S, et al. Molecular characterization of multidrug-resistant tuberculosis against levofloxacin, moxifloxacin, bedaquiline, linezolid, clofazimine, and delamanid in southwest of China. BMC Infect Dis. 2021;21(1).
33. Kaniga K, Hasan R, Jou R, Vasiliauskienė E, Chuchottaworn C, Ismail N, et al. Bedaquiline Drug Resistance Emergence Assessment in Multidrug-Resistant Tuberculosis (MDR-TB): a 5-Year Prospective in Vitro Surveillance Study of Bedaquiline and Other Second-Line Drug Susceptibility Testing in MDR-TB Isolates. J Clin Microbiol. 2022;60(1).
34. Derendinger B, Dippenaar A, de Vos M, Alberts R, Sirgel F, Dolby T, et al. High frequency of bedaquiline resistance in programmatically treated drug-resistant TB patients with sustained culture-positivity in Cape Town, South Africa. Int J Mycobacteriol. 2021;9(5).
35. Ismail NA, Omar SV, Moultrie H, Bhyat Z, Conradie F, Enwerem M, et al. Assessment of epidemiological and genetic characteristics and clinical outcomes of resistance to bedaquiline in patients treated for rifampicin-resistant tuberculosis: a cross-sectional and longitudinal study. Lancet Infect Dis. 2022;22(4).

36. Ahmed I, Jabeen K, Inayat R, Hasan R. Susceptibility testing of extensively drug-resistant and pre-xtensively drug-resistant mycobacterium tuberculosis against levofloxacin, linezolid, and amoxicillin-clavulanate. Antimicrob Agents Chemother. 2013;57(6).
37. Gavali DM, Aring B, Mullan S, Nathametha AA, Dave AB. Evaluation of Sensitivity and Resistance of Linezolid in Pre Extensively Drug Resistance Tuberculosis and Extensively Drug Resistance Tuberculosis at a Tertiary Care Hospital, Jamnagar, Gujarat, India. JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH. 2019;
38. Nambiar R, Tornheim JA, Diricks M, Bruyne K De, Sadani M, Shetty A, et al. Linezolid resistance in mycobacterium tuberculosis isolates at a tertiary care centre in Mumbai, India. Indian Journal of Medical Research, Supplement. 2021;154(1).
39. Azimi T, Khoshnood S, Asadi A, Heidary M, Mahmoudi H, Kaviar VH, et al. Linezolid resistance in multidrug-resistant mycobacterium tuberculosis: A systematic review and meta-analysis. Vol. 13, Frontiers in Pharmacology. 2022.
40. Gomez GB, Siapka M, Conradie F, Ndjeka N, Garfin AMC, Lomtadze N, et al. Cost-effectiveness of bedaquiline, pretomanid and linezolid for treatment of extensively drug-resistant tuberculosis in South Africa, Georgia and the Philippines. BMJ Open. 2021;11(12).
41. Masuku SD, Berhanu R, Van Rensburg C, Ndjeka N, Rosen S, Long L, et al. Managing multidrug-resistant tuberculosis in South Africa: A budget impact analysis. International Journal of Tuberculosis and Lung Disease. 2020;24(4).
42. Mulder C, Rupert S, Setiawan E, Mambetova E, Edo P, Sugiharto J, et al. Budgetary impact of using BPaL for treating extensively drug-resistant tuberculosis. BMJ Glob Health. 2022;7(1).
43. Franke MF, Appleton SC, Bayona J, Arteaga F, Palacios E, Llaro K, et al. Risk factors and mortality associated with default from multidrug-resistant tuberculosis treatment. Clinical Infectious Diseases. 2008;46(12).
44. Value TB Data verse. Available: https://dataverse.harvard.edu/dataverse/Value-TB.
45. Groessl EJ, Ganiats TG, Hillery N, Trollip A, Jackson RL, Catanzaro DG, et al. Cost analysis of rapid diagnostics for drug-resistant tuberculosis. BMC Infect Dis. 2018;18(1).

46. Mueller DH, Mwenge L, Muyoyeta M, Muvwimi MW, Tembwe R, McNerney R, et al. Costs and cost-effectiveness of tuberculosis cultures using solid and liquid media in a developing country. International Journal of Tuberculosis and Lung Disease. 2008;12(10).
47. Cates L, Crudu V, Codreanu A, Ciobanu N, Fosburgh H, Cohen T, et al. Laboratory costs of diagnosing TB in a high multidrug-resistant TB setting. Vol. 25, International Journal of Tuberculosis and Lung Disease. 2021.
48. GDF STP. DIAGNOSTICS, MEDICAL DEVICES & OTHER HEALTH PRODUCTS CATALOG. 2023.
49. Vassall A, Siapka M, Foster N, Cunnama L, Ramma L, Fielding K, et al. Cost-effectiveness of Xpert MTB/RIF for tuberculosis diagnosis in South Africa: a real-world cost analysis and economic evaluation. Lancet Glob Health. 2017;5(7).
50. Hao X, Lou H, Bai J, Ding Y, Yang J, Pan W. Cost-effectiveness analysis of Xpert in detecting Mycobacterium tuberculosis: A systematic review. International Journal of Infectious Diseases. 2020 Jun;95:98–105.
51. Horne DJ, Pinto LM, Arentz M, Grace Lin SY, Desmond E, Flores LL, et al. Diagnostic accuracy and reproducibility of WHO-endorsed phenotypic drug susceptibility testing methods for first-line and second-line antituberculosis drugs. Vol. 51, Journal of Clinical Microbiology. 2013.
52. Kaniga K, Aono A, Borroni E, Cirillo DM, Desmaretz C, Hasan R, et al. Validation of bedaquiline phenotypic drug susceptibility testing methods and breakpoints: A multilaboratory, multicountry study. J Clin Microbiol. 2020;58(4).
53. Nathavitharana RR, Cudahy PGT, Schumacher SG, Steingart KR, Pai M, Denkinger CM. Accuracy of line probe assays for the diagnosis of pulmonary and multidrug-resistant tuberculosis: A systematic review and meta-analysis. Vol. 49, European Respiratory Journal. 2017.
54. Gardee Y, Dreyer AW, Koornhof HJ, Omar S V., Da Silva P, Bhyat Z, et al. Evaluation of the GenoType MTBDRsl Version 2.0 Assay for Second-Line Drug Resistance Detection of Mycobacterium tuberculosis Isolates in South Africa. J Clin Microbiol. 2017;55(3).
55. Pillay S, Steingart KR, Davies GR, Chaplin M, De Vos M, Schumacher SG, et al. Xpert MTB/XDR for detection of pulmonary tuberculosis and resistance to isoniazid,

fluoroquinolones, ethionamide, and amikacin. Vol. 2022, Cochrane Database of Systematic Reviews. 2022.

56. Fekadu G, Yao J, You JHS. Bedaquiline-based treatment for extensively drug-resistant tuberculosis in South Africa: A cost-effectiveness analysis. PLoS One. 2022;17(8 August).

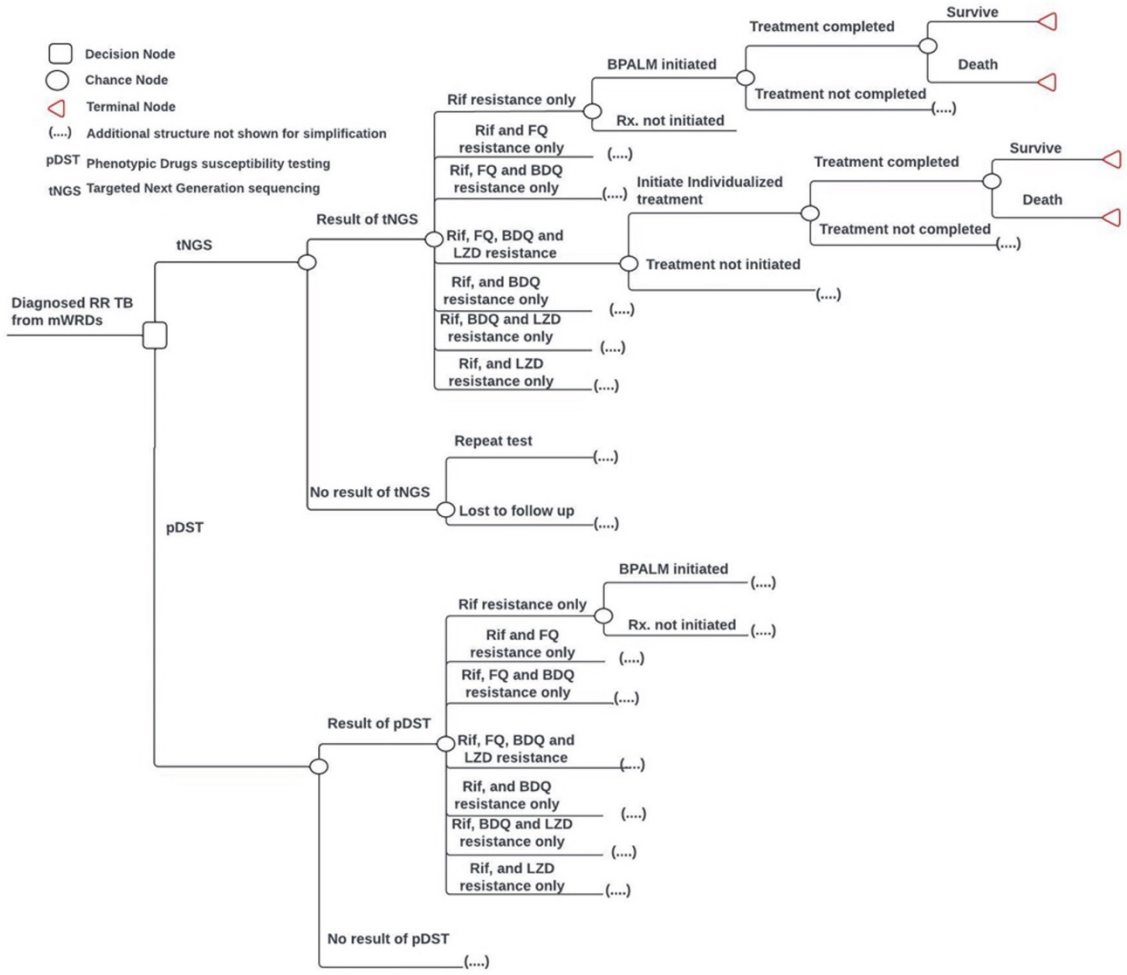


Figure 2.1: Simplified model decision structure. Two strategies were compared: DST with tNGS vs pDST as a test for DST among person with RR: Schematically these strategies are separated by a square representing a decision node. The circles represent chance nodes where individuals may experience one of several possible events shown on subsequent lines. The probabilities of developing each event are listed in Table 1. Dotted lines represent model structure omitted for simplicity. In all cases, this omitted structure parallels that shown. The diamond symbol represents terminal node. RR= Rifampicin resistance; tNGS=Targeted Next Generation sequencing; pDST= Phenotypic Drugs susceptibility testing; Rif=Rifampicin, FQ= Fluroquinolone; BDQ= Bedaquiline; LZD=Linezolid; Rx.=treatment, TB-Tuberculosis

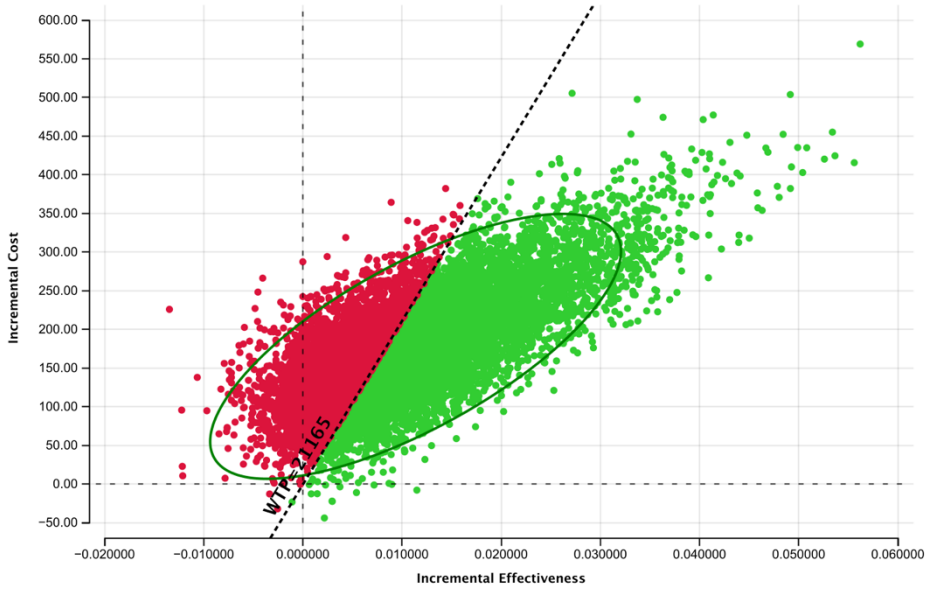


Figure 2.2a: Incremental cost-effectiveness scatterplot comparing tNGS versus South Africa's in-country DST as a test for DST among person with RR. Each dot represents the result of iteration out of 10,000 Mont Carlo simulation. The dashed diagonal shows the willingness to pay threshold of $21,165 per DALY averted. The green DOTs that are below WTP threshold represent cost-effective simulations.

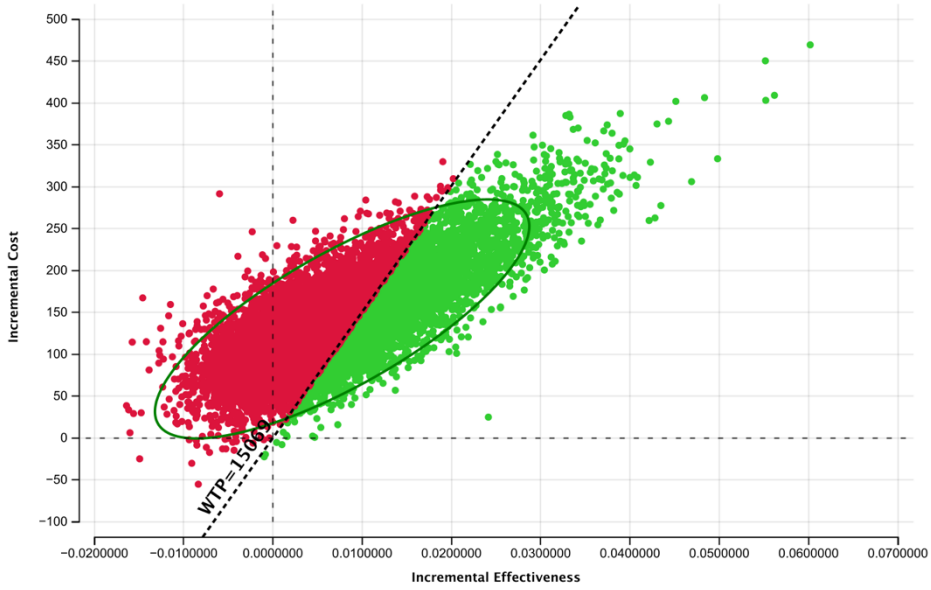


Figure 2.2b: Incremental cost-effectiveness scatterplot comparing tNGS versus Georgia's in-country DST as a test for DST among person with RR**.** Each dot represents the result of iteration out of 10,000 Mont Carlo simulation. The dashed diagonal shows the willingness to pay threshold of $15,069 per DALY averted. The green DOTs that are below WTP threshold represent cost-effective simulations.

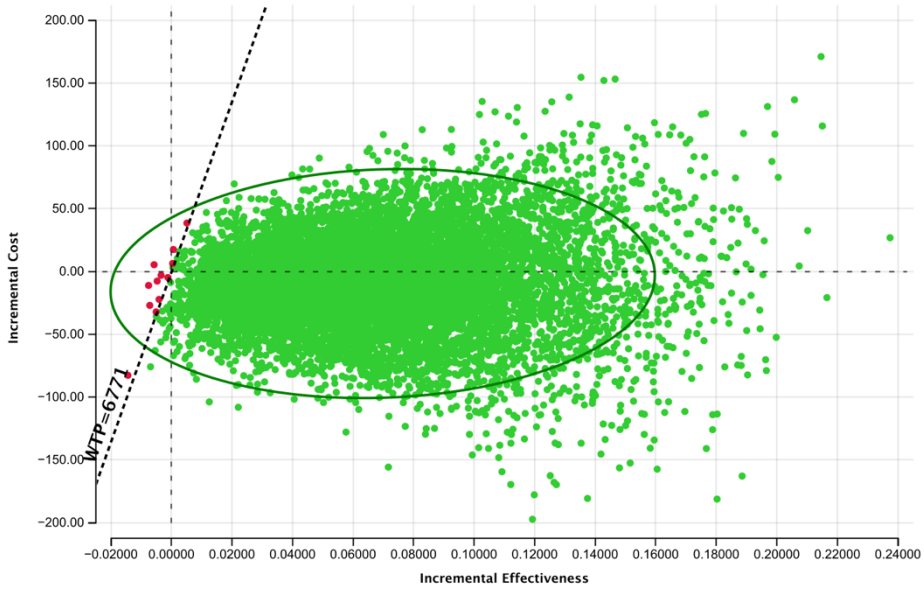


Figure 2.2c: Incremental cost-effectiveness scatterplot comparing tNGS versus India's in-country DST as a test for DST among person with RR. Each dot represents the result of iteration out of 10,000 Mont Carlo simulation. The dashed diagonal shows the willingness to pay threshold of $6,771 per DALY averted. The green DOTs that are below WTP threshold represent cost-effective simulations.

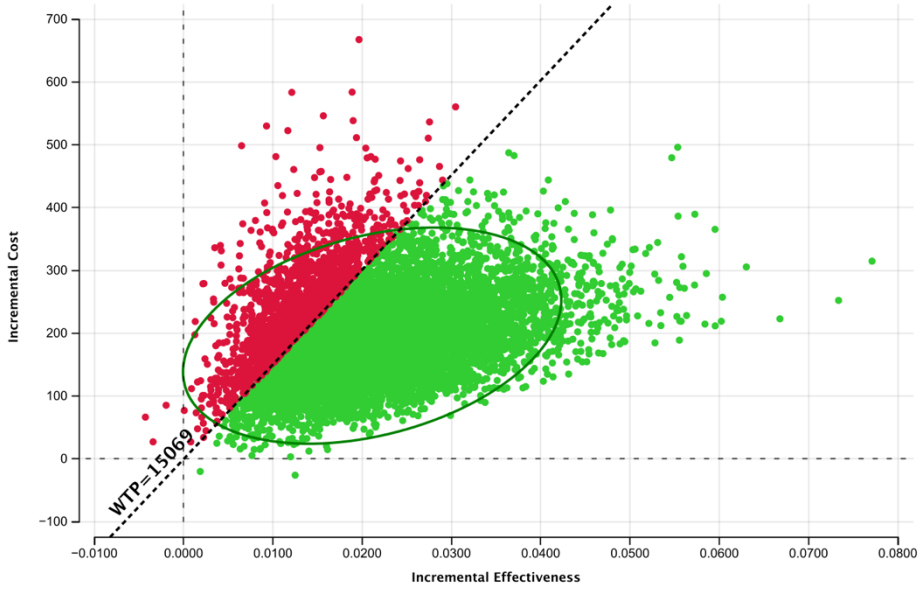


Figure 2.3: Incremental cost-effectiveness scatterplot comparing tNGS as an initial test for TB drug resistance in patients with bacteriologically confirmed TB compared to use of mWRDs followed by pDST. Each dot represents the result of iteration out of 10,000 Mont Carlo simulations. The dashed diagonal shows the willingness to pay threshold of $15,069 per DALY averted. The green DOTs that are below WTP threshold represent cost-effective simulations.

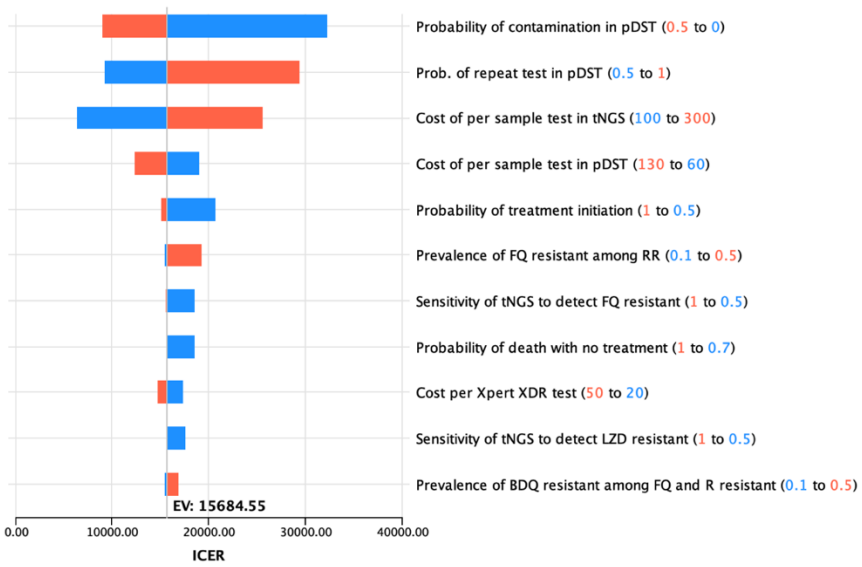


Figure 2.4a: One way sensitivity analyses tornado diagram on incremental cost effectiveness ratio (ICER) of using tNGS as a replacement of South Africa's DST practice as a test for DST among person with RR. In this diagram, the horizontal bars illustrate how the ICER varies as each parameter is adjusted individually within the specified range, while all other parameters are held constant. The length of each bar reflects the degree of influence that parameter has on the ICER, with longer bars indicating greater impact. The orange bars represent the ICER when the parameter is at its high value, and the blue bars represent the ICER when the parameter is at its low value. The parameters are listed in descending order of their impact on the ICER, from top to bottom.

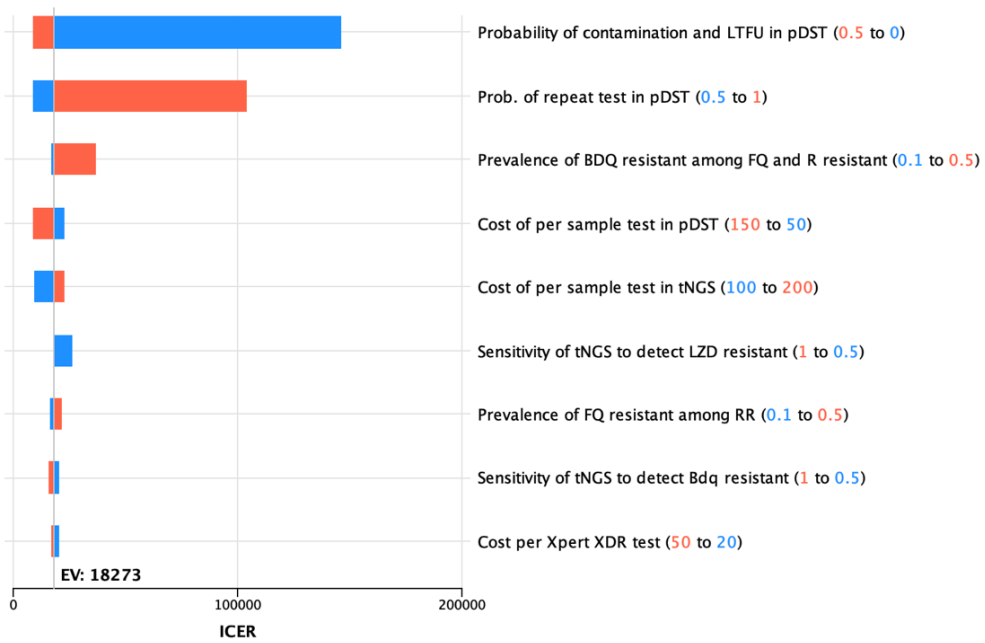


Figure 2.4b: One way sensitivity analyses tornado diagram on incremental cost effectiveness ratio (ICER) of using tNGS as a replacement of Georgia's DST practice as a test for DST among person with RR. In this diagram, the horizontal bars illustrate how the ICER varies as each parameter is adjusted individually within the specified range, while all other parameters are held constant. The length of each bar reflects the degree of influence that parameter has on the ICER, with longer bars indicating greater impact. The orange bars represent the ICER when the parameter is at its high value, and the blue bars represent the ICER when the parameter is at its low value. The parameters are listed in descending order of their impact on the ICER, from top to bottom.

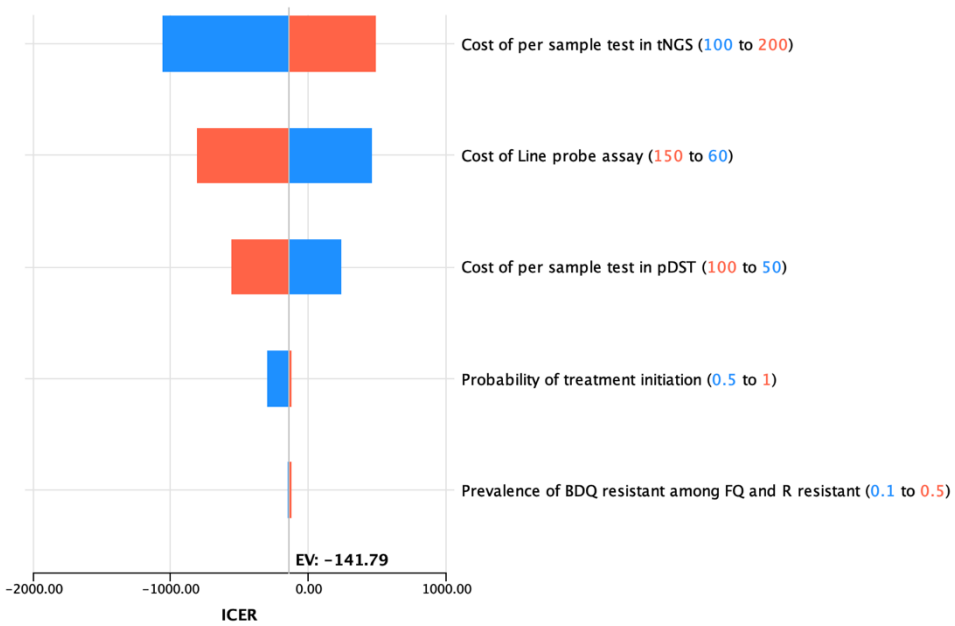


Figure 2.4c: One way sensitivity analyses tornado diagram on incremental cost effectiveness ratio (ICER) of using tNGS as a replacement of India's DST practice as a test for DST among person with RR. In this diagram, the horizontal bars illustrate how the ICER varies as each parameter is adjusted individually within the specified range, while all other parameters are held constant. The length of each bar reflects the degree of influence that parameter has on the ICER, with longer bars indicating greater impact. The orange bars represent the ICER when the parameter is at its high value, and the blue bars represent the ICER when the parameter is at its low value. The parameters are listed in descending order of their impact on the ICER, from top to bottom.

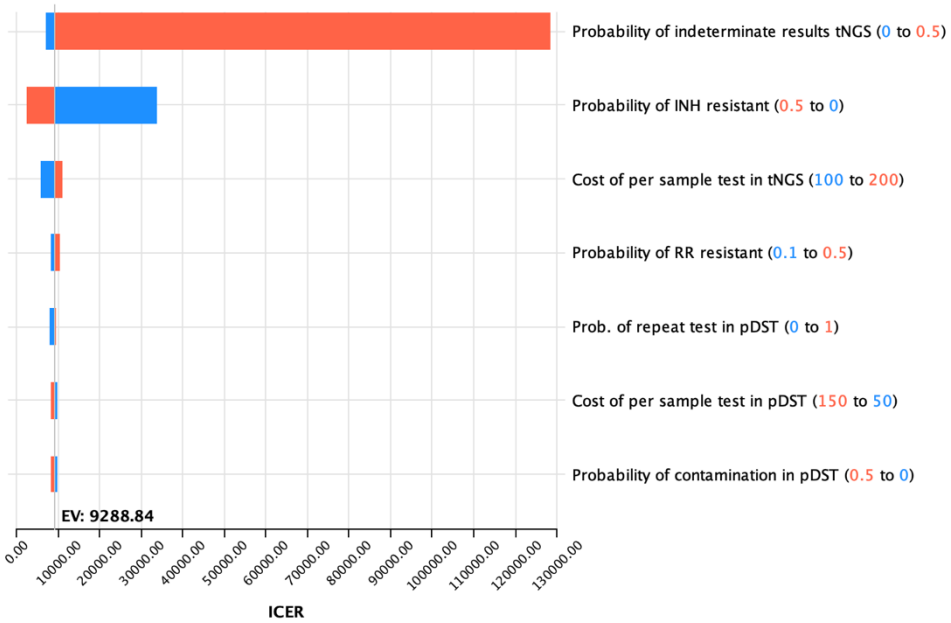


Figure 2.5: One way sensitivity analyses tornado diagram on incremental cost effectiveness ratio (ICER) of using tNGS as initial test for DR diagnosis. In this diagram, the horizontal bars illustrate how the ICER varies as each parameter is adjusted individually within the specified range, while all other parameters are held constant. The length of each bar reflects the degree of influence that parameter has on the ICER, with longer bars indicating greater impact. The orange bars represent the ICER when the parameter is at its high value, and the blue bars represent the ICER when the parameter is at its low value. The parameters are listed in descending order of their impact on the ICER, from top to bottom.

Table 2.1: Key Model Parameter estimate, ranges for sensitivity analysis and data sources

Description	South Africa	India	Georgia	References
	Estimate	Estimate	Estimate	
Prevalence data				
Prevalence of FQ resistance among RR	0.13 (0.05 - 0.21)	0.3 (0.22 - 0.38)	0.29 (0.25 – 0.33)	(15–18)
Prevalence of BDQ resistance among RR and FQR	0.17 (0.07 - 0.27)	0.15 (0.07 - 0.23)	0.15 (0.07 – 0.23)	(15,18,28,29)
Prevalence of BDQ resistance among RR and FQs	0.05 (0.02 - 0.08)	0.035 (0.01 - 0.06)	0.035 (0.01 - 0.06)	(28,30–35)
Prevalence of LZD resistance among RR, FQR and BDQR	0.065 (0.03 - 0.10)	0.065 (0.03 - 0.1)	0.175 (0.1 - 0.25)	(15,18)

Prevalence of LZD resistance among RR, FQR and BDQs	0.026 (0.01 - 0.042)	0.035 (0.01 - 0.06)	0.04 (0.01 - 0.07)	(15,18,36,37)
Prevalence of LZD resistance among RR, FQs and BDQR	0.065 (0.03 - 0.10)	0.065 (0.03 - 0.1)	0.175 (0.1 - 0.25)	(35), Assumption
Prevalence of LZD resistance among RR, FQs and BDQs	0.026 (0.01 - 0.042)	0.0275 (0.01 - 0.045)	0.04 (0.01 – 0.07)	(29,38,39)
Treatment outcome*				
Probability of treatment initiation	0.9 (0.72-1)			(19)
Probability of completion of BPaLM/BPaL	0.9 (0.83-0.95)			(14,20,21)
Probability of Individualized treatment completion	0.73 (0.657-0.766)			(14)
Probability of death with BPaLM regimen	0.03 (0-0.6)			(14,20,21)
Probability of death with BPaL regimen	0.03 (0-0.6)			(14,21,40)
Probability of death with Individualized RX	0.125 (0.06-0.25)			(40,41)
Probability of death no treatment of of DR TB (18 months)	1 (0.648-1)			(40), Assumption
Probability of death with wrong/incomplete treatment of of DR TB (Annual)	0.486 (0.38-0.58)			(42,43)
Percentage of contamination and failure of	0.13 (0.10-0.15)			Country data

growth in control tube pDST				
Percentage of Indeterminate in tNGS	0.1 (0.08-0.13)			tNGS Diagnostic accuracy SR
Percentage of repeat test among contaminated samples in pDST and tNGS	0.9 (0.72-1)			Country data
Cost data				
Cost of BPaLM treatment	3730	953	3505	(23)
Cost of BPaL treatment	3544	918	3421	
Cost of Individualized treatment	4787	1036	4463	
Unit test cost tNGS	$197 ($134-$257)	$159 ($121-$175)	$166 ($120-$198)	tNGS CEA SR, FIND, Manufacturer
Unit test cost pDST	$95 ($68-$120)	$74 ($56-$92)	$83 ($57-$108)	(44–47)
Unit test cost LPA	-	$103 ($60-$115)	-	
Unit test cost Xpert XDR	$39 (37-41)	-	$39 (37-41)	(48); Assumption
Unit test cost Xpert MTB/Rif	$29 (27-31)	$29 (27-31)	$29 (27-31)	(49,50)
Diagnostic Accuracy data*				
	tNGS	**pDST**	**LPA**	
Rif				tNGS Diagnostics accuracy SR; (51–55)
Sensitivity	0.96 (0.91-1)	0.982 (0.93-1)		
Specificity	0.94 (0.86-1)	0.81 (0.69-0.93)		
Inh				
Sensitivity	0.96 (0.93-0.99)	0.99 (0.94-1)	0.89 (0.89-0.92)	
Specificity	0.97 (0.95-0.99)	0.98 (0.95-0.99)	0.98 (0.97-0.99)	
FQ				
Sensitivity	0.97	0.99	0.93	

	(0.94-1)	(0.76-1)	(0.9-0.95)	
Specificity	0.95 (0.91-0.99)	1 (0.98-1)	0.99 (0.98-1)	
BDQ				
Sensitivity	0.68 (0.43-0.93)	1 (0.98-1)		
Specificity	0.97 (0.94-1)	1 (0.99-1)		
LZD				
Sensitivity	0.69 (0.39-0.99)	1 (0.51-1)		
Specificity	1	1 (0.96-1)		
Utility Data*				
DALYs death	1			(22,56)
DALYs DR-TB individuals on treatment	0.33			
DALYs with no treatment/LTFU	0.66			

*Same for all 3 countries

Table 2.2: CEA result of using tNGS for DST

Country	Comparator	DALYs	Cost	ICER ($ per DALY averted, 95% uncertainty ranges)
Cost-effectiveness result when tNGS was used as a test for DST among persons with RR compared to universal pDST				
South Africa	pDST	0.504	$3,289	Ref.
	tNGS	0.508	$3,404	Dominated by pDST (Dominated - $303,635)
Georgia	pDST	0.503	$3,085	Ref.
	tNGS	0.508	$3,183	Dominated by pDST (Dominated - $171,666)
India	pDST	0.503	$878	Ref.
	tNGS	0.508	$970	Dominated by pDST (Dominated - $162,897)

Cost-effectiveness result when tNGS was used as a test for DST among persons with RR compared to in-country DST practice:				
South Africa	XpertXDR+pDST	0.519	$3,223	Ref.
	tNGS	0.509	$3,401	$15,619 (Dominated - $114,782)
Georgia	XpertXDR+pDST	0.516	$3,040	Ref.
	tNGS	0.508	$3,183	$18,375 (Dominated - $158,972)
India	LPA and pDST	0.5073	$981	Ref.
	tNGS	0.5072	$971	Dominates LPA and pDST (Cost saving- $60,083)
Cost-effectiveness result when tNGS was used as an initial test for TB drug resistance in patients with bacteriologically confirmed TB				
Georgia	Xpert MTB/Rif +pDST	0.51	$1,180	Ref.
	tNGS	0.488	$1,377	$9,261 ($5258-$32,040)

DALY: Disability Adjusted Life year; ICER: Incremental cost effectiveness ratio; tNGS: Targeted Next Generation Sequencing; pDST: Phenotypic Drugs Susceptibility Test

Table 2.3: Scenario analysis tNGS compared to pDST and in country DST practice among RR individuals

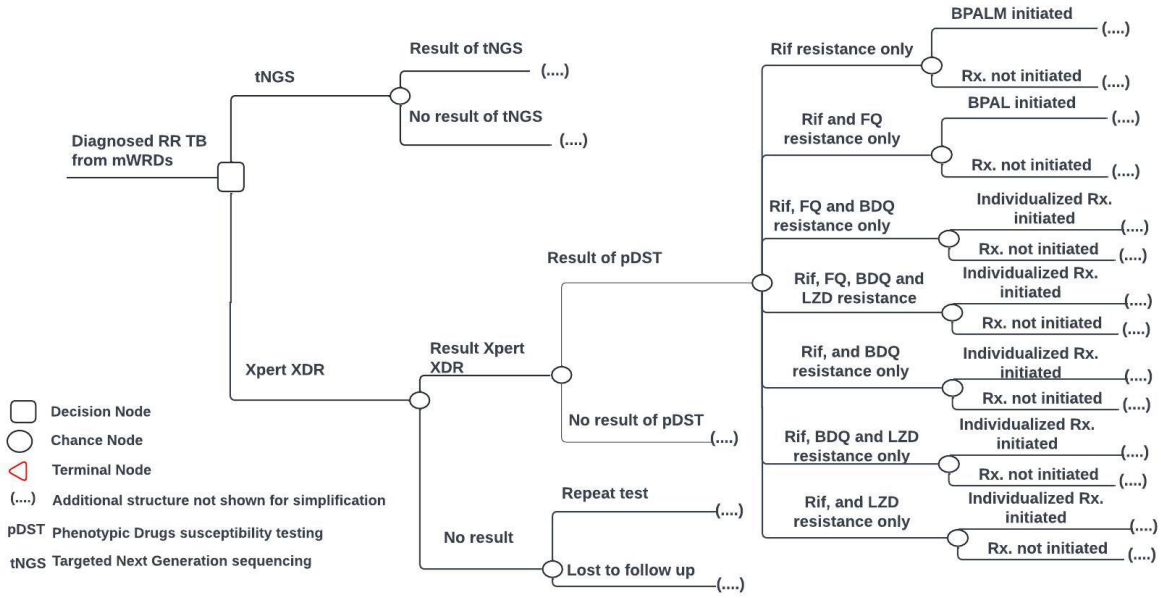
Country	Comparator	DALYs	Cost	ICER ($ per DALY averted, 95% uncertainty ranges)
Increased mortality among individual initiated in individualized treatment in pDST arm				
South Africa	pDST	0.510	$3,237	Ref.
	tNGS	0.508	$3,404	$103,195 (Dominated -$655,752)
Georgia	pDST	0.513	$3031	Ref.
	tNGS	0.508	$3,183	$29,961 (Dominated -$284,646)
India	pDST	0.511	$872	Ref.
	tNGS	0.508	$970	$23,065 (Cost saving - $241,534)
Multiuse for multi-disease with reduced tNGS cost*				

South Africa	XpertXDR+pDST	0.52	$3,224	Ref.
	tNGS	0.509	$3,367	$12,530 (Cost saving -$86,202)
Georgia	XpertXDR+pDST	0.516	$3,038	Ref.
	tNGS	0.508	$3,162	$15,808 (Cost saving - $137,387)
India	LPA and pDST	0.5076	$981	Ref.
	tNGS	0.5075	$961	Dominates LPA and pDST (Cost saving - $55,713)
Reduced tNGS kit cost (50% price reduction) *				
South Africa	XpertXDR+pDST	0.52	$3,222	Ref.
	tNGS	0.508	$3,368	$12,757 (Cost saving - $79,122)
Georgia	XpertXDR+pDST	0.516	$3,043	Ref.
	tNGS	0.508	$3,157	$14,077 (Cost saving - $112,771)
India	LPA and pDST	0.5074	$982	Ref.
	tNGS	0.5073	$939	Dominates (Cost saving - $22)
20% fewer samples and increased unit test cost*				
South Africa	XpertXDR+pDST	0.52	$3,222	Ref.
	tNGS	0.508	$3,421	$17,763 (Cost saving - $152,515)
Georgia	XpertXDR+pDST	0.516	$3,040	Ref.
	tNGS	0.508	$3,133	$20,130 (Cost saving - $185,104)
India	LPA and pDST	0.5075	$980	Ref.
	tNGS	0.5073	$981	$7,520 (Cost saving - $70,187)
Reduced LTFU in tNGS (0%vs. 10%)*				
South Africa	XpertXDR+pDST	0.52	$3,223	Ref.
	tNGS	0.504	$3,435	$13,004 ($7,075-$44,119)
Georgia	XpertXDR+pDST	0.516	$3,039	Ref.
	tNGS	0.503	$3,212	$13,640 (Cost saving-$91,130)
India	LPA and pDST	0.507	$982	Ref.
	tNGS	0.502	$981	Dominates LPA and pDST (Cost saving - $48,801)
80% sensitivity of tNGS to BDQ and LZD*				
South Africa	XpertXDR+pDST	0.52	$3,226	Ref.

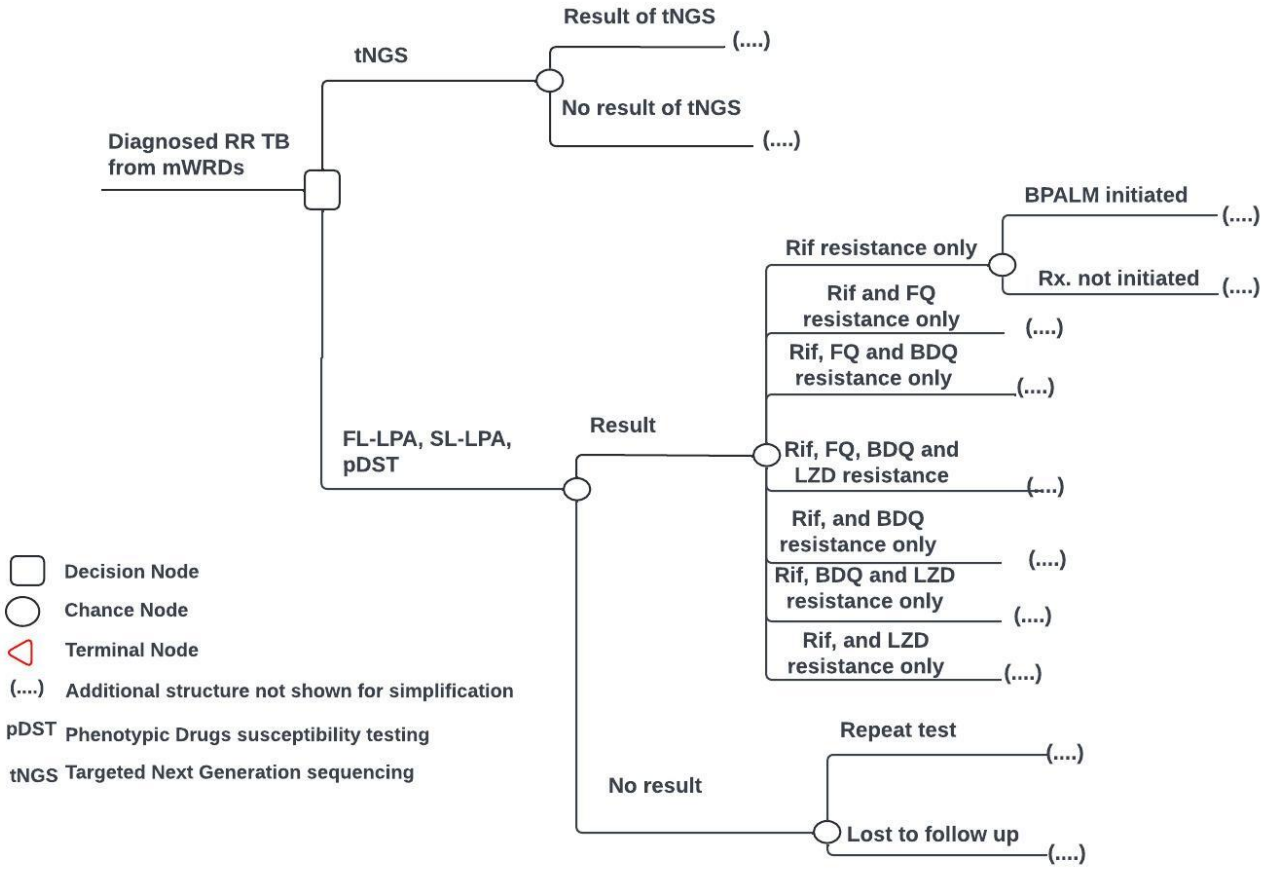
	tNGS	0.508	$3,406	$15,758 (Cost saving - $114,193)
Georgia	XpertXDR+pDST	0.516	$3,040	Ref.
	tNGS	0.507	$3,186	$17,124 (Cost saving - $176,728)
India	LPA and pDST	0.508	$981	Ref.
	tNGS	0.507	$971	Dominates LPA and pDST (Cost saving - $53,695)
Increasing BDQ resistant at 30%*				
South Africa	XpertXDR+pDST	0.52	$3,234	Ref.
	tNGS	0.51	$3,408	$16,144 (Cost saving - $128,456)
Georgia	XpertXDR+pDST	0.519	$3,062	Ref.
	tNGS	0.513	$3,199	$22,889 (Cost saving - $186,593)
India	LPA and pDST	0.584	$981	Ref.
	tNGS	0.513	$971	Dominates LPA and pDST (Cost saving - $911)

*These scenarios compared use of tNGS as test for DST among person with RR replacing in-country DST practice.

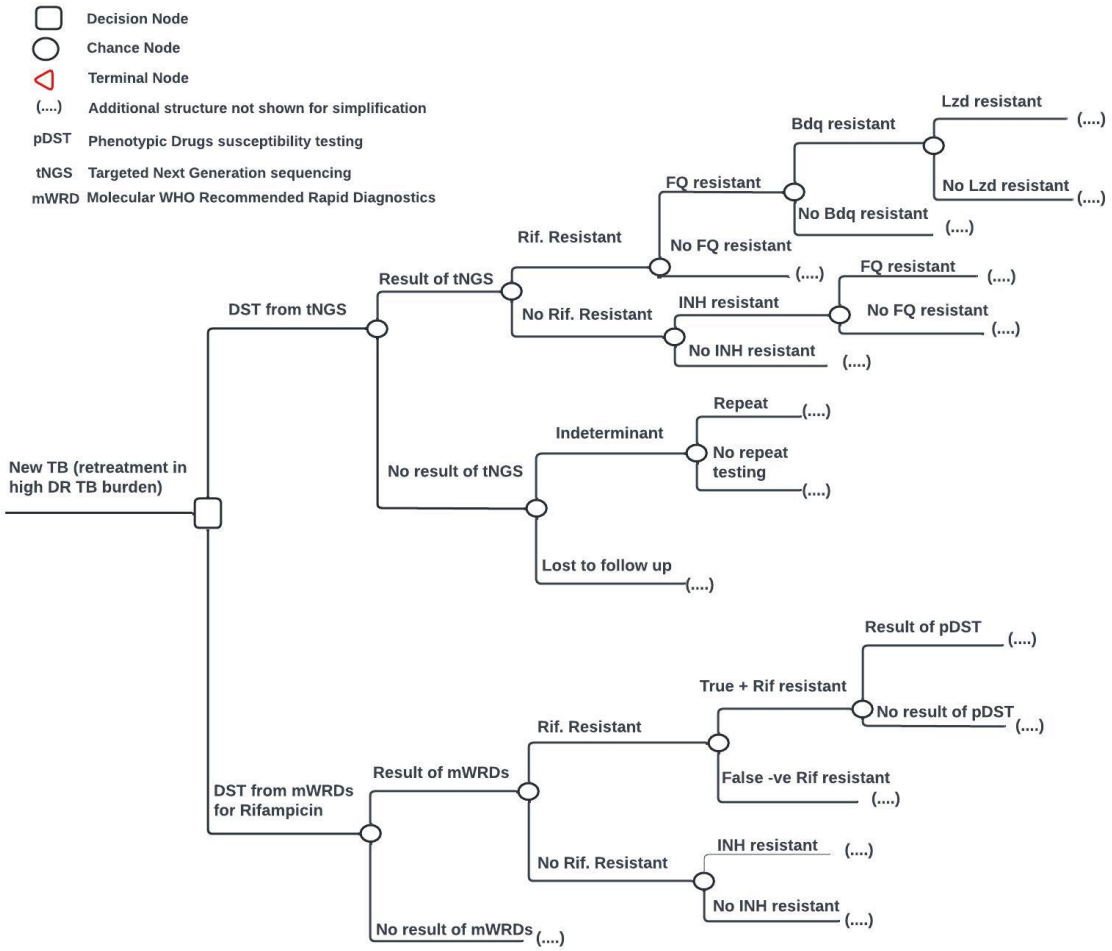
2.13 Supplement



Supplement Figure 2.1 : Simplified model decision structure. Two strategies were compared: DST with tNGS vs South Africa and Georgia's in country DST practice as a subsequent test for DST following detection of RR. Schematically these strategies are separated by a square representing a decision node. The circles represent chance nodes where individuals may experience one of several possible events shown on subsequent lines. The probabilities of developing each event are listed in Table 1. Dotted lines represent model structure omitted for simplicity. In all cases, this omitted structure parallels that shown. The diamond symbol represents terminal node. RR= Rifampicin resistance; tNGS=Targeted Next Generation sequencing; pDST= Phenotypic Drugs susceptibility testing; Rif=Rifampicin, FQ= Fluroquinolone; BDQ= Bedaquiline; LZD=Linezolid; Rx.=treatment, TB-Tuberculosis

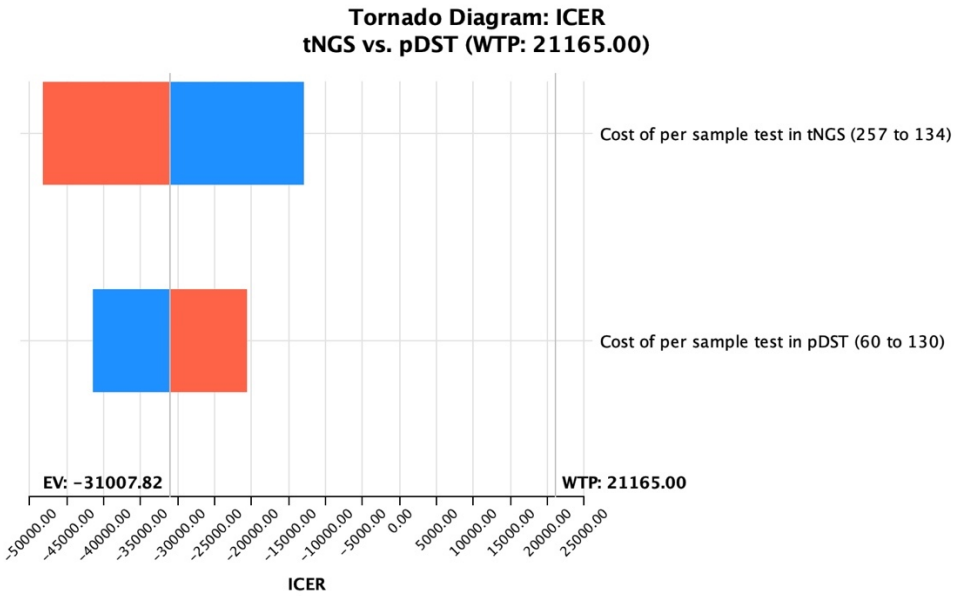


Supplement Figure 2.2: Simplified model decision structure. Two strategies were compared: DST with tNGS vs India's in country DST practice as a subsequent test for DST following detection of RR. Schematically these strategies are separated by a square representing a decision node. The circles represent chance nodes where individuals may experience one of several possible events shown on subsequent lines. The probabilities of developing each event are listed in Table 1. Dotted lines represent model structure omitted for simplicity. In all cases, this omitted structure parallels that shown. The diamond symbol represents terminal node. RR= Rifampicin resistance; tNGS=Targeted Next Generation sequencing; pDST= Phenotypic Drugs susceptibility testing; Rif=Rifampicin, FQ= Fluroquinolone; BDQ= Bedaquiline; LZD=Linezolid; Rx.=treatment, TB-Tuberculosis ; LPA= Line Probe As

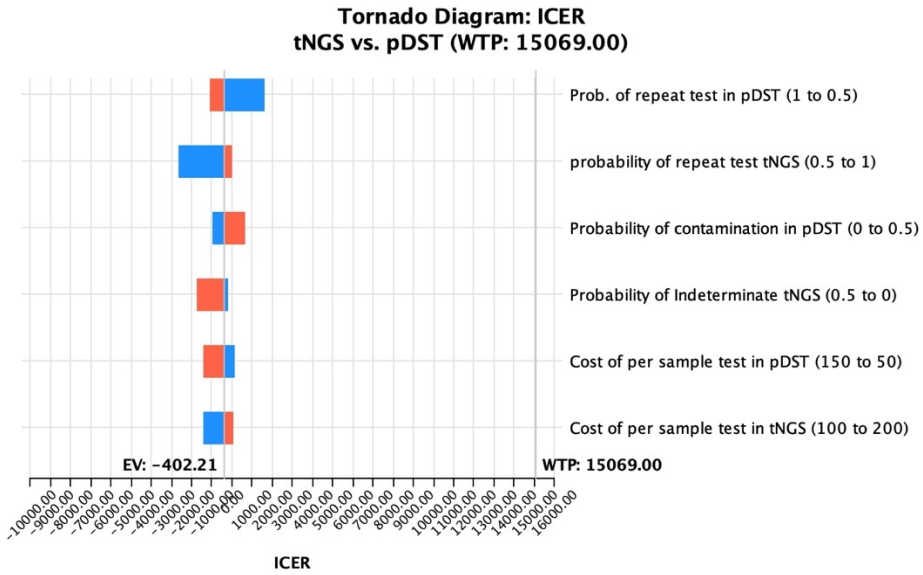


Supplement Figure 2.3: Simplified model decision structure. Two strategies were compared: DST with tNGS vs mWRDs followed by pDST among individuals with bac. confirmed TB. Schematically these strategies are separated by a square representing a decision node. The circles represent chance nodes where individuals may experience one of several possible events shown on subsequent lines. The probabilities of developing each event are listed in Table 1. Dotted lines represent model structure omitted for simplicity. In all cases, this omitted structure parallels that shown. The diamond symbol represents terminal node. RR= Rifampicin resistance; tNGS=Targeted Next Generation sequencing; pDST= Phenotypic Drugs susceptibility testing; Rif=Rifampicin, FQ= Fluroquinolone; BDQ= Bedaquiline; LZD=Linezolid; Rx. =treatment, TB-Tuberculosis; mWRD= Molecular WHO recommended Rapid Diagnostics

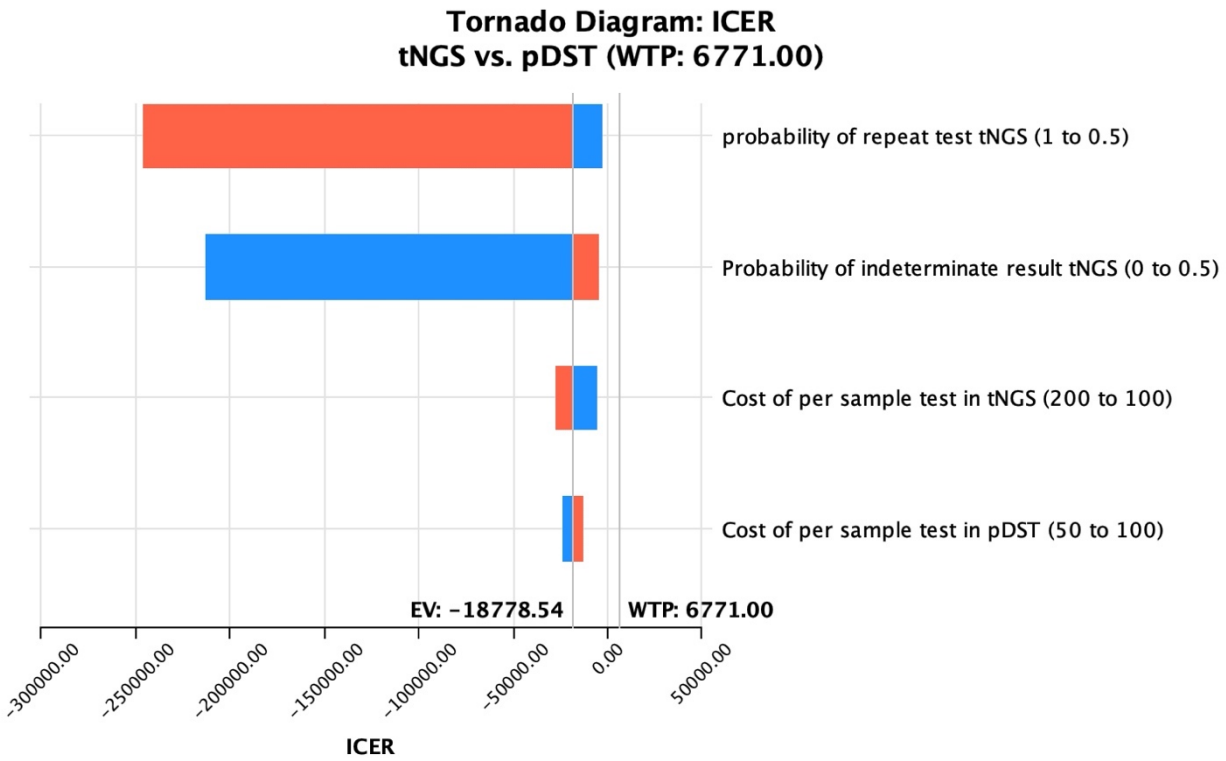
Supplement figure 4: One way sensitivity of Objective 1



Supplement Figure 2.4a: One way sensitivity analyses tornado diagram on incremental cost effectiveness ratio (ICER) of using tNGS as a replacement of pDST in South Africa as a subsequent test for DST following detection of RR. In this diagram, the horizontal bars illustrate how the ICER varies as each parameter is adjusted individually within the specified range, while all other parameters are held constant. The length of each bar reflects the degree of influence that parameter has on the ICER, with longer bars indicating greater impact. The orange bars represent the ICER when the parameter is at its high value, and the blue bars represent the ICER when the parameter is at its low value. The parameters are listed in descending order of their impact on the ICER, from top to bottom.



Supplement Figure 2.4b: One way sensitivity analyses tornado diagram on incremental cost effectiveness ratio (ICER) of using tNGS as a replacement of pDST in Georgia as a subsequent test for DST following detection of RR. In this diagram, the horizontal bars illustrate how the ICER varies as each parameter is adjusted individually within the specified range, while all other parameters are held constant. The length of each bar reflects the degree of influence that parameter has on the ICER, with longer bars indicating greater impact. The orange bars represent the ICER when the parameter is at its high value, and the blue bars represent the ICER when the parameter is at its low value. The parameters are listed in descending order of their impact on the ICER, from top to bottom.



Supplement Figure 2.4c: One way sensitivity analyses tornado diagram on incremental cost effectiveness ratio (ICER) of using tNGS as a replacement of pDST in India as a subsequent test for DST following detection of RR. In this diagram, the horizontal bars illustrate how the ICER varies as each parameter is adjusted individually within the specified range, while all other parameters are held constant. The length of each bar reflects the degree of influence that parameter has on the ICER, with longer bars indicating greater impact. The orange bars represent the ICER when the parameter is at its high value, and the blue bars represent the ICER when the parameter is at its low value. The parameters are listed in descending order of their impact on the ICER, from top to bottom.

Supplementary table 2.1: Additional scenario analysis tNGS compared to in-country DST practice

Country	Comparator	DALYs	Cost	ICER ($ per DALY averted, 95% uncertainty ranges)
Decreasing probability of death among those without treatment				
South Africa	XpertXDR+pDST	0.51	$3,223	Ref.
	tNGS	0.50	$3,401	$ 18,592
Georgia	XpertXDR+pDST	0.50	$3,035	Ref.
	tNGS	0.49	$3,180	$25,371
India	LPA and pDST	0.56	$981	Ref.
	tNGS	0.50	$971	Dominates LPA and pDST

Cost-effectiveness of targeted next-generation sequencing (tNGS) for detection of tuberculosis drug resistance in India, South Africa and Georgia: a modeling analysis

Suvesh Shrestha,[a] Angelina Addae,[a] Cecily Miller,[b] Nazir Ismail,[b,c] and Alice Zwerling[a,*]

[a]School of Epidemiology and Public Health, University of Ottawa, Ottawa, Canada
[b]Global Tuberculosis Program, World Health Organization, Geneva, Switzerland
[c]Department of Clinical Microbiology and Infectious Diseases, Faculty of Health Sciences, Wits University, Johannesburg, South Africa

eClinicalMedicine 2025;79: 103003
Published Online 24 December 2024
https://doi.org/10.1016/j.eclinm.2024.103003

Summary

Background Targeted next-generation sequencing (tNGS) is promising alternative to phenotypic drug susceptibility testing (pDST) for detecting drug-resistant tuberculosis (DRTB). This study explored the potential cost-effectiveness of tNGS for the diagnosis of DR-TB across 3 settings: India, South Africa and Georgia.

Methods To inform WHO guideline development group (GDG) on tNGS we developed a stochastic decision analysis model and assessed cost-effectiveness of tNGS for DST among rifampicin resistance individuals. We also assessed tNGS as initial test for TB drug resistance in bacteriologically confirmed TB. Diagnostic accuracy and cost data were sourced from a systematic review conducted for GDG, covering studies published until September 2022. The primary outcome was incremental cost (2021 US$) per disability-adjusted life year (DALY) averted.

Findings tNGS when compared with in-country DST, tNGS proved cost-effective in South Africa (ICER: $15,619/DALY averted, WTP: $21,165) but not in Georgia (ICER: $18,375/DALY averted, WTP: $15,069). In India, tNGS dominated in-country DST practice, providing greater health impact at lower cost. When comparing tNGS with universal pDST, tNGS was dominated by pDST in all three countries. In Georgia, using tNGS as initial test for TB drug-resistance compared to Xpert MTB/Rif followed by pDST appeared cost-effective. Scenario with 50% reduction in tNGS test kit costs made tNGS cost-effective across all three countries, while a high Bedaquiline resistance prevalence (30%) led to a worsening cost-effectiveness.

Interpretation tNGS may be cost-effective in India, South Africa and Georgia when comprehensive DST is not routinely performed. Thus, existing DST practice and healthcare infrastructure should be considered before implementation and scale-up of tNGS.

Funding Global Tuberculosis Program, World Health Organization (2022/1249364-0).

Keywords: Targeted next-generation sequencing (tNGS); Drug-resistant tuberculosis (DRTB); Cost-effectiveness analysis; Incremental cost-effectiveness ratio (ICER); Disability-adjusted life year (DALY)

Introduction

Drug-Resistant Tuberculosis (DR-TB) has become growing public health threat, with incidence increasing and only one third of people with multi-drug resistance newer DR-TB drugs i.e. bedaquiline (BDQ) and linezolid (LZD).[2,3]

To end the global DR-TB epidemic, universal DST which includes new and repurposed TB drugs should be

Chapter 3

Costs of Tuberculosis Preventive Treatment: Insights from Five Sub-Saharan African Countries

Suvesh Shrestha[1], Olivia D'Silva[1], Rose Mary Tazinya Asong[1], Anca Vasiliu[2], Nompumelelo Olive Mzizi[2], Debrah Vambe[2,3],Nokwanda Kota[3], Phumzile Dlamini[3], Teresa Steffy[4,2], Moliehi Lephosa[4], Jeany Matchado[5], Adamson Munthali[5], Brigid O'Brien[2,5], Martha Hope Ayuro[6], Peter Elyanu[6], Moses Mugerwa[6], Lilian Bernardine Komba[7], Egbert Busigazi[7], Alexander Kay[2,3], Anna Mandalakas[2], Alice Zwerling[1]

[1] School of Epidemiology and Public Health, University of Ottawa, Ottawa, Canada
[2] Baylor College of Medicine and Texas Children's Hospital, Houston, USA
[3] Baylor College of Medicine Children's Foundation, Mbabane, Eswatini
[4] Baylor College of Medicine Children's Foundation, Maseru, Lesotho
[5] Baylor College of Medicine Children's Foundation, Lilongwe, Malawi
[6] Baylor College of Medicine Children's Foundation, Kampala, Uganda
[7] Baylor College of Medicine Children's Foundation, Mbeya, Tanzania

3.1 Preface

This chapter presents the manuscript titled " Cost of Tuberculosis Preventive Treatment: Insights from five sub-Saharan African countries". This manuscript addresses the second research objective of this thesis: to estimate the economic cost of implementing tuberculosis preventive treatment (TPT) programs across different health system contexts, and to identify key cost drivers in high TB and HIV burden settings.

This study provides detailed micro-costing evidence from Eswatini, Lesotho, Malawi, Uganda and Tanzania using standardized costing methods to estimate per-individual and activity-based cost of TPT delivery. This empirical cost date contributes to inform economic evaluation, national budgeting and global policy on TPT implementation within resource-constrained settings.

The manuscript has been finalized and approved by all co-authors. Submission has been temporarily delayed allowing for internal review and alignment with current funding and dissemination considerations.

Author Contribution:

SS and AZ contributed to the conceptualization and design of the study, development of the standardized costing framework, data analysis, interpretation of findings, and manuscript preparation. SS led the micro-costing analysis.

AV, NOM, DV, NK, PD, TS, ML, JM, AM, BB, MHA, PE, MS, LBK, EB, AK, and AN contributed to the development of country-specific patient pathways, provision of programmatic

cost data, and primary data collection. ODS and RMT contributed to data entry and database management.

AZ and AM provided overall supervision, methodological guidance, and critical revision of the manuscript. All authors reviewed and approved the final version of the manuscript.

Ethical Approval:

Ethical approval was obtained from the University of Ottawa Research Ethics Boards (H-01-23-8344 – MOD4-8344).

Publication Status:

This manuscript has been submitted in The International Journal of Tuberculosis and Lungs Disease for publication and is currently under review.

3.2 Abstract

Background: Scaling up tuberculosis preventive treatment (TPT) is essential but hindered by operational and financial challenges, including limited cost evidence. This study estimated TPT delivery costs across five sub-Saharan African TB high-burden countries.

Methods: Micro-costing study was conducted from health system perspective across five clinics in Eswatini, Lesotho, Malawi, Uganda and Tanzania. Data were collected using standardized templates covering overhead, human resources, equipment, consumables, and drugs, using bottom-up and top-down approaches. Human resource time was measured via 648 observations using time-and-motion studies, questionnaires and timesheets. Costs are reported per patient in 2024 USD.

Results: Among adults, total cost per individual ranged from US$27-59 for 3 months of isoniazid plus rifapentine (3HP) and from US$22-67 for 6 months of isoniazid (6H). Among children, the cost of 6H ranged from US$32-80, while 3 months of daily rifampicin plus isoniazid (3RH) ranged from US$27-46. Human resources and drugs were the principal cost drivers, accounting for the majority of total costs across all countries. Consultation for TPT initiation and adherence monitoring was the most time-consuming and costly activity.

Conclusion: TPT implementation costs extend significantly beyond drug prices. National programs must adopt full-cost accounting that prioritizes workforce efficiency and service integration to ensure sustainable scale-up.

Keywords: Tuberculosis preventive treatment; Costing; Human resources; Time and Motion; Sub-Saharan Africa.

3.3 Background

Tuberculosis (TB) remains a leading cause of death globally, with an estimated 1.23 million deaths in 2024.(1) The burden is particularly significant in the African region, which accounts for 23% of incident TB cases and 31% of TB-related deaths, despite the region comprising only 15% of the world's population.(2) In sub-Saharan Africa, over 50% of TB cases are co-infected with HIV where (3,4) TB remains the leading cause of death among people with HIV (PWH) who have increased risk for TB infection and progression to TB disease.(5–7) Tuberculosis preventive treatment (TPT) is therefore a critical strategy in reducing the incidence of TB among PWH, as it prevents the progression from TB-infection to TB disease, averting morbidity and mortality and reducing ongoing transmission.(8)

TPT is a cornerstone of the WHO End TB Strategy, reinforced by UN High-Level Meetings in 2018 and 2023.(9,10) WHO recommends TPT for all PWH to prevent TB disease. The recommendations include shorter regimens like three months of daily isoniazid with rifampicin (3HR) and three months of weekly isoniazid plus rifapentine (3HP), which have improved adherence compared to longer traditional regimens such as 6 months of isoniazid (6H).(11–13) Evidence from community-based programs suggests that shorter regimens can also be successfully delivered in routine settings, achieving high levels of treatment completion.(14) However, Effective TPT scale-up in high-burden settings has been hindered by significant implementation challenges, including limited resources and health system logistics.(15)

Detailed cost evidence and analyses are crucial to guide the sustainable expansion of TPT programs. Nevertheless, evidence on the cost of implementing newer TPT regimens, particularly

in sub-Saharan Africa, remains limited. Existing frameworks, like the Value TB project, provide important guidance on TB care and prevention costs but largely focus on general TB services.(16) While studies like the CaP-TB initiative (17) and several cost-effectiveness studies (15,18–21) have assessed the cost-effectiveness of specific regimens, comprehensive cost data are lacking, posing challenges for cost estimates to optimize TPT delivery and ensure financial sustainability. In sub-Saharan Africa, where health systems are often under-resourced, and the economic burden of TB and HIV is substantial, understanding these costs is essential for avoiding additional strain on existing systems.(22)

This study aims to fill the existing knowledge gap by conducting a comprehensive costing analysis of the operational cost of providing different TPT regimens in five sub-Saharan African countries: Eswatini, Lesotho, Uganda, Malawi and Tanzania in clinics affiliated with Baylor College of Medicine. By estimating the costs associated with different TPT regimens and identifying key cost drivers, this research provides valuable data to support the scale-up of TPT programs in settings where they are most needed. The findings will also help to ensure that TPT delivery is both efficient and sustainable, ultimately contributing to the reduction of TB-related morbidity and mortality among PWH in sub-Saharan Africa.

3.4 Methods

3.4.1 Study Design

We conducted micro-costing study to estimate costs of providing TPT among PWH in clinics of Eswatini, Lesotho, Uganda, Malawi and Tanzania. All clinics are embedded within Ministry of Health service delivery framework, providing integrated TB/HIV care and operate as public-

private partnership managed by local non-governmental organizations. This study was nested within the Closing TB GAPs for people living with HIV (TB GAPs) study, which evaluated novel TB screening and diagnostic strategies, differentiated service delivery models on TPT uptake and completion, and cost-effectiveness of these interventions. Data collection for the costing analysis was conducted between 2022-2024.

Costing was conducted from healthcare system perspective using an ingredients-based approach, combining top-down and bottom-up methods to capture resource usage.(23) Costs were grouped in five categories: overhead, human resources (HR), equipment, consumables and drug costs. All costs were inflated to 2024 US dollars.

3.4.2 Calculating cost per individual on different TPT regimens:

TPT-related activities were identified based on country-specific pathways and TB management guidelines, which included TB screening, consultation to initiate TPT, treatment literacy, TPT dispensing, and follow-up visits for compliance and adverse event (AE) monitoring. While screening, consultation, and treatment literacy typically occurred during a single visit, TPT dispensing and follow-up visits varied by regimen and national guidelines, with full details shown in supplemental Table 3.1. Cost per-individual treated for different TPT regimens was calculated by summing costs associated with all required TPT-related activities, including screening, clinical visits, and medication dispensing, where each activity included HR, overhead, equipment, consumables, and drug costs.

3.4.3 Cost data collection and cost calculation by component:

Overhead costs included building and recurrent facility expenditures like utilities, communication, and administrative services. These costs were collected from clinic financial records. We used a top-down approach, where building cost was annualized assuming a 30-year useful life and a 3% discount rate, using the WHO amortization factor of 19.6.(23) An allocation factor for TB services reflecting the TB program contributions was used to obtain the overhead share attributable to TB activities. Overhead costs were converted to a per-minute rate and applied to activities based on measured activity duration.

HR costs were estimated using bottom-up approach. Staff time per activity was measured using three empirical methods: time and motion (TAM) observation, time estimation questionnaires (TEQ), and self-reported timesheets (TS) to intentionally triangulate our findings. Because individual tools may systematically over-represent or under-represent specific tasks, utilizing multiple complementary methods allowed us to capture an operational range reflecting true clinical time. In total, 648 time observations were collected across health care worker cadres involved in different TPT-related activities using these three tools. Of these, TEQ accounted for the largest share (n=389), followed by TAM (n=131), and TS (n=128) (Supplemental Figure 3.2). A detailed instructions document was developed to guide using these tools (Supplemental Methods 1.3), and research staff were trained accordingly. Across methods, the distributions showed substantial overlap in ranges, with no systematic differences. Given this consistency, and because these tools were designed for triangulation rather than independent evaluation, pooled median estimates were used and separate sensitivity analyses by tool were not conducted. Cadre-specific annual salaries were converted to a per-minute salary using facility-specific working hours. Human resource cost

per activity was calculated by multiplying the median activity time by per-minute salary and summing across cadres where applicable.

Equipment and consumables used for each activity were identified through TEQ data. Unit costs were obtained from financial records and procurement documents. Equipment costs were annuitized and converted to a per-minute rate, and the activity-based equipment cost was calculated by multiplying the per-minute cost by the measured time. Consumables were costed based on item-specific utilization per activity. Donated resources were valued using economic costing (market replacement value) to reflect their full opportunity cost.

TPT drug costs were calculated using both top-down and bottom-up approaches to account for wastage, shipping, storage and customs costs. Procurement and pharmacy records to estimate average consumption per patient. Regimen-specific cost was calculated based on national dosing guidelines and treatment duration. Detailed costing methods of overheads, HR, equipment, consumables and drugs are provided in supplemental methods and illustrated in supplemental figure 3.1.

3.4.4 Ethical Considerations

Ethical approval was obtained from the University of Ottawa Research Ethics Board (REB), CDC USA, Baylor College of Medicine and all relevant ethical boards in Eswatini, Lesotho, Malawi, Uganda and Tanzania. Informed consent was obtained from all HCW participants before data collection.

3.5 Results

3.5.1 TPT drugs cost across country

For 3HP regimen, drug regimen costs ranged narrowly from US$11 to US$15. Adult INH (300mg) was consistently the least expensive (US$3–4), whereas pediatric INH (100mg) costs varied widely (US$3-24), driven by use of child-friendly formulation. The 3RH regimen was used in Tanzania and Lesotho, where the pediatric regimen cost US$13 in Tanzania and US$23 in Lesotho (Supplemental Table 3.2). While all regimens were procured through the global drug facility, cost variations were impacted by country-specific procurement and pricing policies, including differences in national procurement agencies' handling and distribution charges applied beyond manufacturer or global drug facility prices.

3.5.2 Cost of TPT activities and components, excluding drugs

Table 1 summarizes cost per activity for TPT delivery, broken down by overheads, consumables (excluding drugs), equipment, and HR. The most expensive activities varied by country: consultation to initiate TPT was the most costly activity in Eswatini (US$5.3), Lesotho (US$7.7), and Malawi (US$18.7); while compliance and AE monitoring visits were the most costly activity in Uganda (US$5.5); and treatment literacy sessions were the most costly activity in Tanzania (US$6.1). Across all five settings, HR constituted the largest cost component within these activities. Supplemental Figure 3.3 illustrates cost components by activity. Given the prominent contribution of HR to the activity-level costs, we also examined staff time and associated costs. Figures 3.1 and 3.2 present the median, minimum and maximum staff time and associated cost per activity. Across settings, activities associated with higher total cost generally corresponded to higher staff time and cost. Specifically, consultation to initiate TPT in Eswatini, Lesotho and

Malawi, compliance and AR monitoring in Uganda, and treatment literacy in Tanzania were among the activities with both high total costs and high HR cost contributions.

3.5.3 Total cost per-patient treated with TB preventive treatment:

Table 3.2 presents the cost per patient treated with various TPT regimens across 5 countries. Cost of providing TPT varied by regimen and country. For the adult 3HP regimen, per-patient treatment costs ranged from US$27 to US$59. For the 6H regimen in adults, costs ranged from US$22 to US$67 per person treated. Pediatric TPT costs were generally higher, with 6H ranging from US$32 to $80 per child treated. The 3RH regimen was used in Lesotho and Tanzania, with a per-patient treatment cost of US$30 for adults and ranging from US$27 to US$46 for children.

Deterministic sensitivity analysis using minimum and maximum time bounds showed consistent cost estimates across most settings (Supplemental Figure 3.4). Malawi exhibited wider variance under maximum time inputs, reflecting higher baseline salary structures magnifying time fluctuations. These variations highlight how country-specific visit intervals, contact hours, and cadres interact with parameter uncertainty.

3.5.4 Key drivers of per-patient TPT cost by regimen and country:

In Lesotho and Tanzania, drug costs dominated when TPT regimen was 3HP, 3RH, or pediatric 6H, contributing 39–51% of total cost. For adult 6H, overhead was the major cost driver in Lesotho, while HR cost dominated in Tanzania. In Eswatini, Malawi, and Uganda, HR were the principal cost driver across most regimens, accounting for 41% to 80% of total cost. In Eswatini and Malawi, overhead costs were generally second-largest contributor (23% to 39%), except for

3HP regimen in Eswatini, where drug costs represented second-largest share (32%). In Uganda, drug costs ranked second for the 3HP (34%) and pediatrics 6H (29%). Figure 3a–e shows composition of per-patient TPT costs by regimen and country. Regimen-and country-specific totals are presented in supplemental table 3.3.

3.6 Discussion:

In this multi-country comprehensive cost analysis, the total costs per-patient treated with 3HP, 6H (adult), 6H (children), and 3RH (children) ranged from US$35 to US$59, US$22 to US$67, US$32 to US$80, and US$27 to US$46, respectively. Drug and human resource costs were consistently important drivers of cost. Activities such as consultation to initiate TPT and follow-up adherence and compliance monitoring were the most time-consuming and costly activities across all sites highlighting the importance of these activities to ensure patient comprehension and adherence. Overall costs were consistently further driven by drug costs, reflecting procurement processes that incorporate wastage, shipping, storage and customs costs.

Few studies have comprehensively examined the cost of TPT in sub-Saharan Africa, and most available evidence captures only limited components of service delivery. Ferguson et al. (2020) estimated cost of delivering 3HP in Uganda was US$22.7, while Jo et al reported a cost of US$24 per person for 3HP in Malawi; (15,24) Ryckman et al. reported 3HP costs ranging from approximately US$10 to US$32 across Eswatini, Lesotho, Malawi, and Uganda, with variations by age group. (19) Across these studies, reported drug costs ranged from approximately US$13 to US$15, which is comparable to our estimates. Differences in total per-patient costs are primarily driven by how service delivery costs were estimated. Previous studies approximated clinic costs

using WHO-CHOICE outpatient unit costs, which are generalised, top-down estimates of the average economic cost of a routine outpatient visit, yielding low per-visit cost (US$1-3).(25) In contrast, our study used a TB-specific, activity-based micro-costing approach directly measuring staff time and accounting for clinic-level overheads, consumables, and materials. Hence, these costs reflect a more comprehensive assessment of TPT delivery compared with previous estimates reported in the published literature.

Both drugs and HR were critical cost drivers in our analysis, consistent with findings from previous studies. Among all TPT specific activities, HR costs were the primary driver of cost, aligns with the evidence from other settings. A comparative costing study in Pakistan reported that clinic staff salaries constituted the single largest cost component of delivering TPT.(26) Similarly, Mafirakureva et al., in a study conducted across nine sub-Saharan African countries (Cameroon, Côte d'Ivoire, DRC, Kenya, Lesotho, Malawi, Tanzania, Uganda, Zimbabwe), found that personnel time accounted for most intervention costs for TB treatment. (17) Alsdurf et al., using TAM methods across multiple countries (Benin, Ghana, Indonesia, Vietnam and Canada), also showed that expanding TPT-related services substantially increased healthcare worker time for preventive activities.(27)

Importantly, these findings should be interpreted in the context of improving transparency around the full resources required for implementation. By capturing the actual activities and time required to deliver TPT services, this study aims to provide more realistic estimates that can inform program planning and resource allocation, rather than suggesting that TPT delivery itself is inherently costly.

Drug costs were key driver of overall TPT cost, particularly when TPT included rifapentine-based regimens and pediatric formulations. This aligns with prior studies showing that the cost-effectiveness of short-course TPT regimens is highly sensitive to rifapentine price.(15,19) Although most TB drugs were procured through the Global Drug Facility, cross-country variation in drug costs persisted due to additional country-specific handling, storage, distribution, and administrative charges. The substantial cross-country cost variations, notably between Tanzania and Malawi, reflect differences in baseline salary structures and localized service delivery models, including clinical visit schedules and contact hours. Furthermore, these totals are influenced by country-specific national procurement practices for commodities and site-specific overhead allocation methods, rather than varying clinical protocols. By accounting for these structural realities, this study provides empirical cost estimates to inform future cost-effectiveness models. Crucially, cost alone should not guide regimen choices as shorter regimens improve adherence and completion. Evaluating our findings therefore requires complementary cost-effectiveness analysis to determine if gains in adherence outweigh the costs of short-course and child-friendly regimens.

This study has several notable strengths. By combining bottom-up and top-down costing approaches, we captured patient-level resource use and shared facility costs. (28) The integration of multiple empirical time estimation methods like TAM, TEQ, and time sheets enabled triangulation and improved robustness of staff time cost estimates. Standardized data collection enhanced cross-country comparability, while country-specific patient pathways ensured that estimates reflected operational realities. Time data relied partly on observation and self-report, which may introduce recall or measurement bias, particularly in the self-reported timesheet. This

was addressed through the triangulation and use of different data collection modalities.(29) While the study clinics operate within national frameworks as public-private partnerships following Ministry of Health guidelines, the transferability of these economic findings may vary across different healthcare settings. Core clinical delivery aligns nationwide because these sites perform identical mandated clinical tasks, and program logistics are largely standardized through central procurement. However, these results reflect specific implementation models and may not fully represent peripheral or rural health centers with different resources. Therefore, care is needed when translating these estimates to diverse healthcare environments where operational capacity or human resource scales differ

TB preventive treatment is an important element in the END TB Strategy, and the successful scale-up of TPT for PWH will require innovative solutions, particularly within resource-limited settings. This work highlights examples of efficiency-focused workforce strategies in TPT implementation. Task-shifting by delegating TPT initiation and follow-up to nurses may reduce reliance on higher-cost clinical staff. (30) Integrating TPT into existing differentiated service delivery (DSD) models (12), such as aligning TPT visits with routine ART refill appointments, can further minimize personnel time and patient visits. Given that follow-up visits for adherence and AE monitoring are among the most time-consuming and costly components of TPT delivery, differentiated service delivery models incorporating enhanced adherence support, such as bidirectional messaging, could reduce unnecessary clinic visits by targeting in-person follow-up to individuals who require clinical assessment, thereby improving efficiency and optimizing health system resources.(31) In parallel, reducing the cost of TPT medications, especially rifapentine, is critical for sustainable scale-up. While recent global agreements have lowered adult 3HP to under US$10, national TB

programs should leverage pooled procurement mechanisms and platforms like the GDF to secure these lower prices.(32) Drugs procured through GDF may still incur additional national charges, underscoring the need to strengthen procurement and supply chain systems to reduce downstream costs. Together, workforce optimization, service integration, and strategic procurement can minimize TPT delivery cost and support progress toward ending TB.

3.7 Acknowledgement:

This research has been supported by the U.S. Centers for Disease Control and Prevention (CDC) under the terms of cooperative agreement number U01GH002278 (PI Mandalakas). We gratefully acknowledge the five Baylor Centers of Excellence, healthcare workers, and study participants for their contributions.

3.8 Reference:

1. 2025 tuberculosis Global report.
2. Brazzaville. Tuberculosis in the WHO African Region: 2023 progress update [Internet]. 2023. Available from: http://apps.who.int/bookorders.
3. Zumla A, Petersen E, Nyirenda T, Chakaya J. Tackling the Tuberculosis Epidemic in sub-Saharan Africa - unique opportunities arising from the second European Developing Countries Clinical Trials Partnership (EDCTP) programme 2015-2024. International Journal of Infectious Diseases. 2015;32.
4. Vasiliu A, Abelman R, Kherabi Y, Iswari Saktiawati AM, Kay A. Landscape of TB Infection and Prevention among People Living with HIV. Vol. 11, Pathogens. 2022.
5. Ford N, Matteelli A, Shubber Z, Hermans S, Meintjes G, Grinsztejn B, et al. TB as a cause of hospitalization and in-hospital mortality among people living with HIV worldwide: A systematic review and meta-analysis. Vol. 19, Journal of the International AIDS Society. 2016.
6. Williams BG, Dye C. Antiretroviral drugs for tuberculosis control in the era of HIV/AIDS. Science (1979). 2003;301(5639).

7. World Health Organization. WHO consolidated guidelines on tuberculosis Module 2: Screening Systemic screening for tuberculosis disease. World Health Organization. 2020.
8. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database of Systematic Reviews. 2010;
9. World Health Organization. WHO | WHO End TB Strategy. World Health Organization. 2015;
10. Fuady A, Hutanamon T, Herlinda O, Luntungan N, Wingfield T. Achieving universal social protection for people with tuberculosis. Vol. 9, The Lancet Public Health. 2024.
11. WHO. WHO consolidated guidelines on tuberculosis. Module 1: Prevention. Infection prevention and control. WHO. 2022.
12. WHO. WHO Operational Handbook on Tuberculosis Module 1: Tuberculosis Preventive Treatment. World Health Organisation. 2020.
13. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection. New England Journal of Medicine. 2011;365(23).
14. Kay AW, Sandoval M, Mtetwa G, Mkhabela M, Ndlovu B, Devezin T, et al. Vikela Ekhaya: A Novel, Community-based, Tuberculosis Contact Management Program in a High Burden Setting. Clin Infect Dis [Internet]. 2021 May 1 [cited 2026 Jan 22];74(9):1631. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC9070808/
15. Ferguson O, Jo Y, Pennington J, Johnson K, Chaisson RE, Churchyard G, et al. Cost-effectiveness of one month of daily isoniazid and rifapentine versus three months of weekly isoniazid and rifapentine for prevention of tuberculosis among people receiving antiretroviral therapy in Uganda. 2020; Available from: http://onlinelibrary.wiley.com/doi/10.1002/jia2.25623/full
16. Sweeney S, Laurence Y V., Cunnama L, Gomez GB, Garcia-Baena I, Bhide P, et al. Cost of TB services: approach and summary findings of a multi-country study (Value TB). International Journal of Tuberculosis and Lung Disease. 2022;26(11).
17. Mafirakureva N, Mukherjee S, de Souza M, Kelly-Cirino C, Songane MJP, Cohn J, et al. Cost-effectiveness analysis of interventions to improve diagnosis and preventive therapy for paediatric tuberculosis in 9 sub-Saharan African countries: A modelling study. PLoS Med. 2023;20(9 September).

18. Kim HY, Hanrahan CF, Martinson N, Golub JE, Dowdy DW. Cost-effectiveness of universal isoniazid preventive therapy among HIV-infected pregnant women in South Africa. International Journal of Tuberculosis and Lung Disease. 2018 Dec 1;22(12):1435–42.
19. Ryckman T, Weiser J, Gombe M, Turner K, Soni P, Tarlton D, et al. Impact and cost-effectiveness of short-course tuberculosis preventive treatment for household contacts and people with HIV in 29 high-incidence countries: a modelling analysis. Lancet Glob Health. 2023;11(8).
20. Zhu J, Lyatuu G, Sudfeld CR, Kiravu A, Sando D, Machumi L, et al. Re-evaluating the health impact and cost-effectiveness of tuberculosis preventive treatment for modern HIV cohorts on antiretroviral therapy: a modelling analysis using data from Tanzania. Lancet Glob Health. 2022;10(11).
21. Mandalakas AM, Hesseling AC, Gie RP, Schaaf HS, Marais BJ, Sinanovic E. Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting. Thorax [Internet]. 2012 [cited 2026 Jan 22];68(3):247. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11967563/
22. Xue Y, Zhou J, Wang P, Lan JH, Lian WQ, Fan YY, et al. Burden of tuberculosis and its association with socio-economic development status in 204 countries and territories, 1990–2019. Front Med (Lausanne). 2022;9.
23. Cunnama L et al. Costing Guidelines for Tuberculosis Interventions. World Health Organization; 2020.
24. Jo Y, Gomes I, Flack J, Salazar-Austin N, Churchyard G, Chaisson RE, et al. Cost-effectiveness of scaling up short course preventive therapy for tuberculosis among children across 12 countries. EClinicalMedicine. 2021;31.
25. Bertram MY, Lauer Id JA, Stenberg Id K, Tan T, Id TE, Askheim C, et al. Methods for the Economic Evaluation of Health Care Interventions for Priority Setting in the Health System: An Update From WHO CHOICE Politics and Power in Global Health: The Constituting Role of Conflicts Comment on "Navigating Between Stealth Advocacy …. Int J Health Policy Manag [Internet]. 2021 [cited 2025 Dec 7];10(11):117–9. Available from: http://ijhpm.com
26. Yuen CM, Majidulla A, Jaswal M, Safdar N, Malik AA, Khan AJ, et al. Cost of Delivering 12-Dose Isoniazid and Rifapentine Versus 6 Months of Isoniazid for Tuberculosis Infection in a High-Burden Setting. Clinical Infectious Diseases. 2021;73(5).

27. Alsdurf H, Oxlade O, Adjobimey M, Ahmad Khan F, Bastos M, Bedingfield N, et al. Resource implications of the latent tuberculosis cascade of care: a time and motion study in five countries. BMC Health Services Research 2020 20:1 [Internet]. 2020 Apr 21 [cited 2025 Dec 16];20(1):341-. Available from: https://link.springer.com/article/10.1186/s12913-020-05220-7
28. Cunnama L, Sinanovic E, Ramma L, Foster N, Berrie L, Stevens W, et al. Using Top-down and Bottom-up Costing Approaches in LMICs: The Case for Using Both to Assess the Incremental Costs of New Technologies at Scale. Health Economics (United Kingdom). 2016;25.
29. McElwee E, Cresswell JA, Yao C, Bakeu M, Cavallaro FL, Duclos D, et al. Comparing time and motion methods to study personnel time in the context of a family planning supply chain intervention in Senegal. Hum Resour Health. 2018;16(1).
30. Dam TA, Forse RJ, Tran PMT, Vo LNQ, Codlin AJ, Nguyen LP, et al. What makes community health worker models for tuberculosis active case finding work? A cross-sectional study of TB REACH projects to identify success factors for increasing case notifications. Hum Resour Health. 2022;20(1).
31. Mavhu W, Willis N, Mufuka J, Bernays S, Tshuma M, Mangenah C, et al. Effect of a differentiated service delivery model on virological failure in adolescents with HIV in Zimbabwe (Zvandiri): a cluster-randomised controlled trial. Lancet Glob Health. 2020;8(2).
32. Stop TB Partnership | Global Drug Facility Global Health.

Table 3.1: Cost of TPT delivery activities by country, disaggregated by cost components (human resources, consumables, equipment, and overheads)

Country	Component	Activities				
		TB screening	Consultation to initiate TPT	Treatment literacy for TPT	TPT dispensing	Compliance and AE monitoring
Eswatini	Overhead	$1.1	$1.6	$1.5	$0.9	$1.0
	Consumable	$0.3	$0.0	$0.0	$0.7	$0.0
	Equipment	$0.0	$0.0	$0.0	$0.0	$0.0
	Human resource	$0.4	$3.8	$3.6	$0.7	$2.5
	Total cost	$1.8	$5.3	$5.1	$2.2	$3.5
Lesotho	Overhead	$0.9	$3.6	$3.9	$0.4	$3.2
	Consumable	$1.2	$0.5	$0.0	$0.4	$0.5
	Equipment	$0.1	$0.2	$0.2	$0.0	$0.3
	Human resource	$0.2	$3.4	$1.1	$0.2	$3.0
	Total cost	$2.3	$7.7	$5.3	$0.9	$6.9
Malawi	Overhead	$1.4	$3.7	$2.3	$1.0	$1.8
	Consumable	$0.3	$0.2	$0.1	$0.1	$0.2
	Equipment	$0.0	$0.1	$0.1	$0.0	$0.0
	Human resource	$1.3	$14.7	$2.1	$0.9	$1.6
	Total cost	$2.9	$18.7	$4.5	$2.0	$3.7
Uganda	Overhead	$0.6	$0.5	$0.5	$0.5	$0.5
	Consumable	$0.2	$0.0	$0.2	$0.0	$0.1
	Equipment	$0.03	$0.02	$0.04	$0.1	$0.01

	Human resource	$1.3	$4.4	$0.7	$1.2	$4.9
	Total cost	$2.1	$4.9	$1.4	$1.7	$5.5
Tanzania	Overhead	$0.3	$0.5	$1.9	$0.3	$0.6
	Consumable	$0.3	$0.0	$0.0	$0.2	$0.0
	Equipment	$0.1	$0.0	$0.1	$0.0	$0.0
	Human resource	$0.3	$0.8	$4.1	$0.2	$0.6
	Total cost	$0.9	$1.3	$6.1	$0.6	$1.3

Notes: Activity-level costs are presented by country and disaggregated into human resources, consumables (excluding drugs), equipment, and overheads. Costs reflect the health system perspective and represent the average cost per activity per participant. Total cost represents the sum of all cost components for each activity. Abbreviations: TB: Tuberculosis; TPT – Tuberculosis Preventive Treatment; AE – Adverse Event

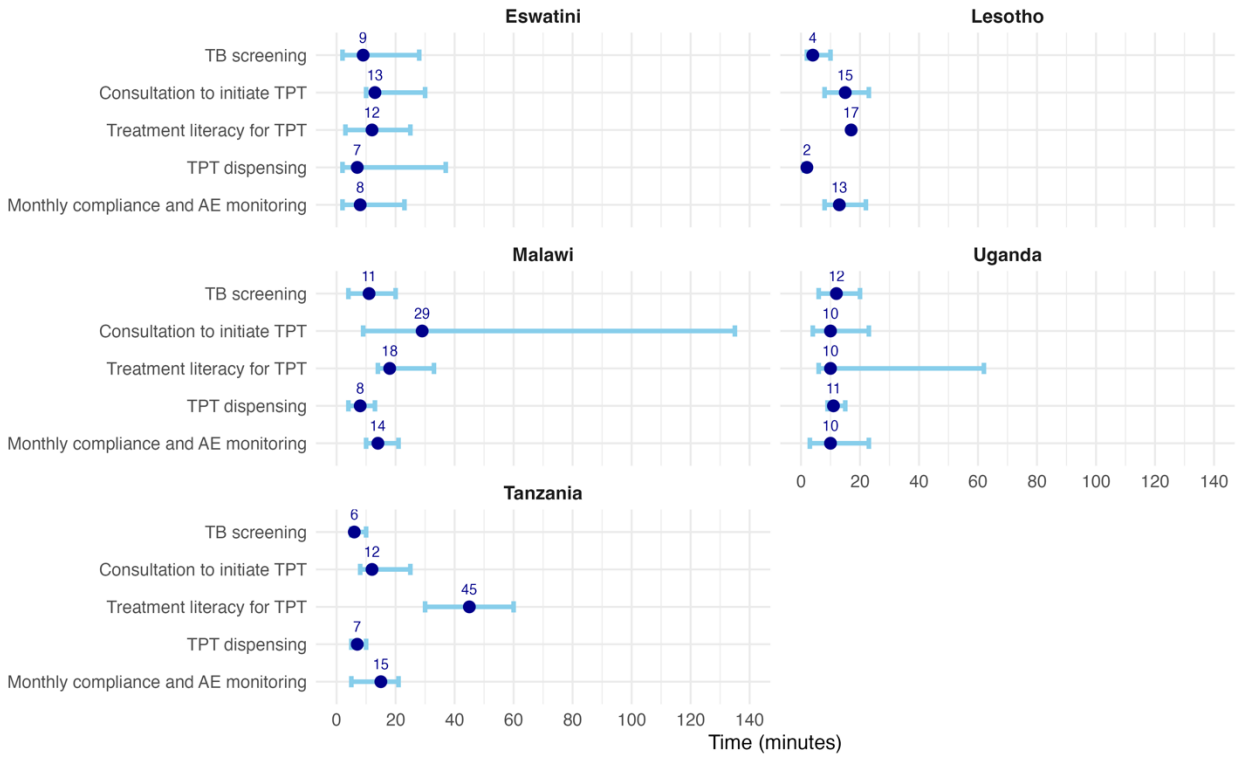


Figure 3.1. Median human resource time (in minutes) spent on tuberculosis preventive treatment (TPT) activities in Eswatini, Lesotho, Malawi, Uganda and Tanzania.
The figure displays the median time required by healthcare workers to complete five TPT-related activities: tuberculosis (TB) screening, consultation to initiate TPT, TPT dispensing, monthly compliance and adverse event (AE) monitoring, and treatment literacy for TPT. Dots represent the median time, and horizontal lines indicate the minimum and maximum values observed across facilities.

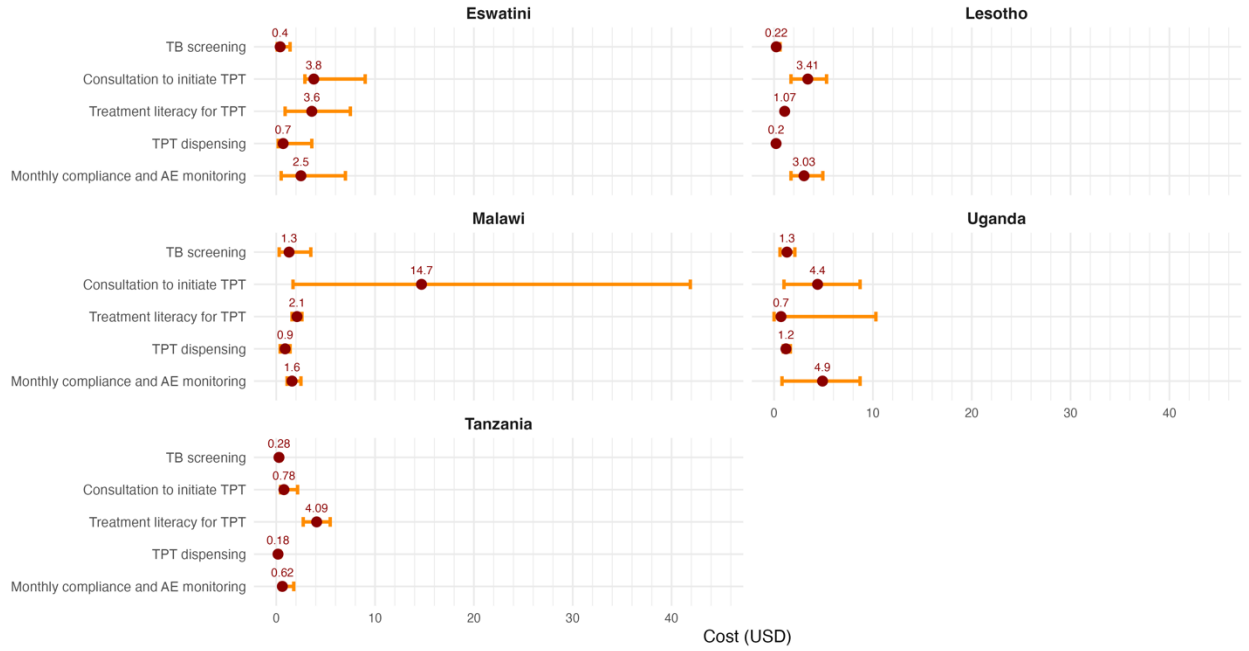


Figure 3.2. Median human resource cost (in US$) for tuberculosis preventive treatment (TPT) activities in Eswatini, Lesotho, Malawi, Uganda and Tanzania.
The figure illustrates the median personnel cost incurred for five key TPT-related activities: tuberculosis (TB) screening, consultation to initiate TPT, TPT dispensing, monthly compliance and adverse event (AE) monitoring, and treatment literacy for TPT. Dots represent the median time, and horizontal lines indicate the minimum and maximum values observed across facilities.

Table 3.2: Cost per-patient treated with different TPT regimens by country (US$, 2024)

Country	Cost of 3HP	Cost of 6H (Adult)	Cost of 6H (Children)	Cost of 3RH (Adult)	Cost of 3RH (Children)
Eswatini	$35	$34	$32	-	-
Lesotho	$38	$27	$47	-	$46
Malawi	$59	$67	$80	-	-
Uganda	$43	$41	$54	-	-
Tanzania	$27	$22	$34	$30	$27

Notes: Costs include overhead, human resources, equipment, consumables, and drug costs, and reflect the health system perspective. Costs represent the total cost incurred for a participant who completes the full TPT regimen. Dashes indicate regimens not implemented in the respective country.
Abbreviations: 3HP = 3-month weekly isoniazid–rifapentine; 6H = 6-month isoniazid; 3RH = 3-month rifampicin–isoniazid

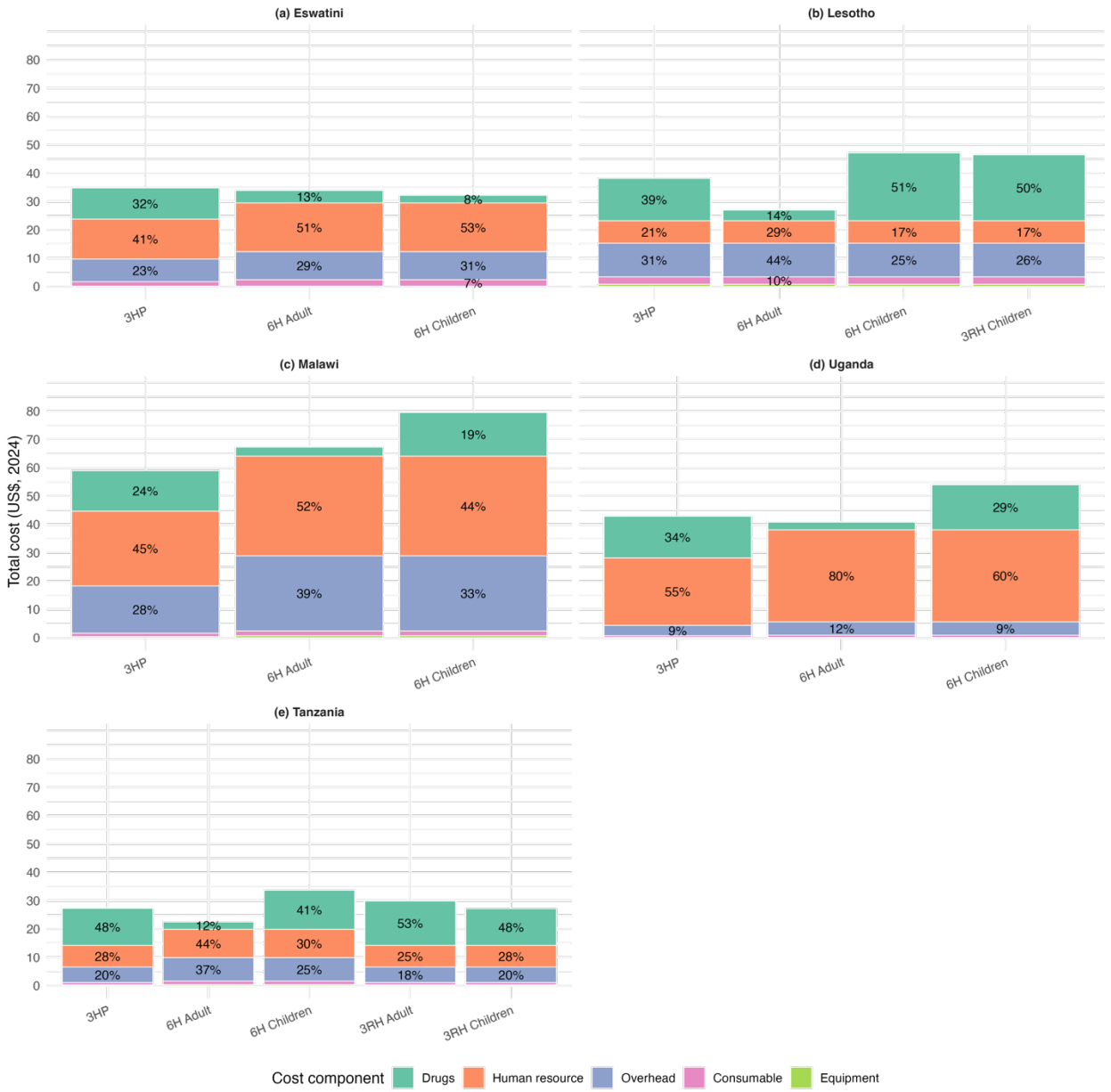


Figure 3.3. Share of total per-patient cost by component for each TPT regimen, by country. Panels show (a) Eswatini, (b) Lesotho, (c) Malawi, (d) Uganda, (e) Tanzania. Within each panel, bars correspond to regimens implemented in that country—3HP, 6H (Adult), 6H (Children), and where available 3RH (Adult) and 3RH (Children). Bars are scaled to 100%; segments denote cost components (Drugs, Human resource, Overhead, Consumables, Equipment). Numbers inside segments are within-regimen percentages; values <3% are not displayed. 3RH (Children) is reported for Lesotho and Tanzania; 3RH (Adult) is reported only for Tanzania. Abbreviations: 3HP = 3-month once-weekly isoniazid–rifapentine; 6H = 6-month isoniazid; 3RH = 3-month rifampicin–isoniazid; HR = human resources.

3.9. Supplemental appendix

This appendix is a part of the original submission.

Supplemental to: Shrestha S, et al. Costs of Tuberculosis Preventive Treatment: Insights from Five Sub-Saharan African Countries

3.9.1Supplemental methods:

3.9.1.1 Framework for calculating per-patient cost on different TPT

To estimate the per-patient cost of TPT across different TPT regimens and populations, we mapped the key activities and visit schedules for each country-regimen combination. The table below summarizes the regimen duration, activities involved and visit frequency by country.

Supplemental Table 3.1. Framework for calculating cost per individual receiving tuberculosis preventive treatment (TPT): Activities and calculation by country.

Country	Population & Regimen	Regimen Duration	Activities included	Visit Frequency
Eswatini	Adults/children on 3HP	3 months	Screening + Consultation + (Dispensing × # of visits) + (Compliance & AE monitoring × # of visits) + Treatment literacy	Every 2 month (2 visit for 3HP and 3 visit for 6H)
	Adults on 6H	6 months		
	Children on 6H	6 months		
Lesotho	Adults/children on 3HP	3 months		All TPT drugs dispensed during initiation with monthly follow-up visits
	Adults on 6H	6 months		
	Children on 6H	6 months		
	Children on 3RH	3 months		
Malawi	Adults/children on 3HP	3 months		Month follow up visit (3 visit for 3HP and 6 visit for 6H)
	Adults on 6H	6 months		
	Children on 6H	6 months		
Uganda	Adults/children on 3HP	3 months		Every 3 month (2 visit for 3HP and 3 visit for 6H)
	Adults on 6H	6 months		
	Children on 6H	6 months		
Tanzania	Adults/children on 3HP	3 months		Monthly follow up visit (3 visit for 3HP and 6 visit for 6H)
	Adults on 6H	6 months		
	Children on 6H	6 months		
	Adult on 3RH	3 months		
	Children on 3RH	3 months		

Abbreviations: TPT – Tuberculosis Preventive Treatment; AE – Adverse Event; 6H – Isoniazid Preventive Therapy; 3HP – 3-month regimen of isoniazid and rifapentine; 3RH – 3-month regimen of rifampicin and isoniazid.

3.9.1.2 Details on cost data collection and cost calculation by component:

The cost of different components was collected in the standardized data collection tools as shown in Supplementary_CostingSheet_S1. Figure 2 shows the cost estimation approach for TB activities by cost component, data source, and method.

For overhead, the cost of building was collected from the financial records. In addition to building costs, annual recurrent expenditures like utilities, communication and administration costs were also collected from financial records. For overhead costing (building + recurrent), we used a top-down approach, with data sourced from clinic financial records. Building cost was annualized assuming a 30-year useful life and a 3% discount rate, using the WHO amortization factor of 19.6.(21) Annual recurrent overheads were also considered, including utilities, communication, administration, and similar non-capital items. The allocation factor for TB services reflecting the TB program contributions was used to obtain the overhead share attributable to TB activities. A per-minute overhead rate was calculated by dividing by the facility's operating days per year and hours of operation per day. Overhead cost per activity was calculated by multiplying the median time of the activity by the per-minute overhead cost.

For human resource costs, the salary scale of each staff cadre was collected from financial records, and staff time per activity was recorded using three empirical methods: Time and Motion (TAM) studies, which observed healthcare workers performing TB screening, diagnosis, and TPT delivery; TEQ surveys completed by clinic staff to estimate activity durations; and self-reported Time Sheets (TS) documenting time spent on TB-related tasks. A detailed instructions document was developed to guide the use of these three tools, which are explained in detail in the next chapter, and research staff were trained using these documents. To calculate HR costs, a bottom-up approach was used. A median time per activity was calculated from the data recorded in the

three tools: TAM, TS, and TEQ. Each cadre's annual salary was converted to a per-minute salary using the facility's number of working days per year and hours worked per day.

$$\text{Salary}_{\text{per min}} = \frac{\text{Annual salary}}{\text{Working days/year} \times \text{Hours/day} \times 60}.$$

Then the human resource cost per activity was calculated as:

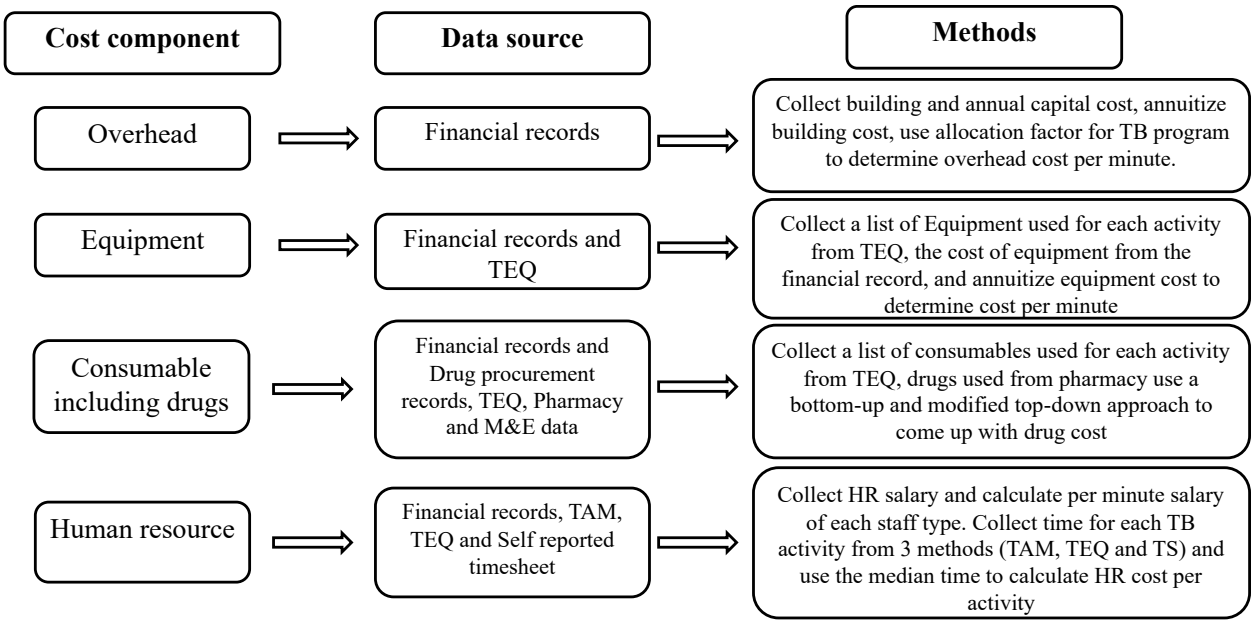
$$\text{HR cost per activity} = \text{Salary}_{\text{per min}} \times \text{Median time (minutes)}.$$

When multiple cadres contributed to an activity, the calculation was applied to each cadre and summed to obtain the total HR cost for that activity.

For equipment and consumables, a comprehensive list of equipment and consumables used for each activity was compiled using the TEQ and cost of each equipment and consumable was sourced form financial records, procurement documents, or online using current market value when necessary. For equipment cost each equipment item was annuitized using its expected useful life and a 3% annualization rate. The resulting annual equipment cost was converted to a per-minute rate using the facility's operating days per year and hours per day (as for overhead). For each activity, we used the TEQ equipment list to sum the per-minute cost of all relevant items and then multiply this summed per-minute rate by the measured activity time to obtain the equipment cost per activity. For consumables, utilization was assessed according to each TB activity and collected in the TEQ. For each item, unit costs were sourced from facility financial records.

TPT regimen costs were calculated using top-down and bottom-up approaches to account for wastage and shipping, and customs costs. Data were sourced from procurement records, and total dose dispersion data were collected from pharmacy records and enrollment data from Monitoring and Evaluation (M&E) records. Using average weights for children and adults, we determined the tablets per dose, then calculated total tablets per regimen by multiplying tablets per dose by the

treatment duration (days); multiplying by the cost per tablet yielded the total drug cost per regimen. In the modified top-down approach, we used dispensing data to estimate average consumption per patient by dividing the total number of tablets dispensed by the number of patients initiated on that regimen, and then multiplying this average by the cost per tablet to obtain the dispensing-based drug cost per regimen



Supplemental Figure 3.1. Cost estimation approach for tuberculosis (TB) activities by cost component, data source, and method.
This figure outlines the methodology used to estimate the cost of TB service delivery activities, categorized into four main cost components: overhead, equipment, consumables (including drugs), and human resources. For each component, the corresponding data sources are indicated, including financial records, time estimation tools (Time Estimate Questionnaire [TEQ], Time-and-Motion [TAM], and timesheets), and drug procurement or monitoring and evaluation (M&E) data. The methods column details how unit costs were derived, including annuitization of capital costs and calculation of per-minute human resource costs using median time estimates across three measurement methods.

3.9.1.3 Human Resource time data collection tools and guidelines:

This package includes the following data collection tools for economic data collection of health care system costs:

1. Informed Consent form: Each participating HCW must sign an informed consent prior to any direct observation or completion of TEQ or self-reported timesheet. Reassure HCWs that this is not being used for performance evaluation, all responses will be anonymous, supervisors will not see responses and their position is not dependent on their participation.

2. Time and motion studies (TAM): The objective of the Time and Motion Study is to determine a 'normal' or average time for a specific activity by observing exactly how much time is being devoted to each task of interest. TAM should be done on a typical clinic workday (avoid half days, days mostly scheduled for meetings, etc.). TAM should be conducted for the entire day's work (i.e. follow the staff from beginning of their work day until end of their work day). At least three TAM observations per clinic staff type identified.

3. Interviews and observations of time equipment and consumables/Time estimation questionnaires (TEQ): These sheets are used to list the consumables and equipment used for each service being costed and the average time spent per patient on each relevant activity. During your first interview with staff, please fill one sheet per service/activity of interest. Ideally, we want to have 3-5 observations for each service/activity of interest collected from different providers (can be same staff cadre).

4. Self-reported time sheet: The self-reported time sheet can be completed by the health care worker at the end of each day for a typical week or the research staff can help facilitate

completion of the form by working with the HCW at the end of each day. Daily or weekly reminders can be very helpful in encouraging timely completion. Research staff should review the timesheet and instructions for completion during the consent and TEQ interview.

TB GAPS TIME AND MOTION STUDY FORMS (TAMs)

Time and Motion Studies are useful to determine a 'normal' or average time for a specific activity by observing exactly how much time is being devoted to each task of interest.

- TAM should be done on a typical clinic workday (avoid half days, days mostly scheduled for meetings, etc.).
- TAM should be conducted for the entire day's work (i.e. follow the staff from beginning of their work day until end of their work day).
- Please stay outside the clinical room or out of earshot to maintain provider client privacy and confidentiality.
- Please collect at least three TAM observations per clinic staff type identified.
- Please scan all the hard copy and share with uOttawa team every week.

EXAMPLE SCRIPT

Thank you for your willingness to participate in the TAM measurements today. As you can see on this sheet [show TAM form], I will be recording the exact time that you begin and end an activity. For example, if a patient comes into your clinic room at 9:37am, I will write that down and then when the patient leaves the room at 9:52am. I will note that time as the end of the patient encounter. I will always wait outside the consultation room, so once the consultation has

ended, please tell me the type of patient activity so I can record it on the form. You can then continue on to your next task.

I will be here for the entire workday, and will need to note when you take breaks (for tea or coffee, lunch, personal time, or to use the restroom), but I do not need to know what you are doing during this time. This information will not be provided to supervisors or management. It may not be obvious to me when you are taking a break, so please let me know when you are starting a break so I will know not to follow you, or attribute the time to a clinical activity.

Lastly, I have an additional questionnaire and time sheet that I will need to ask you about your typical work activities [show other forms]. If there is a good time, such as lunch, for me to ask these questions please let me know.

Do not hesitate to ask me questions throughout the day. Again, thank you for your participation in these TAM measurements

INTERVIEWS & OBSERVATIONS OF TIME, EQUIPMENT AND CONSUMABLES (TEQs)

These sheets are used to list the consumables and equipment used for each service being costed. We also ask about average time spent per patient on each relevant activity before the implementation of TB GAPs project (Pre-TB GAPs) and after the implementation of TB GAPs (Post TB GAPs).

During your first interview with staff, please fill one sheet per service/activity of interest. Ideally, we want to have 5 observations for each service/activity of interest collected from different providers (can be same staff cadre).

SELF REPORTED TIME SHEETS

The self-reported time sheet can be completed by the health care worker at the end of each day for a typical week or the research staff can help facilitate completion of the form by working with the HCW at the end of each day. Daily or weekly reminders can be very helpful in encouraging timely completion. Research staff should review the timesheet and instructions for completion during the consent and TEQ interview.

- Please collect at least five-time sheet per clinic staff type identified.
- Please scan all the hard copy and share with uOttawa team every week.

3.9.1.3.1 TB GAPS economic data collection tool: TAM

ENTER CODE FOR STAFF TYPE, TIME IN AND OUT, AND CODES OF ANY SERVICE PROVIDED. PLEASE USE ONE SHEET FOR ONE STAFF.

Number	STAFF CODE	TIME IN	TIME OUT	SERVICE CODE	SERVICE CODE	SERVICE CODE
Date & Clinic:						
Arrival time						
Activity 1						
Activity 2						
Activity 3						
Activity 4						
Activity 5						
Activity 6						
Activity 7						
Activity 8						
Activity 9						
Activity 10						

Activity 11						
Activity 12						
Activity 13						
Activity 14						
Activity 15						
Activity 16						
Activity 17						
Activity 18						
Activity 19						
Activity 20						
Activity 21						
Activity 22						
Activity 23						
Time exiting						

Note: These sheet needs to be completed and shared within one week.

Baylor COE			
STAFF	CODE	SERVICE	CODE
Triage nurse	A	Triage	1
Prescribing nurse/Nurse clinician	B	Consultation to prescribe TPT	2
Adherence counseling/ Nurse	C	Consultation to rule out TB	3
Pediatrician	D	Consultation to diagnose TB and initiate TB treatment	4
Clinical officer	E	Non-TB related consultation	5
Pharmacy supervisor /Pharmacy technician	F	Sputum collection	6
Pharmacy assistant	G	Sputum induction	7
Nutritionist	H	TPT dispensing	8
Psychosocial counselor	I	ATT dispensing	9
Social worker	J	Monthly compliance and AE monitoring of TPT	10
Community health worker	K	Monthly compliance and AE monitoring of ATT	11
Peer supporter	L	Consultation to initiate TPT / Adherence counseling for TPT	12
	M	Adherence counseling for ATT	13
	N	Adherence counseling for ART and other non-TB medications	14
	O	Nutrition consultation for severely malnourished individuals	15
	P	Nutrition consultation for moderately malnourished individuals	16
	Q	Nutrition consultation for those with non-malnourished individuals	17
		General psychosocial consultation	18

		Psychosocial consultation for Active TB individuals	19
		Psychosocial consultation for non-TB related individuals	20
		Phone call for active TB related issues	21
		Phone call for latent TB related issues	22
		Phone call for non-TB related issues	23
		Community visits for active TB related issues	24
		Community visits for latent TB related issues	25
		Outreach community visit- non-TB related issue	26
		Admin work (record keeping, email etc.)	27
		Break/Lunch	28
		Training	29
		Focused Assessment with Sonography for HIV-associated tuberculosis (FASH) test	30
			33

3.9.1.3.2 TEQ: Observations, Equipment and Consumables

Service: ……..

Type of provider: ……..

Date: ……..

Average time spent per client: ……..… Min: …… Max: ……

Category	Description	Details	Quantity
Consumables			
Equipment			

Drugs			

3.9.1.3.3 Self-reported Time Sheet

This time sheet is intended for	
Type of health care professional	
Month & Year	
Involved in TB Gaps (please tick the correct response):	Yes ☐ No ☐

							Break	Training	Admin work (record keeping, email etc.)	Other/ Non TB related Work	Total time (mins)
	Number of patients seen	Total time spent	Number of patients seen	Total time spent	Number of patients seen	Total time spent	Total time spent (mins)	Total time spent (mins)	Total time spent (mins)	Total time spent	

		(mins)		(mins)		(mins)	(mins)			(mins)	
Monday 7.30 - 13.00											
Monday 13.00 – 16.00											
Tuesday 7.30 - 13.00											
Tuesday 13.00 – 16.00											
Wednesday 7.30 - 13.00											
Wednesday 13.00 – 16.00											
Thursday 7.30 - 13.00											
Thursday 13.00 – 16.00											
Friday 7.30 - 15.00											

*Please insert time in minutes

3.9.2. Supplemental results

Supplemental Table 3.2: Drug costs of different TPT regimens by country

Country	Cost (3HP)	Cost 6H (300mg Adult)	Cost 6H (100mg Child)	Cost of 3RH (Adult)	Cost of 3RH (Child)
Eswatini	$11	$4	$3	-	-
Lesotho	$15	$4	$24	-	$23
Malawi	$14	$3	$15	-	-
Uganda	$15	$3	$16	-	-
Tanzania	$13	$3	$14	$16	$13

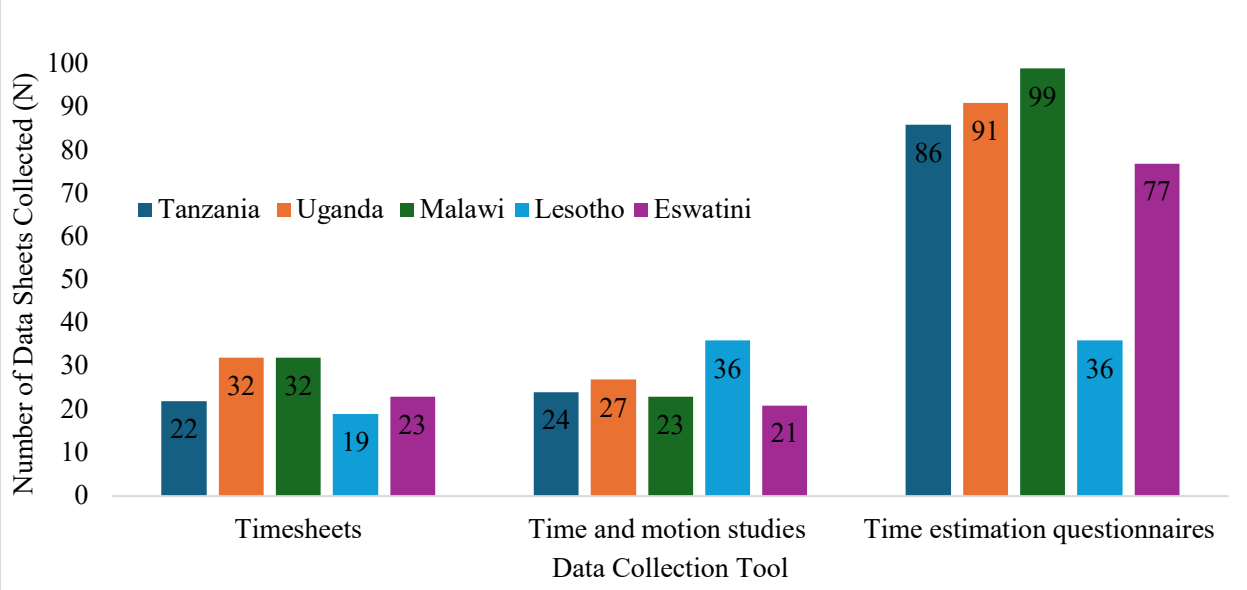
Abbreviations: TPT – Tuberculosis Preventive Treatment; 6H – Isoniazid Preventive Therapy; 3HP – 3-month regimen of isoniazid and rifapentine; 3RH – 3-month regimen of rifampicin and isoniazid.

Supplemental Table 3.3: Share of total per-patient cost by component for each TPT regimen, by country

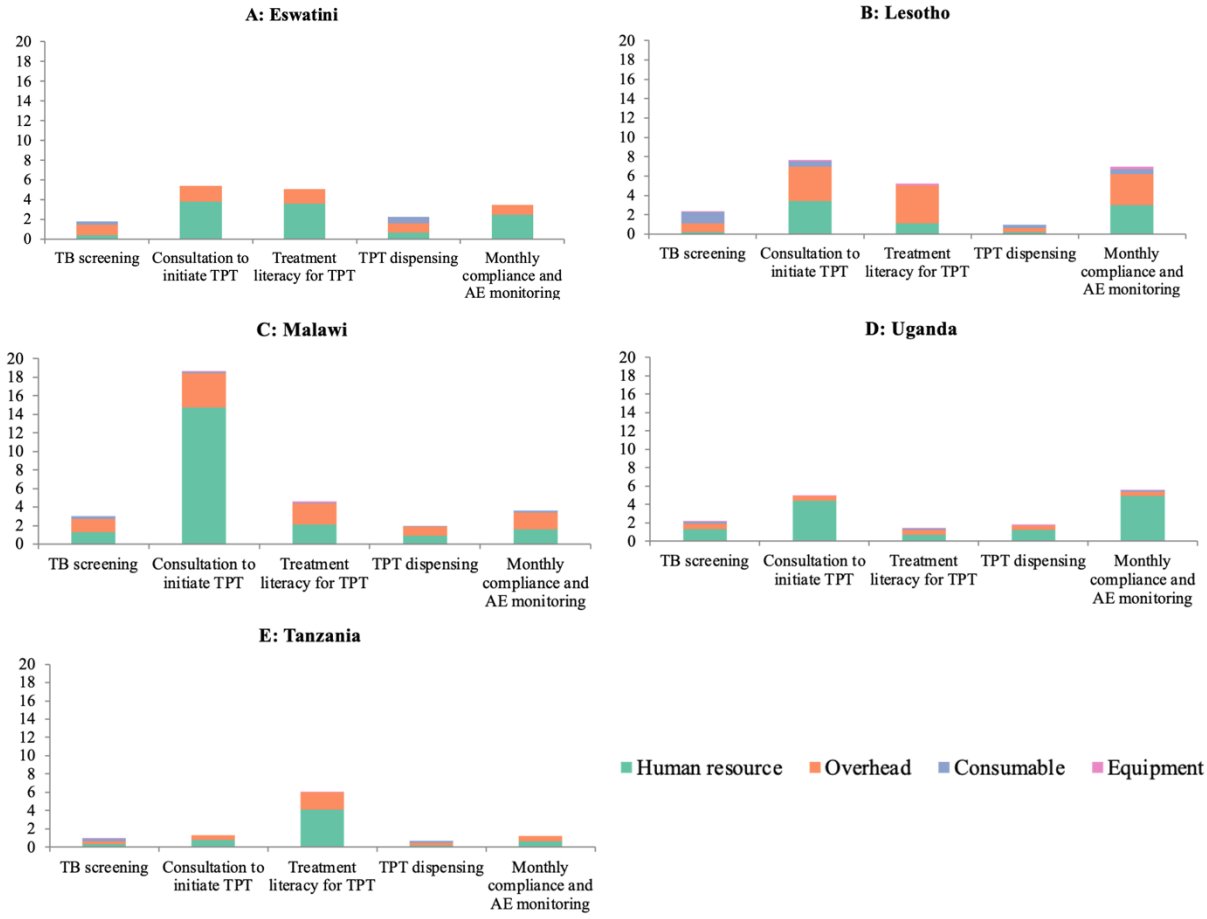
Country	Cost component	Cost of 3HP	Cost of 6H (Adult)	Cost of 6H (Children)	Cost of 3RH (Adult)	Cost of 3RH (Children)
Eswatini	Overhead	8 (22.9%)	9.9 (29.2%)	9.9 (30.7%)		
	Consumable	1.6 (4.7%)	2.3 (6.8%)	2.3 (7.1%)		
	Equipment	0.1(0.3%)	0.1(0.4%)	0.1(0.4%)		
	Human resource	14.1 (40.5%)	17.2 (50.8%)	17.2 (53.5%)		
	Drugs	11(31.6%)	4.4 (12.9%)	2.7 (8.3%)		
	Total cost	$35	$34	$32		
Lesotho	Overhead	11.9 (31.2%)	11.9 (44.2%)	11.9 (25.3%)		11.9 (25.6%)
	Consumable	2.6 (6.7%)	2.6 (9.5%)	2.6 (5.4%)		2.6 (5.5%)
	Equipment	0.8 (2%)	0.8 (2.9%)	0.8 (1.7%)		0.8 (1.7%)
	Human resource	7.9 (20.8%)	7.9 (29.4%)	7.9 (16.8%)		7.9 (17.1%)
	Drugs	15 (39.3%)	3.8 (14.1%)	24 (50.9%)		23.3 (50.1%)
	Total cost	$38	$27	$47		$46
Malawi	Overhead	$16.7 (28.3%)	$26.5 (39.3%)	$26.5 (33.3%)		
	Consumable	$1.2 (2%)	$1.7 (2.6%)	$1.7 (2.2%)		
	Equipment	$0.4 (0.8%)	$0.7 (1.1%)	$0.7 (0.9%)		
	Human resource	$26.4 (44.8%)	$35.2 (52.2%)	$35.2 (44.3%)		
	Drugs	$14.3 (24.2%)	$3.2 (4.8%)	$15.4 (19.3%)		
	Total cost	$59	$67	$80		
Uganda	Overhead	3.7 (8.6%)	4.7 (11.6%)	4.7 (8.8%)		
	Consumable	0.6 (1.5%)	0.8 (1.9%)	0.8 (1.4%)		
	Equipment	0.1 (0.3%)	0.1 (0.3)	0.1 (0.2%)		
	Human resource	23.8 (55.4%)	32.5 (79.5%)	32.5 (60.1%)		
	Drugs	14.7 (34.3%)	2.7 (6.7%)	15.9 (29.5%)		

	Total cost	$43	$41	$54		
Tanzania	Overhead	$5.5 (20%)	$8.3 (37%)	$8.3 (25%)	$5.5 (18%)	$5.5 (20%)
	Consumable	$0.8 (3%)	$1.2 (5%)	$1.2 (4%)	$0.8 (3%)	$0.8 (3%)
	Equipment	$0.3 (1%)	$0.4 (2%)	0.4 (1%)	$0.3 (1%)	$0.3 (1%)
	Human resource	$7.6 (28%)	$10.0 (44%)	$10.0 (30%)	$7.6 (25%)	$7.6 (28%)
	Drugs	$13.1 (48%)	$2.6 (12%)	$13.8 (41%)	$15.7 (53%)	$15.7 (48%)
	Total cost	$27	$22	$34	$30	$27
All countries	**Average total cost (min and max)**	**$43 ($35-$55)**	**$41 ($27-$64)**	**$52 ($32-$76)**	**$30**	**$37 ($27-$46)**

Abbreviations: TPT – Tuberculosis Preventive Treatment; 6H – Isoniazid Preventive Therapy; 3HP – 3-month regimen of isoniazid and rifapentine; 3RH – 3-month regimen of rifampicin and isoniazid.

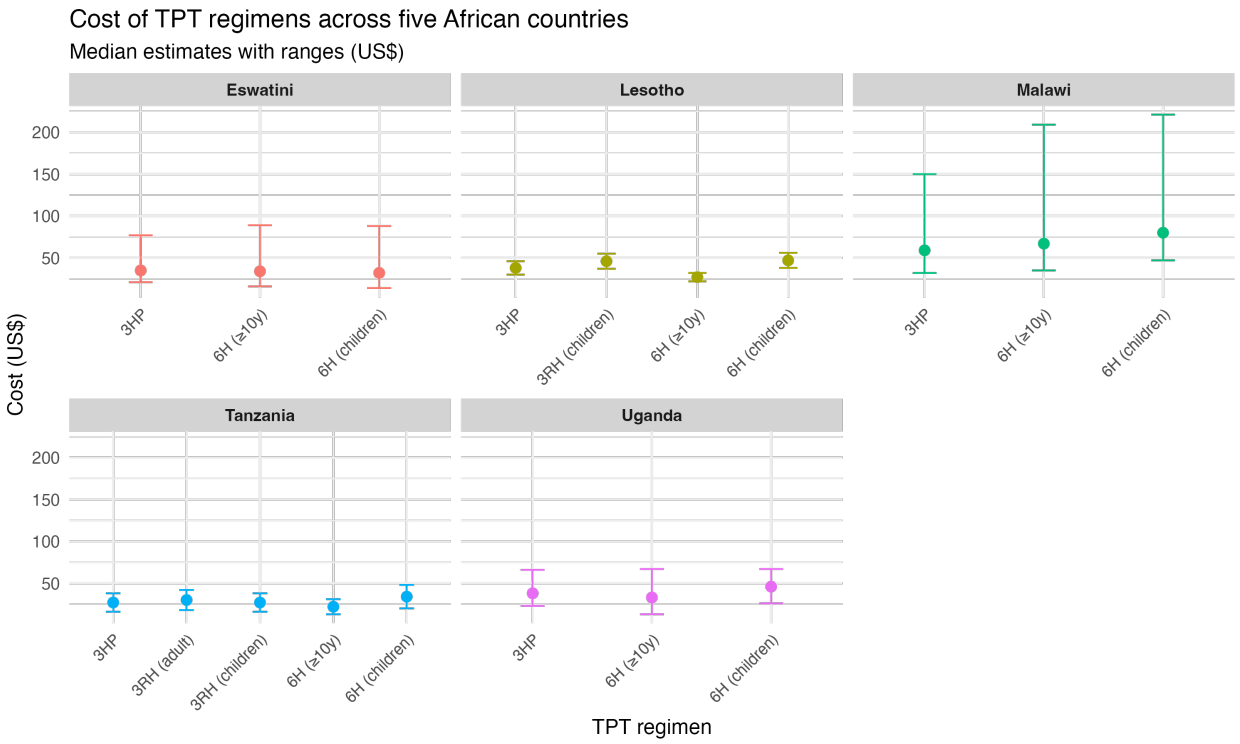


Supplemental Figure 3.2: Summary of time data collected using three data collection tools



Supplemental Figure 3.3: Panels A–E show country-specific costs for five TPT service activities:

Panels show (a) Eswatini, (b) Lesotho, (c) Malawi, (d) Uganda, (e) Tanzania. TB screening, consultation to initiate TPT, TPT dispensing, monthly compliance and adverse-event (AE) monitoring, and treatment literacy for TPT. Stacked bars display the share of each cost component—Human resource, Overhead, Consumable, and Equipment—with bar heights indicating the absolute cost (US$) for that activity. Note that y-axis scales differ by panel to reflect country-specific magnitudes.



Supplemental Figure 3.4: Cost ranges for TPT regimens across five countries. This figure displays the median, minimum, and maximum costs (USD) per patient for completing various TPT regimens across Eswatini, Lesotho, Malawi, Tanzania, and Uganda, derived from the TB GAPs micro-costing study. Error bars represent the observed minimum and maximum values.

Supplemental Table 3.4: CHEERS checklist for economic studies

Topic	No.	Item	Location where item is reported
Title			
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Title page
Abstract			
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Abstract
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Yes, background section
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Yes, methods section
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Yes, methods section
Setting and location	6	Provide relevant contextual information that may influence findings.	Yes, methods section
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Yes, methods section
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Yes, methods section

Topic	No.	Item	Location where item is reported
Time horizon	9	State the time horizon for the study and why appropriate.	Not Applicable
Discount rate	10	Report the discount rate(s) and reason chosen.	Not Applicable
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Yes, methods section
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Yes, methods section
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Yes, methods section
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Yes, methods section
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Yes, methods section
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Not Applicable
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Not Applicable
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Yes, methods section
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Yes, methods section
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Not Applicable
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Not Applicable
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Yes, results section
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Yes, results section
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Not Applicable
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Not Applicable
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Yes, discussion section
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Yes
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Yes

From: Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force. Value Health 2022;25. doi:10.1016/j.jval.2021.10.008

Chapter 4:

Evaluating person-centered tuberculosis preventive treatment delivery approach among people with HIV in Eswatini: a cost-effectiveness analysis

Suvesh Shrestha[1], Olivia D'Silva[1], Rose Mary Tazinya Asong[1], Anca Vasiliu[2], Nompumelelo Olive Mzizi[2], Debrah Vambe[2,3], Nokwanda Kota[2,3], Phumzile Dlamini[3], Alexander Kay[2,3], Anna Mandalakas[2], Alice Zwerling[1]

[1] School of Epidemiology and Public Health, University of Ottawa, Ottawa, Canada
[2] Baylor College of Medicine and Texas Children's Hospital, Houston, USA
[3] Baylor College of Medicine Children's Foundation, Mbabane, Eswatini

4.1: Preface

This chapter presents the manuscript titled *"*Evaluating shared decision-making and enhanced adherence support for tuberculosis preventive treatment among people with HIV in Eswatini: a cost-effectiveness analysis.*"* This manuscript addresses the third research objective of this thesis: to evaluate the cost-effectiveness of alternative TPT delivery strategies designed to improve treatment completion and health outcomes in high-burden settings.

Building upon the empirical costing data presented in Chapter 3, this study developed a hybrid decision-analytic model integrating a decision tree and a Markov model to compare four tuberculosis preventive treatment (TPT) delivery strategies: (1) standard of care, (2) 3HP for all eligible age groups, (3) TPT with shared decision-making (SDM), and (4) hypothetical scenario of proving TPT with shared decision-making combined with enhanced adherence support (SDM + EAS). The decision tree component captured short-term treatment initiation and completion outcomes, while the Markov model projected long-term health and economic consequences, including progression to active tuberculosis and associated costs and disability-adjusted life years (DALYs).

To our knowledge, this is the first economic evaluation to assess the cost-effectiveness of integrating shared decision-making and structured adherence support within TPT delivery using a hybrid modelling framework in high-burden settings.

The manuscript has been finalized and approved by all co-authors and is being prepared for submission to a peer-reviewed journal.

Author Contributions

AZ and SS contributed to the conceptualization of the project, data curation, modelling, formal analysis, and manuscript writing. In addition, AZ also provided supervision of the overall project. ODS, RMT, AV, NOM, DV, NK, PD, AK, and AZ contributed to the conceptualization of the project and manuscript writing. AA contributed to data curation and analysis. The underlying data were verified by AZ and SKS. All authors read and approved the manuscript.

Ethics Approval

Ethical approval was obtained from the University of Ottawa Research Ethics Boards (H-01-23-8344 – MOD4-8344). This analysis did not involve human subjects.

Publication Status

Finalized manuscript; not yet submitted.

4.2 Abstract:

Background: Improving uptake and completion of TB preventive treatment (TPT) among people with HIV (PWH) remains paramount to reducing TB incidence and mortality. Shortened TPT regimen and person-centred care strategies such as shared decision-making (SDM) and enhanced adherence support (EAS) have the potential to increase initiation and completion rates, but their economic value has not been comprehensively evaluated. We evaluated the cost-effectiveness of these person-centred interventions within the Closing TB GAPs study, a multinational implementation study among PWH.

Methods: We developed a hybrid decision-analytic Markov model to evaluate three strategies among PWH eligible for TPT: (1) standard of care (SoC; 6 months of isoniazid [6H] for children ≤9 years and three months of weekly isoniazid–rifapentine [3HP] among other age groups), (2) universal 3HP for all age groups, (3) TPT with shared decision making. Model parameters were primarily informed by local programmatic and trial data from the TB GAPs study, supplemented with published literature where necessary. The primary outcome was incremental cost per disability-adjusted life year (DALY) averted, and uncertainty was assessed using probabilistic and deterministic sensitivity analyses, alongside alternative scenario analyses.

Results: Both interventions (universal 3HP and shared decision making) increased costs and improved health outcomes compared to SoC. Universal 3HP averted 17 TB cases and 1 TB death per 1,000 PWH, with an incremental cost-effectiveness ratio (ICER) of $105 per DALY averted. TPT provided with shared decision making averted 29 TB cases and 3 TB deaths per 1,000 PWH,

yielding an ICER of $125 per DALY averted. At a willingness-to-pay threshold of $780 per DALY averted, both strategies were cost-effective.

Conclusions: Universal access to 3HP and inclusion of person-centred shared decision-making as a part of the TPT delivery approach improve health outcomes and are cost-effective compared to standard care. Public health programs should prioritize universal scale-up of 3HP and inclusion of shared decision-making within the routine TPT program.

4.3 Background:

Tuberculosis (TB) remains major public health problem globally, with more than 10 million new cases diagnosed each year.(1) Although TB is both curable and preventable, it is the leading cause of death among people with HIV (PWH).(2) The TB burden is particularly high in sub-Saharan Africa, where HIV co-infection amplifies the risk of progressing *from Mycobacterium tuberculosis* infection to TB disease and mortality.(2,3) By weakening the host immune system, HIV increases vulnerability to TB, and PWH are about 15–21 times more likely to develop TB disease than people without HIV.(4) This elevated risk highlights the importance of TB Preventive Treatment (TPT), which effectively reduces the individual's risk of progressing to TB disease .(5,6) Accordingly, TPT is a critical component of the World Health Organization (WHO) End TB Strategy, and WHO recommends that all PWH aged one year and older with no TB disease should be offered TPT.(7–9) Despite these recommendations, only 58% of eligible PWH initiated TPT in 2024, well below the global target of 90% coverage by 2027.(1) Uptake of TPT remains particularly limited among children and adolescents with HIV (CAWH), who face a disproportionately high burden of TB due to immune suppression and social vulnerabilities.(10–12) TB remains among the leading causes of death in CAWH, mainly in the Sub-Saharan Africa region, which accounts for 36% of child TB deaths globally.(13)

For decades, daily isoniazid for 6 months (6H) was the standard TPT regimen (14), but its characteristically low completion rate has limited its effectiveness.(15) Informed by a growing body of evidence demonstrating non-inferiority and improved completion rates, WHO now also recommends shorter once-weekly isoniazid plus rifapentine for 3 months (3HP), three months of daily rifampicin/isoniazid (3HR), and one month of daily rifapentine/isoniazid (1HP).(5) Seminal

studies relevant to children and PWH have shown that 3HP is noninferior to 6H in children (16,17), and 1HP is well tolerated among PWH.(18)

Despite clinical advantages, adherence and implementation challenges persist.(19) Even when TPT is initiated, a considerable proportion of patients fail to complete treatment.(20–24) A key contributor is the continued use of a "one-size-fits-all" approach to TB prevention, which does not reflect the needs of different groups.(25) In HIV care, similar challenges have been addressed through person-centered care models (26), which adapt how care is provided based on the needs and preferences of different groups.(27,28) These approaches may include shared decision-making between providers and patients and enhanced adherence support (EAS) interventions.

SDM is a core element of person-centred care where providers and patients jointly choose a regimen that aligns with clinical needs, preferences and daily realities.(29) The WHO People-Centred TB Care Framework emphasizes SDM as essential for improving treatment acceptability and completion.(30) Recent discrete choice experiment evidence among PWH in Uganda suggests that offering TPT regimens aligned with patient preferences, including lower pill burden and compatibility with antiretroviral therapy, may substantially improve treatment uptake.(31,32)

EAS interventions, including mobile short message services and voice call reminders, have demonstrated benefits for ART adherence.(33) A meta-analysis of randomised trials by Wald et al. found that two-way text messaging was associated with a 23% relative improvement in medication adherence (RR 1.23, 95% CI 1.13–1.35, $p = 0.007$).(34) Similar benefits have been observed in HIV care, where bidirectional messaging improves adherence and appointment

outcomes; Kibu et al. found a significant increase in adherence among HIV/TB patients when combined one-way and two-way SMS was used.(35–39) However, evidence for TPT is mixed. Johnston et al. found no benefit from two-way SMS for TPT adherence, (40) and a recent systematic review concluded that digital adherence technologies offer only modest and uncertain improvements, with no consistent effect on TB treatment completion.(41)

Economic evidence on TPT has primarily focused on comparisons between preventive therapy regimens rather than delivery strategies that support adherence. Evidence suggest that 3HP can be cost-effective in high-burden settings if rifapentine prices are sufficiently reduced and completion rates are high.(42) A multi-country analysis further indicated that scaling up short-course TPT for PWH and household contacts across 29 high-incidence countries would reduce tuberculosis incidence and be cost-effective in most settings.(43) Similar findings have been reported for scaling up short-course preventive therapy among children across multiple high-burden countries.(44) However, existing analyses focus on regimen comparisons and often do not incorporate the programmatic costs of adherence support or patient engagement strategies.(36–39) To address this evidence gap, this study evaluates the cost-effectiveness of two TPT delivery strategies: universal 3HP and TPT with shared decision-making, compared to standard-of-care TPT among people with HIV in Eswatini. Because the evidence for EAS in TPT is conflicting and uncertain (with some studies showing promise in HIV care but others finding no benefit for TPT), we do not include EAS in the main conclusions. To explore the exact conditions under which EAS becomes a viable addition, we conducted a scenario analysis evaluating its cost-effectiveness threshold. Additionally, based on HIV literature, we modelled an optimistic scenario assuming a 15% absolute improvement in TPT to illustrate the potential impact of a highly effective future

intervention. These analyses are conducted within the Closing-TB GAPs for people living with HIV (TB GAPs) study, a multi-country study conducted across high TB–HIV burden settings.(45)

4.4 Methods:

4.4.1 Study Design and Setting

This cost-effectiveness study was nested within the TB GAPs study designed to evaluate novel TB screening and diagnostic strategies, assess the impact of differentiated service delivery models on TPT uptake and completion, and examine the cost-effectiveness of these interventions.(45) The present analyses focuses on the site in Eswatini, a country where 66% of new or relapse TB cases are individuals living with HIV. (46)

We developed a hybrid decision-analytic Markov cohort model to simulate TPT delivery among PWH who attended TB/HIV clinics affiliated with the Baylor Global TB program in Eswatini. The target population are PWH (on ART) who are eligible for TPT according to national guidelines. (47) Eligibility follows WHO recommendations: all symptom-negative PWH are offered TPT without routine IGRA or TST testing. Eligible groups include newly diagnosed individuals, those with detectable viral load, and patients returning to care after loss to follow-up, all of whom have an increased risk of underlying TB infection.

The population was stratified by three age group: 9 years and below, 10 to 19 years, and 20 years and older. The population was stratified to account for the differences in TB progression risk and likelihood of treatment-related adverse events across age strata.

We estimate the incremental costs, effectiveness and cost-effectiveness of TPT delivered under different strategies as shown in supplemental table 1. Strategy 1, where the standard of care for TPT provision in Eswatini is followed. Among children (9 years and below), 6H is recommended, whereas, among the 10 to 19 years and 20 years and older age groups, 3HP was the standard regimen. This strategy does not involve any shared decision-making, and no EAS is provided. In strategy 2, we model all age groups receiving 3HP, as the country is planning to introduce 3HP among children as well. For strategy 3, we assessed TPT provided with SDM as a part of person-centred care, where individuals 10 to 19 years and 20 years and older have the option to choose between 3HP and 6H. Finally, in strategy 4 (ie hypothetical scenario analysis), we assess TPT with SDM as in strategy 3, but also with EAS, where bidirectional messaging and weekly reminders supported TPT completion. Because evidence for EAS in TPT is mixed and uncertain, this strategy is not part of the main conclusions; it assumes an optimistic 15% absolute improvement in TPT completion.

4.4.2 Modelling

We developed a hybrid decision-analytic model comprising an initial decision tree, followed by a Markov state-transition model to evaluate the cost-effectiveness of alternative TPT delivery strategies, as shown in supplemental table 4.1. The decision tree captured short-term events following clients eligible for TPT, initiation, adverse events and treatment completion, accounting for all associated costs. The subsequent Markov component projected long-term outcomes, allowing for progression to TB disease and death due to TB or natural progression where relevant. TPT efficacy was modelled as a sustained reduction in the risk of progression to TB disease over

the individual's lifetime in the base-case analysis. Age-specific probabilities of AEs, progression to TB disease and mortality were applied and allowed to vary over time. (Figure 4.1)

4.4.3 Time Horizon and Perspective

The model followed participants over a lifetime horizon, with six-month cycle lengths, to allow sufficient time for the development of TB disease and downstream outcomes. The analysis was conducted from the healthcare system perspective. Costs and health outcomes were discounted at an annual rate of 3%, in accordance with international economic evaluation guidelines.

4.4.4 Model parameters:

4.4.4.1 Epidemiological Parameters

Model epidemiological parameters were primarily informed by local programmatic and trial data from the TB GAPs study, supplemented with published literature where necessary. TPT initiation probabilities were obtained from local programmatic data and published literature for standard-of-care strategies, while probabilities of initiating different TPT regimens under strategies incorporating SDM were derived from TB GAPs study data.(43,48–51) Treatment completion probabilities were also informed by published literature and the TB Gaps study. Parameters related to adverse events, TPT efficacy, and mortality were derived from published literature, including the probability of death following severe AEs, death due to TB disease, and death from other causes. The details of all the model parameters and their references are provided in Table 4.1.

4.4.4.2 Cost Parameters

A comprehensive costing study was conducted as part of the TB GAPS project. We used the micro costing approach to calculate the cost of different components like overheads, human resources, equipment, consumables and drugs. Specific details of the costing methodology and results are available in a previously published piece Shrestha et al, 2026. This study provided detailed per-person costs for different TPT regimens, enhanced adherence support (EAS), and treatment activities. Costs related to the management of mild to moderate and severe adverse events (AEs) and the cost of antiretroviral therapy (ART) were obtained from published literature. In addition, a systematic review was conducted on the cost and cost-effectiveness of TPT to supplement the cost estimates, as shown in Table 4.1. All costs were expressed in 2024 United States dollars (USD), with values originally reported in local currencies first adjusted to 2024 price levels using country-specific inflation indices and then converted using the average 2024 exchange rates. (52)

4.4.5 Assumption:

The model assumed that all TPT-eligible individuals have tuberculosis infection. This programmatic simplification was made in consultation with the Eswatini National TB/HIV Programme team, as all eligible individuals are considered a high-risk group, and it follows Eswatini's national policy of offering TPT to everyone who is symptom-negative without any further test to rule out TB infection. We assumed there was no reinfection, as the analysis focuses on the incremental differences between TPT delivery strategies in a cohort already presumed to have TB infection. TPT was assumed to provide lifetime protection against TB, although scenario analyses varied the protection duration (5, 10, 20 years, and lifetime) to test this assumption and as proxy to reinfection. In the absence of empirical data on treatment completion for strategies

incorporating EAS, we assumed a 15% absolute increase in treatment completion among individuals enrolled in EAS. This assumption reflects optimist estimate of the potential benefit of EAS and was partly informed by evidence from published studies evaluating bidirectional messaging interventions in antiretroviral therapy among people with HIV. (35–39) In addition, the model assumed that all individuals in the cohort were receiving antiretroviral therapy (ART). Among those who progressed to active TB disease, we assumed that all cases were diagnosed and subsequently initiated on appropriate TB treatment.

4.4.6 Analysis

The primary outcome was the incremental cost-effectiveness ratio (ICER), expressed as the incremental cost per DALY averted. In addition, a sequential incremental analysis was conducted in which strategies were ordered by increasing cost and compared with the next least costly alternative to assess the additional cost per additional health benefit gained. Secondary outcomes included additional TB cases averted, and deaths averted, as well as incremental cost per death averted and per TB case averted.

Cost-effectiveness was primarily evaluated by reporting ICERs rather than applying a fixed willingness-to-pay threshold, allowing decision-makers to interpret results across a range of potential thresholds. Net monetary benefit was subsequently calculated using a reference threshold of $780 per DALY averted (approximately 20% of Eswatini's GDP per capita), reflecting an opportunity cost–based estimate (53–55), and was used in two-way deterministic sensitivity analyses.

4.4.7 Uncertainty, sensitivity and scenario analysis

To address parameter uncertainty, we used probabilistic sensitivity analysis with 10,000 Monte Carlo sampling to generate 95% uncertainty range (UR). One-way deterministic sensitivity analysis was conducted on the parameter that had the greatest influence on ICER, and the results were presented using tornado diagrams. We also conducted a two-way deterministic sensitivity analysis jointly varying the cost of EAS and the incremental improvement in treatment completion attributable to EAS to evaluate how variations in the cost and effectiveness of EAS would influence cost-effectiveness.

A separate hypothetical scenario analysis was conducted to assess the potential impact of adding EAS to SDM, assuming an optimistic 15% absolute improvement in TPT completion rate. In addition, a series of scenario analyses was conducted to assess the structural uncertainty surrounding key assumptions in the model. In each of these scenarios, the four strategies were evaluated: SoC, universal 3HP, TPT with SDM, and TPT with SDM + EAS (the latter as a hypothetical scenario). First, we conducted a scenario analysis with 30% prevalence of TB infection among the TPT-eligible population to assess the impact of a lower TB infection prevalence among those initiated on TPT. Second, the annual TB progression rate in the first two years was reduced from 7% to 3.5% (while the 2% annual rate thereafter remained unchanged) to test a more conservative estimate of early TB risk. Third, the efficacy of 6H was decreased from 70% to 60% to examine the implications if 6H were less effective than other regimens. Fourth, the duration of TPT protection after treatment completion was varied across five scenarios: no protection, 5-year protection, 10-year protection, and 20-year protection, which also indirectly captured the potential impact of reinfection. Fifth, shared decision-making (SDM) was extended to children aged ≤9 years, giving them a choice between 3HP and 6H instead of 6H for this age

group, to evaluate whether offering choice to younger children affects cost-effectiveness. Sixth, a higher first-year TB progression risk was examined. Finally, a scenario of incomplete TB diagnosis and treatment was evaluated, in which a proportion of individuals who progressed to active TB were assumed not to be diagnosed or not to initiate appropriate treatment, to account for real-world diagnostic and treatment gaps. Results of these scenario analyses are presented as ICERs per DALY averted compared to the SoC.

4.5 Results:

4.5.1 Incremental Cost-Effectiveness of TPT Implementation Strategies

Compared to SoC, both strategies 1 and 2 (universal 3HP and TPT provided with SDM) were associated with incremental cost and incremental health gain (Table 4.2). Compared with SoC, Strategy 2: scaling up 3HP for all age groups resulted in an increased cost ($7) and improved health outcomes (0.06 DALYs averted), yielding an ICER of $105 per DALY averted. Strategy 3 (TPT with SDM) was associated with an incremental cost of $10 and a greater health gain (0.08 DALYs averted), resulting in an ICER of $124 per DALY averted (95% CI: $77-$197). The higher cost relative to strategy 2 was primarily driven by increased uptake of TPT through SDM, resulting in more individuals initiating treatment. Improved health outcomes are related to greater TPT coverage and a reduction in TB incidence.

In the sequential analysis, strategies were ordered by increasing cost and compared incrementally with the next least costly alternative to estimate the additional cost per additional health benefit gained. In this analysis (supplemental table 4.2), the ICER was $105 per DALY averted for Strategy 2, and $182 for Strategy 3. No strategy was dominated in the base-case analysis.

4.5.2 TB cases averted and deaths averted

Projected health outcomes per 1,000 PWH eligible for TPT are presented in Table 4.3. Compared with the standard of care, all intervention strategies reduced incident TB cases and TB-related deaths. Strategy 2 averted 18 TB cases and 2 death per 1,000 individuals, while Strategy 3 increased this impact to 29 TB cases and 3 deaths averted.

4.5.3 Probabilistic sensitivity analysis:

Probabilistic sensitivity analysis results are presented as cost-effectiveness acceptability curves (Figure 4.2), illustrating the probability that each strategy is cost-effective across a range of willingness-to-pay (WTP) thresholds per DALY averted. At lower WTP thresholds, SoC and Strategy 2 had the highest probability of being cost-effective, reflecting their lower implementation cost compared to other strategies. As the WTP increased, the strategy with greater health gains (Strategy 3) became the preferred strategy, exceeding a 50% probability of cost-effectiveness at approximately $180 per DALY averted and maintaining the highest probability at higher thresholds.

In Supplemental 4.1a-b, the ICER scatterplot based on 10,000 Monte Carlo simulations presents the cost-effectiveness results comparing the strategy providing TPT with SDM and HP with SoC. Results consistently show incremental effectiveness greater than zero, indicating that both strategy results in improved TPT yield, and thus more DALYs averted compared to SoC.

4.5.4 Deterministic sensitivity analysis:

Deterministic one-way sensitivity analyses were performed to evaluate the impact of parameter uncertainty on the baseline ICERs for both strategy comparisons (supplemental 4.2 a-b). For Strategy 1 (SoC) versus Strategy 2 (3HP all age group), where the baseline ICER was 104, the model was highly sensitive to the cost of a complete 6H regimen among children, followed by the clinical efficacy of the 6H regimen and the efficacy of the 3HP regimen across all age groups. In contrast, the comparison between Strategy 1 (SoC) and Strategy 3 (TPT with SDM) yielded a baseline ICER of 125, with the model being most sensitive to the efficacy of the 6H regimen across all age groups. Other notable drivers in the latter comparison included annual progression to TB disease among 10 years and above.

4.5.5 Scenario analysis results:

4.5.5.1 Scenario analysis: Cost effectiveness of TPT is delivered with SDM and EAS:

We also conducted a two-way deterministic sensitivity analysis (Figure 4.3), simultaneously varying the cost of enhanced adherence support and the incremental increase in treatment completion attributable to EAS. For each combination of parameter values, net monetary benefit (NMB) was calculated at a willingness-to-pay threshold of $780 per DALY averted, and the strategy with the highest NMB was identified. The analysis demonstrated that SDM with EAS was the optimal strategy across a wide range of parameter combinations, particularly when the intervention cost was low or its clinical efficacy was high. For example, at a minimal EAS cost of $5 per person, an incremental completion gain of only 2% was required to make the strategy cost-effective. However, the threshold for cost-effectiveness increased linearly with the intervention's cost; if the cost of EAS reached $115, the strategy required at least a 17% absolute increase in

treatment completion to maintain the highest NMB. Below this diagonal threshold line, the added expenditure of the support program was no longer justified by the health gains achieved, making SDM alone the preferred and most cost-effective intervention.

Building on these thresholds, we evaluated a specific hypothetical scenario assuming a 15% absolute improvement in treatment completion. In this analysis, the combined SDM and EAS strategy increased costs by $37 and averted 0.15 DALYs relative to SoC, yielding an ICER of $238 per DALY averted (95% CI: $129–$1,420). This exploratory approach generated the highest population-level clinical impact, preventing 61 TB cases and 7 deaths per 1,000 individuals. While it outperformed both universal 3HP and TPT with SDM in absolute health gains, the increased incremental cost reflects the combined expenses of expanded TPT uptake and digital infrastructure. Conversely, the health gains are driven by higher treatment completion rates and a subsequent reduction in downstream TB cases (Table 4.4).

The cost-effectiveness acceptability curve (CEAC) shown in supplemental figure 3 revealed that TPT with SDM and EAS was not cost-effective at lower thresholds, maintaining a 0% probability below $150 per DALY averted. However, its probability rose sharply beyond this point, indicating that at a WTP threshold of $250 per DALY averted or higher, more than 50% of simulated iterations showed SDM and EAS to be cost-effective choices.

4.5.5.2 Other scenarios analysis:

The cost-effectiveness of TPT strategies remained highly robust across most scenario analyses, with ICERs consistently staying well under $500 per DALY averted. The model was most sensitive

to the duration of TPT protection. In a conservative scenario assuming no protection after treatment completion, ICERs escalated sharply to $743 for 3HP, $708 for TPT with SDM, and $1,244 for TPT with SDM + EAS. Conversely, extending the duration of protection lowered the ICERs closer to base-case values (e.g., 20-year protection resulted in $119, $132, and $268 per DALY averted, respectively). Variations in latent TB infection (LTBI) prevalence, progression risks, and diagnostic gaps caused minor fluctuations but did not alter the overall economic ranking of the strategies. Results are presented in detail in the supplemental table 4.3.

4.6 Discussion:

Our study demonstrates that TPT strategies for people living with HIV in Eswatini – including universal 3HP as a regimen strategy and shared decision-making (SDM) as a person-centred delivery approach – are cost-effective and clinically impactful. Both strategies substantially improve health outcomes at an incremental cost well below local willingness-to-pay thresholds. Crucially, integrating shared decision-making yielded the highest health gains, nearly doubling the number of TB cases and deaths averted compared to a universal strategy alone. These findings suggest that incorporating patient preferences into TPT delivery provides an economically sound pathway to accelerating progress toward national TB elimination targets.

In our study, universal 3HP for all age groups demonstrated health benefit with ICER of US$105 per DALY averted, indicating that expanding access to short-course rifapentine-based regimens yields substantial health gains at relatively low additional cost. This finding aligns with growing body of evidence supporting shorter TPT regimens due to improved adherence, higher completion rates, and lower overall programmatic burden. More recently, Ryckman et al. modelled short-

course TPT among household contacts and PWH across 29 high-incidence countries and concluded that short-course TPT is likely to be cost-effective in many settings.(43) Similarly, Jo et al. evaluated short-course preventive therapy delivered through contact investigation for children across 12 high-burden countries and reported favorable cost-effectiveness across settings, emphasizing that preventive therapy can yield substantial health gains when programmatically scaled.(44) In a high-burden modelling context, Johnson et al. demonstrated that the cost-effectiveness of 3HP relative to isoniazid preventive therapy is highly sensitive to rifapentine price and completion assumptions, highlighting that the value of 3HP is fundamentally implementation-dependent.(56)

Our findings strongly support the integration of SDM as a highly effective mechanism for TPT delivery. Rather than relying on a rigid, top-down clinical mandate, SDM alone generated substantial health gains over the standard of care, with an ICER of US$125 per DALY averted. This economic and clinical viability aligns with extensive behavioural health literature demonstrating that SDM significantly improves treatment uptake, patient activation, and early treatment adherence.(57) By actively engaging patients, explaining risks and benefits, and aligning care with individual lifestyle preferences, SDM transforms the preventive treatment process into a collaborative effort. While pairing SDM with intensive EAS yields the highest absolute effectiveness in a hypothetical scenario, the mixed and uncertain evidence for EAS in TPT suggests that implementing SDM as a standalone programmatic strategy remains a powerful, cost-effective, and evidence-based tool for improving patient outcomes.

Our evaluation of enhanced adherence support highlights a critical trade-off between the costs of digital health platforms and their real-world clinical utility. Although bidirectional messaging shows success in general HIV care (35–38) global evidence for latent TB remains deeply mixed.(39) For instance, Johnston et al. found no adherence benefit from two-way SMS for TPT (40) and recent systematic reviews report only modest, low-certainty improvements in overall treatment success.(41) Our model demonstrates that under an optimistic 15% completion gain, the combined SDM+EAS strategy reduces disease burden—averting an additional 61 TB cases and 6 deaths per 1,000 PLHIV ($235/DALY averted) compared to standard care. However, our sensitivity analysis clarifies that this value is highly conditional. If completion gains fall below 2%, EAS is completely inefficient even at a minimal cost of $5 per patient; conversely, gains must exceed 7% to justify a maximum cost of $50. For resource-constrained settings like Eswatini, investing in digital infrastructure is economically risky unless substantial completion gains can be operationally guaranteed. Public health systems should therefore prioritize foundational, client-centered frameworks like standalone SDM before scaling up complex digital adherence packages.

This study has several important strengths. Cost inputs were derived from a comprehensive costing study conducted within the TB GAPs program, in which resource use was identified at the activity level and valued using locally collected data on personnel time, consumables, drugs, overhead, and equipment. Parameters related to SDM were informed by data from the parent TB GAPs trial, which makes the TPT uptake parameter grounded in real-world implementation. To our knowledge, this is the first economic evaluation to assess the incremental impact of SDM and EAS on TPT outcomes among PWH. The use of a hybrid modelling approach allowed us to capture

both short-term outcomes and long-term outcomes. Extensive probabilistic sensitivity and scenario analyses further strengthened the robustness of the findings.

Several limitations should be noted. The incremental benefit of EAS on TPT completion was informed primarily by evidence from HIV adherence studies rather than TPT-specific trials, and the true effect in TB prevention settings may differ. Given mixed evidence for SMS-based interventions in TB prevention, this assumption may overestimate the real-world effectiveness of EAS. In addition, the model did not explicitly incorporate TB reinfection following successful preventive therapy. In high-incidence settings such as Eswatini, reinfection may occur and could attenuate the long-term protective effect of TPT, potentially leading to a modest overestimation of projected health benefits. Furthermore, the analysis was conducted from a healthcare system perspective and did not incorporate a societal perspective. As such, indirect costs and broader economic consequences, including patient out-of-pocket expenses, productivity losses, and caregiver time, were not captured. Excluding these costs may underestimate the full economic benefits of interventions that improve treatment adherence and completion, particularly in high-burden settings. However, the healthcare system perspective was selected to align with decision-making contexts relevant to national TB programs and available data sources. In addition, children under two years of age were excluded due to limited data availability, which may limit generalizability; however, this age group represents a small proportion of the target population and is often managed under different clinical protocols, reducing the likelihood of substantial impact on overall cost-effectiveness estimates. Future studies incorporating age-specific data and direct evaluation of adherence interventions within TPT programs would strengthen the evidence base.

Taken together, our findings demonstrate that optimizing TPT outcomes among people living with HIV demands equal attention to regimen selection and the delivery framework. While the universal expansion of short-course 3HP offers highly robust and cost-effective health gains, integrating standalone shared decision-making provides vital person-centred benefits. Conversely, the added value of enhanced adherence support remains uncertain and heavily contingent upon optimistic operational assumptions. For decision-makers, the critical insight is that digital adherence interventions are not universally cost-effective but are strictly bounded by their ability to achieve the specific completion thresholds modelled here. Given the fragmented external evidence regarding digital tools for latent TB, national programs should prioritize scaling up short-course 3HP and providing TPT with SDM. Combined SDM and EAS should be reserved exclusively for settings where high-quality digital engagement and substantial completion gains can be operationally guaranteed. As high-burden countries accelerate TPT scale-up under the End TB Strategy, pairing shortened regimens with people-centred delivery is essential, though widespread adoption of bidirectional messaging should await more robust, TB-specific evidence.

4.7 Acknowledgement:

This research has been supported by the U.S. Centers for Disease Control and Prevention (CDC) under the terms of cooperative agreement number U01GH002278 (PI Mandalakas). We gratefully acknowledge the Baylor College of Medicine Children's Foundation - Eswatini, TB Gaps research staff, healthcare workers, and study participants for their contributions.

4.8 References:

1. Global Tuberculosis Report 2025 [Internet]. [cited 2026 Mar 10]. Available from: https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/tb-reports/global-tuberculosis-report-2025
2. 2024 Global tuberculosis report.
3. Shah GH, Ewetola R, Etheredge G, Maluantesa L, Waterfield K, Engetele E, et al. Risk factors for tb/hiv coinfection and consequences for patient outcomes: Evidence from 241 clinics in the Democratic republic of Congo. Int J Environ Res Public Health. 2021;18(10). doi:10.3390/ijerph18105165
4. Martinson NA, Hoffmann CJ, Chaisson RE. Epidemiology of tuberculosis and HIV: Recent advances in understanding and responses. In: Proceedings of the American Thoracic Society. 2011. doi:10.1513/pats.201010-064WR
5. WHO. Module 1-Consolidated guidelines on tuberculosis. : prevention - tuberuculosis preventive treatment. World Health Organization. 2020.
6. Yanes-Lane M, Ortiz-Brizuela E, Campbell JR, Benedetti A, Churchyard G, Oxlade O, et al. Tuberculosis preventive therapy for people living with HIV: A systematic review and network meta-analysis. PLoS Med. 2021;18(9). doi:10.1371/journal.pmed.1003738
7. World Health Organisation. Antiretroviral Therapy For HIV Infection In Infants And Children: Towards Universal Access. WHO Library Cataloguing-in-Publication Data. 2010;4911(866).
8. World Health Organization. WHO | WHO End TB Strategy. World Health Organization. 2015.
9. Zhang L, Liu Y. Interpretation of the Political Declaration of the Second High-level Meeting of the General Assembly of United Nations on the Fight Against Tuberculosis. Chinese Journal of Antituberculosis. 2023;45(12). doi:10.19982/j.issn.1000-6621.20230380
10. Martinez L, Cords O, Horsburgh CR, Andrews JR, Acuna-Villaorduna C, Desai Ahuja S, et al. The risk of tuberculosis in children after close exposure: a systematic review and individual-participant meta-analysis. The Lancet. 2020;395(10228). doi:10.1016/S0140-6736(20)30166-5
11. Basu Roy R, Whittaker E, Seddon JA, Kampmann B. Tuberculosis susceptibility and protection in children. The Lancet Infectious Diseases. 2019. doi:10.1016/S1473-3099(18)30157-9

12. Mandalakas AM, Kay AW, Bacha JM, Devezin T, Golin R, Simon KR, et al. Tuberculosis among children and adolescents at HIV treatment centers in Sub-Saharan Africa. Emerg Infect Dis. 2020;26(12). doi:10.3201/EID2612.202245
13. Vonasek BJ, Rabie H, Hesseling AC, Garcia-Prats AJ. Tuberculosis in Children Living With HIV: Ongoing Progress and Challenges. J Pediatric Infect Dis Soc. 2022;11. doi:10.1093/jpids/piac060
14. WHO. Latent tuberculosis infection Updated and consolidated guidelines for programmatic management. WHO, Geneva. 2018.
15. McClintock AH, Eastment MK, McKinney CM, Pitney CL, Narita M, Park DR, et al. Treatment completion for latent tuberculosis infection: A retrospective cohort study comparing 9 months of isoniazid, 4 months of rifampin and 3 months of isoniazid and rifapentine. BMC Infect Dis. 2017;17(1). doi:10.1186/s12879-017-2245-8
16. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection. New England Journal of Medicine. 2011;365(23). doi:10.1056/nejmoa1104875
17. Villarino ME, Scott NA, Weis SE, Weiner M, Conde MB, Jones B, et al. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. JAMA Pediatr. 2015 Mar 1;169(3):247–55. doi:10.1001/JAMAPEDIATRICS.2014.3158 PubMed PMID: 25580725.
18. Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Mwelase N, et al. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis. New England Journal of Medicine. 2019;380(11). doi:10.1056/nejmoa1806808
19. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16(11). doi:10.1016/S1473-3099(16)30216-X
20. Reddy MM, Thekkur P, Ramya N, Kamath PBT, Shastri SG, Kumar RBN, et al. To start or to complete?–Challenges in implementing tuberculosis preventive therapy among people living with HIV: a mixed-methods study from Karnataka, India. Glob Health Action. 2020;13(1). doi:10.1080/16549716.2019.1704540

21. Pathmanathan I, Ahmedov S, Pevzner E, Anyalechi G, Modi S, Kirking H, et al. TB preventive therapy for people living with HIV: Key considerations for scale-up in resource-limited settings. International Journal of Tuberculosis and Lung Disease. 2018. doi:10.5588/ijtld.17.0758
22. Gunde L, Wang A, Payne D, O'connor S, Kabaghe A, Kalata N, et al. Characteristics of TPT initiation and completion among people living with HIV. IJTLD Open. 2024;1(1). doi:10.5588/ijtldopen.23.0194
23. Bastos ML, Melnychuk L, Campbell JR, Oxlade O, Menzies D. The latent tuberculosis cascade-of-care among people living with HIV: A systematic review and meta-analysis. PLoS Med. 2021;18(9). doi:10.1371/journal.pmed.1003703
24. Szkwarko D, Hirsch-Moverman Y, Du Plessis L, Du Preez K, Carr C, Mandalakas AM. Child contact management in high tuberculosis burden countries: A mixed-methods systematic review. PLoS One. 2017 Aug 1;12(8):e0182185. doi:10.1371/JOURNAL.PONE.0182185 PubMed PMID: 28763500.
25. Makone A, Angami K, Bhattacharya D, Frick M, Castillo JG, Herrera R, et al. One size does not fit all: community views on choices for TB treatment and prevention. Public Health Action. 2023;13(3). doi:10.5588/pha.23.0034
26. Mavhu W, Willis N, Mufuka J, Bernays S, Tshuma M, Mangenah C, et al. Effect of a differentiated service delivery model on virological failure in adolescents with HIV in Zimbabwe (Zvandiri): a cluster-randomised controlled trial. Lancet Glob Health. 2020;8(2). doi:10.1016/S2214-109X(19)30526-1
27. Tran CH, Moore BK, Pathmanathan I, Lungu P, Shah NS, Oboho I, et al. Tuberculosis treatment within differentiated service delivery models in global HIV/TB programming. Journal of the International AIDS Society. 2021. doi:10.1002/jia2.25809
28. WHO. Updated recommendations on service delivery for the treatment and care of people living with HIV. World Health Organisation Guidelines. 2021.
29. Land V, Parry R, Seymour J. Communication practices that encourage and constrain shared decision making in health-care encounters: Systematic review of conversation analytic research. Health Expectations. 2017. doi:10.1111/hex.12557
30. People-centred framework for tuberculosis programme planning and prioritization User guide.

31. Aschmann HE, Musinguzi A, Kadota JL, Namale C, Kakeeto J, Nakimuli J, et al. Preferences of people living with HIV for features of tuberculosis preventive treatment regimens in Uganda: a discrete choice experiment. J Int AIDS Soc. 2024;27:26390. doi:10.1002/jia2.26390/full
32. Aschmann HE, Musinguzi A, Kadota JL, Namale C, Kakeeto J, Nakimuli J, et al. Predicted choice and acceptability of regimens for tuberculosis preventive treatment among people living with HIV in Uganda – a discrete choice experiment. medRxiv. 2025 Mar 13;2025.03.12.25323350. doi:10.1101/2025.03.12.25323350
33. Amankwaa I, Boateng D, Quansah DY, Akuoko CP, Evans C. Effectiveness of short message services and voice call interventions for antiretroviral therapy adherence and other outcomes: A systematic review and meta-analysis. PLoS One. 2018;13(9). doi:10.1371/journal.pone.0204091
34. Wald DS, Butt S, Bestwick JP. One-way versus two-way text messaging on improving medication adherence: Meta-analysis of randomized trials. American Journal of Medicine. 2015 Oct 1;128(10):1139.e1-1139.e5. doi:10.1016/j.amjmed.2015.05.035 PubMed PMID: 26087045.
35. Finitsis DJ, Pellowski JA, Johnson BT. Text Message Intervention Designs to Promote Adherence to Antiretroviral Therapy (ART): A Meta-Analysis of Randomized Controlled Trials. PLoS One. 2014 Feb 5;9(2):e88166. doi:10.1371/journal.pone.0088166 PubMed PMID: 24505411.
36. Ingersoll KS, Dillingham RA, Hettema JE, Conaway M, Freeman J, Reynolds G, et al. Pilot RCT of Bidirectional Text Messaging for ART Adherence Among Nonurban Substance Users with HIV. Health Psychol. 2015;34(0):1305. doi:10.1037/hea0000295 PubMed PMID: 26651472.
37. Gross R, Ritz J, Hughes MD, Salata R, Mugyenyi P, Hogg E, et al. Two-way mobile phone intervention compared with standard-of-care adherence support after second-line antiretroviral therapy failure: a multinational, randomised controlled trial. Lancet Digit Health. 2019 May 1;1(1):e26. doi:10.1016/S2589-7500(19)30006-8 PubMed PMID: 31528850.
38. Horvath T, Azman H, Kennedy GE, Rutherford GW. Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection. Cochrane Database Syst Rev. 2012 Mar 14;2012(3):CD009756. doi:10.1002/14651858.CD009756 PubMed PMID: 22419345.
39. Kibu OD, Siysi VV, Albert Legrand SE, Asangbeng Tanue E, Nsagha DS. Treatment Adherence among HIV and TB Patients Using Single and Double Way Mobile Phone Text Messages: A Randomized Controlled Trial. J Trop Med. 2022;2022. doi:10.1155/2022/2980141 PubMed PMID: 35996467.

40. Johnston JC, Kop ML van der, Smillie K, Ogilvie G, Marra F, Sadatsafavi M, et al. The effect of text messaging on latent tuberculosis treatment adherence: a randomised controlled trial. European Respiratory Journal. 2018 Feb 7;51(2):1701488. doi:10.1183/13993003.01488-2017 PubMed PMID: 29437940.
41. Mohamed MS, Zary M, Kafie C, Chilala CI, Bahukudumbi S, Foster N, et al. The impact of digital adherence technologies on treatment outcomes, adherence, and patient-reported outcomes in tuberculosis: a systematic review and meta-analysis. BMC Infect Dis. 2025 Dec 1;25(1). doi:10.1186/S12879-025-11503-3 PubMed PMID: 41087928.
42. Johnson KT, Churchyard GJ, Sohn H, Dowdy DW. Cost-effectiveness of Preventive Therapy for Tuberculosis With Isoniazid and Rifapentine Versus Isoniazid Alone in High-Burden Settings. Clinical Infectious Diseases. 2018 Sep 14;67(7):1072–8. doi:10.1093/cid/ciy230 PubMed PMID: 29617965.
43. Ryckman T, Weiser J, Gombe M, Turner K, Soni P, Tarlton D, et al. Impact and cost-effectiveness of short-course tuberculosis preventive treatment for household contacts and people with HIV in 29 high-incidence countries: a modelling analysis. Lancet Glob Health. 2023;11(8). doi:10.1016/S2214-109X(23)00251-6
44. Jo Y, Gomes I, Flack J, Salazar-Austin N, Churchyard G, Chaisson RE, et al. Cost-effectiveness of scaling up short course preventive therapy for tuberculosis among children across 12 countries. EClinicalMedicine. 2021;31. doi:10.1016/j.eclinm.2020.100707
45. TB GAPS | BCM [Internet]. [cited 2026 Mar 10]. Available from: https://www.bcm.edu/departments/pediatrics/divisions-and-centers/global-health/global-tb-program/research/tb-gaps
46. TB profile [Internet]. [cited 2026 Apr 12]. Available from: https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&tab=%22tables%22&lan=%22EN%22&iso3=%22SWZ%22&entity_type=%22country%22
47. Eswatini HIV Integrated Management Guidelines, 2022 - PrEPWatch [Internet]. [cited 2026 Jun 9]. Available from: https://www.prepwatch.org/resources/eswatini-hiv-integrated-management-guidelines-2022/
48. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect

Dis. 2016 Nov 1;16(11):1269–78. doi:10.1016/S1473-3099(16)30216-X PubMed PMID: 27522233.

49. Semitala FC, Kadota JL, Musinguzi A, Nabunje J, Welishe F, Nakitende A, et al. Completion of isoniazid–rifapentine (3HP) for tuberculosis prevention among people living with HIV: Interim analysis of a hybrid type 3 effectiveness–implementation randomized trial. PLoS Med. 2021 Dec 1;18(12):e1003875. doi:10.1371/journal.pmed.1003875 PubMed PMID: 34914696.
50. Semitala FC, Kadota JL, Musinguzi A, Welishe F, Nakitende A, Akello L, et al. Comparison of 3 optimized delivery strategies for completion of isoniazid-rifapentine (3HP) for tuberculosis prevention among people living with HIV in Uganda: A single-center randomized trial. PLoS Med. 2024 Feb 1;21(2):e1004356. doi:10.1371/journal.pmed.1004356 PubMed PMID: 38377166.
51. Borse R, Randive B, Mattoo S, Malik P, Solanki H, Gupta A, et al. Three months of weekly rifapentine plus isoniazid for TB prevention among people with HIV. IJTLD OPEN. 2024 Sep 1;1(9):404. doi:10.5588/ijtldopen.23.0609 PubMed PMID: 39301134.
52. Most Accurate Exchange Rates [Internet]. [cited 2025 Nov 9]. Available from: https://www.exchange-rates.org/
53. Ochalek J, Lomas J, Claxton K. Estimating health opportunity costs in low-income and middle-income countries: a novel approach and evidence from cross-country data. BMJ Glob Health. 2018 Jan 1;3(6). doi:10.1136/bmjgh-2018-000964 PubMed PMID: 30483412.
54. Edoka IP, Stacey NK. Estimating a cost-effectiveness threshold for health care decision-making in South Africa. Health Policy Plan. 2020 Jun 1;35(5):546. doi:10.1093/heapol/czz152 PubMed PMID: 32125375.
55. Woods B, Revill P, Sculpher M, Claxton K. Country-Level Cost-Effectiveness Thresholds: Initial Estimates and the Need for Further Research. Value in Health. 2016 Dec 1;19(8):929. doi:10.1016/j.jval.2016.02.017 PubMed PMID: 27987642.
56. Johnson KT, Churchyard GJ, Sohn H, Dowdy DW. Cost-effectiveness of Preventive Therapy for Tuberculosis with Isoniazid and Rifapentine Versus Isoniazid Alone in High-Burden Settings. Clinical Infectious Diseases. 2018 Sep 14;67(7):1072–8. doi:10.1093/cid/ciy230 PubMed PMID: 29617965.

57. Decision aids for people facing health treatment or screening decisions - Stacey, D - 2024 | Cochrane Library [Internet]. [cited 2026 Feb 10]. Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001431.pub6/full
58. Mandalakas AM, Hesseling AC, Gie RP, Schaaf HS, Marais BJ, Sinanovic E. Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting. Thorax. 2012;68(3):247. doi:10.1136/thoraxjnl-2011-200933 PubMed PMID: 22717944.
59. 3HP ADVERSE EVENTS AND MONITORING SCHEDULE Contents.
60. Kinikar A, Borse R, Randive B, Kamath P, Mattoo SK, Parmar M, et al. 3HP preventive treatment among children and adolescents with HIV and child household contacts of TB patients. IJTLD OPEN. 2024 Sep 1;1(9):413. doi:10.5588/ijtldopen.24.0305 PubMed PMID: 39301128.
61. Pease C, Hutton B, Yazdi F, Wolfe D, Hamel C, Barbeau P, et al. A systematic review of adverse events of rifapentine and isoniazid compared to other treatments for latent tuberculosis infection. Pharmacoepidemiol Drug Saf. 2018 Jun 1;27(6):557–66. doi:10.1002/pds.4423 PubMed PMID: 29573031.
62. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New Regimens to Prevent Tuberculosis in Adults with HIV Infection. New England Journal of Medicine. 2011 Jul 7;365(1):11–20. doi:10.1056/nejmoa1005136
63. Kadota JL, Musinguzi A, Aschmann HE, Akello L, Welishe F, Nakimuli J, et al. Adverse Events Reported During Weekly Isoniazid-Rifapentine (3HP) Tuberculosis Preventive Treatment Among People With Human Immunodeficiency Virus in Uganda. Open Forum Infect Dis. 2024 Nov 1;11(11). doi:10.1093/ofid/ofae667 PubMed PMID: 39582503.
64. Winters N, Belknap R, Benedetti A, Borisov A, Campbell JR, Chaisson RE, et al. Completion, safety, and efficacy of tuberculosis preventive treatment regimens containing rifampicin or rifapentine: an individual patient data network meta-analysis. Lancet Respir Med. 2023 Sep 1;11(9):782–90. doi:10.1016/S2213-2600(23)00096-6 PubMed PMID: 36966788.
65. Hahn JA, Ngabirano C, Fatch R, Emenyonu NI, Cheng DM, Adong J, et al. Safety and tolerability of isoniazid preventive therapy for tuberculosis for persons with HIV with and without alcohol use. AIDS. 2023 Aug 1;37(10):1535. doi:10.1097/QAD.0000000000003613 PubMed PMID: 37260251.

66. Masini EO, Sitienei J, Weyeinga H. Outcomes of isoniazid prophylaxis among HIV-infected children attending routine HIV care in Kenya. Public Health Action. 2013 Sep;3(3):204. doi:10.5588/pha.13.0013 PubMed PMID: 26393030.
67. Tsirizani-Galileya L, Milanzi E, Mungwira R, Divala T, Mallewa J, Mategula D, et al. Isoniazid preventive therapy-related adverse events among Malawian adults on antiretroviral therapy: A cohort study. Medicine. 2022 Sep 30;101(39):e30591. doi:10.1097/MD.0000000000030591 PubMed PMID: 36181120.
68. Ayele HT, Van Mourik MSM, Debray TPA, Bonten MJM. Isoniazid Prophylactic Therapy for the Prevention of Tuberculosis in HIV Infected Adults: A Systematic Review and Meta-Analysis of Randomized Trials. PLoS One. 2015 Nov 9;10(11):e0142290. doi:10.1371/journal.pone.0142290 PubMed PMID: 26551023.
69. Zar HJ, Cotton MF, Strauss S, Karpakis J, Hussey G, Schaaf S, et al. Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial. BMJ : British Medical Journal. 2006 Jan 20;334(7585):136. doi:10.1136/bmj.39000.486400.55 PubMed PMID: 17085459.
70. Jo Y, Gomes I, Flack J, Salazar-Austin N, Churchyard G, Chaisson RE, et al. Cost-effectiveness of scaling up short course preventive therapy for tuberculosis among children across 12 countries. EClinicalMedicine. 2021 Jan 1;31:100707. doi:10.1016/j.eclinm.2020.100707
71. Shin H, Jo Y, Chaisson RE, Turner K, Churchyard G, Dowdy DW. Cost-effectiveness of a 12 country-intervention to scale up short course TB preventive therapy among people living with HIV. J Int AIDS Soc. 2020 Oct 1;23(10):e25629. doi:10.1002/jia2.25629 PubMed PMID: 33107219.
72. Ryckman T, Weiser J, Gombe M, Turner K, Soni P, Tarlton D, et al. Impact and cost-effectiveness of short-course tuberculosis preventive treatment for household contacts and people with HIV in 29 high-incidence countries: a modelling analysis. Lancet Glob Health. 2023 Aug 1;11(8):e1205–16. doi:10.1016/S2214-109X(23)00251-6 PubMed PMID: 37474228.
73. Sterling TR, Scott NA, Miro JM, Calvet G, La Rosa A, Infante R, et al. Three Months of Weekly Rifapentine plus Isoniazid for Treatment of M. tuberculosis Infection in HIV Co-infected Persons. AIDS. 2016 Jun 19;30(10):1607. doi:10.1097/QAD.0000000000001098 PubMed PMID: 27243774.

74. Belknap R, Holland D, Feng PJ, Millet JP, Cayla JA, Martinson NA, et al. Self-administered Versus Directly Observed Once-Weekly Isoniazid and Rifapentine Treatment of Latent Tuberculosis Infection: A Randomized Trial. Ann Intern Med. 2017 Nov 21;167(10):689. doi:10.7326/M17-1150 PubMed PMID: 29114781.
75. Kim HY, Hanrahan CF, Martinson N, Golub JE, Dowdy DW. Cost-effectiveness of universal isoniazid preventive therapy among HIV-infected pregnant women in South Africa. International Journal of Tuberculosis and Lung Disease. 2018 Dec 1;22(12):1435–42. doi:10.5588/ijtld.18.0370 PubMed PMID: 30606315.
76. Degtyareva S, Hamada Y, Baggaley RF, Hassan N, Capocci S, van Crevel R, et al. Tuberculosis preventive treatment care pathways in people living with HIV: a systematic review and meta-analysis. Eur Respir J. 2025;66(2). doi:10.1183/13993003.02174-2023 PubMed PMID: 40312113.
77. WHO. WHO consolidated guidelines on tuberculosis. Module 1: Prevention. Infection prevention and control. WHO. 2022.
78. Golub JE, Saraceni V, Cavalcante SC, Pacheco AG, Moulton LH, King BS, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. AIDS. 2007 Jul;21(11):1441. doi:10.1097/QAD.0b013e328216f441 PubMed PMID: 17589190.
79. Shin H, Jo Y, Chaisson RE, Turner K, Churchyard G, Dowdy DW. Cost-effectiveness of a 12 country-intervention to scale up short course TB preventive therapy among people living with HIV. J Int AIDS Soc. 2020;23(10). doi:10.1002/jia2.25629
80. Kerschberger B, Vambe D, Schomaker M, Mabhena E, Daka M, Dlamini T, et al. Sustained high fatality during TB therapy amid rapid decline in TB mortality at population level: A retrospective cohort and ecological analysis from Shiselweni, Eswatini. Tropical Medicine and International Health. 2024 Mar 1;29(3):192–205. doi:10.1111/tmi.13961 PubMed PMID: 38100203.
81. Odone A, Amadasi S, White RG, Cohen T, Grant AD, Houben RMGJ. The Impact of Antiretroviral Therapy on Mortality in HIV Positive People during Tuberculosis Treatment: A Systematic Review and Meta-Analysis. PLoS One. 2014 Nov 12;9(11):e112017. doi:10.1371/journal.pone.0112017 PubMed PMID: 25391135.
82. Derseh NM, Agimas MC, Aragaw FM, Birhan TY, Nigatu SG, Alemayehu MA, et al. Incidence rate of mortality and its predictors among tuberculosis and human immunodeficiency virus

coinfected patients on antiretroviral therapy in Ethiopia: systematic review and meta-analysis. Front Med (Lausanne). 2024;11:1333525. doi:10.3389/fmed.2024.1333525

83. Bukundi EM, Mhimbira F, Kishimba R, Kondo Z, Moshiro C. Mortality and associated factors among adult patients on tuberculosis treatment in Tanzania: A retrospective cohort study. J Clin Tuberc Other Mycobact Dis. 2021 Aug 1;24:100263. doi:10.1016/j.jctube.2021.100263 PubMed PMID: 34355068.
84. Death rate, crude (per 1,000 people) - Africa Eastern and Southern, Eswatini | Data [Internet]. [cited 2026 Feb 15]. Available from: https://data.worldbank.org/indicator/SP.DYN.CDRT.IN?locations=ZH-SZ
85. Countries [Internet]. [cited 2026 Feb 15]. Available from: https://data.who.int/countries/
86. Ferguson O, Jo Y, Pennington J, Johnson K, Chaisson RE, Churchyard G, et al. Cost-effectiveness of one month of daily isoniazid and rifapentine versus three months of weekly isoniazid and rifapentine for prevention of tuberculosis among people receiving antiretroviral therapy in Uganda [Internet]. 2020. doi:10.1002/jia2.25623/full
87. Nichols BE, Cele R, Lekodeba N, Tukei B, Ngorima-Mabhena N, Tiam A, et al. Economic evaluation of differentiated service delivery models for HIV treatment in Lesotho: costs to providers and patients. J Int AIDS Soc. 2021 Apr 1;24(4):e25692. doi:10.1002/jia2.25692 PubMed PMID: 33838012.
88. Tagar E, Sundaram M, Condliffe K, Matatiyo B, Chimbwira F, Chilima B, et al. Multi-Country Analysis of Treatment Costs for HIV/AIDS (MATCH): Facility-Level ART Unit Cost Analysis in Ethiopia, Malawi, Rwanda, South Africa and Zambia. PLoS One. 2014 Nov 12;9(11):e108304. doi:10.1371/journal.pone.0108304 PubMed PMID: 25389777.
89. Minnery M, Mathabela N, Shubber Z, Mabuza K, Gorgens M, Cheikh N, et al. Opportunities for improved HIV prevention and treatment through budget optimization in Eswatini. PLoS One. 2020 Jul 1;15(7):e0235664. doi:10.1371/journal.pone.0235664 PubMed PMID: 32701968.
90. Institute for Health Metrics and Evaluation (IHME). Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME). 2018.
91. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 Diseases and Injuries for

195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018;392(10159). doi:10.1016/S0140-6736(18)32279-7

92. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012 Dec 15;380(9859):2197–223. doi:10.1016/S0140-6736(12)61689-4 PubMed PMID: 23245608.

93. Tomeny EM, Hampton T, Tran PB, Rosu L, Phiri MD, Haigh KA, et al. Rethinking Tuberculosis Morbidity Quantification: A Systematic Review and Critical Appraisal of TB Disability Weights in Cost-Effectiveness Analyses. PharmacoEconomics. Adis; 2024. doi:10.1007/s40273-024-01410-x

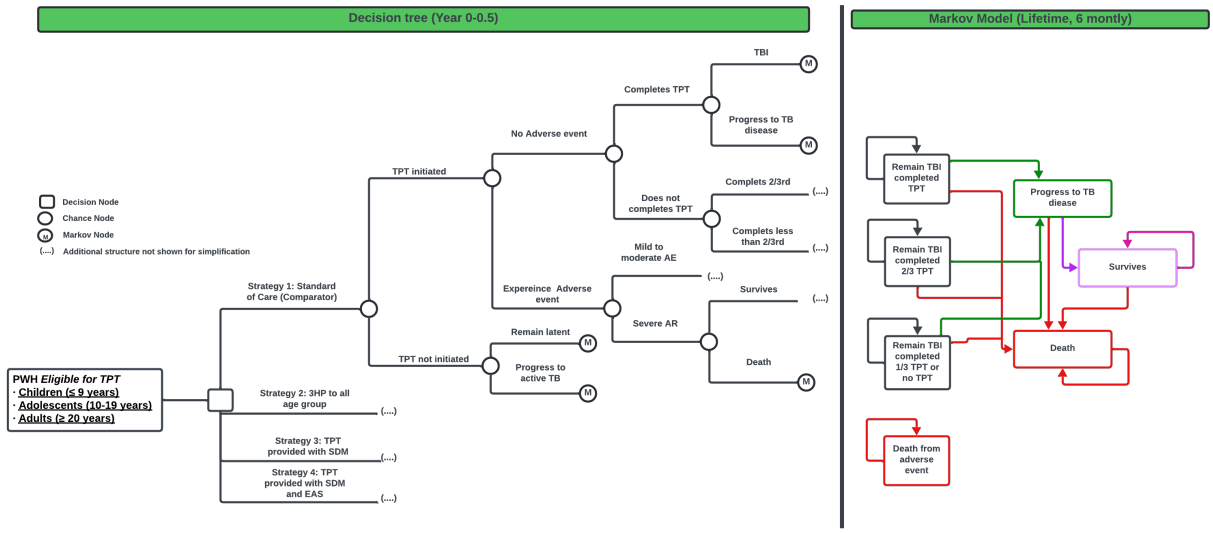


Figure 4.1. Hybrid decision-analytic model structure for tuberculosis preventive treatment (TPT) strategies among people with HIV (PWH): The figure illustrates the combined decision tree and Markov state-transition model used to evaluate different TPT delivery strategies. All eligible PWH, stratified by age group (children ≤9 years, adolescents 10–19 years, adults ≥20 years), enter the decision tree. Strategy-specific pathways determine TPT regimen selection and the presence of differentiated service delivery components, including shared decision-making (SDM) and enhanced adherence support (EAS).

The decision tree captures short-term outcomes during the TPT period, including treatment initiation, occurrence of adverse events (AEs), serious AEs leading to discontinuation, and treatment completion. Individuals then transition into the Markov model, which projects long-term outcomes over six-month cycles and a lifetime horizon. Markov health states include remaining TB infected, progression to TB disease, survival, and death. Transitions represent disease progression, TB-related mortality, and background mortality.

Abbreviations: PWH = people with HIV; TPT = tuberculosis preventive treatment; SDM = shared decision-making; EAS = enhanced adherence support; AE = adverse event; TB = tuberculosis, TBI: TB infection

Table 4.1: Epidemiological parameters for the cost-effectiveness analysis of TB preventive treatment among PWH in Eswatini

Parameter	Description	Point estimate	LL	UL	References
Probability of TPT initiation	Probability of initiating 6H	0.77	0.50	0.85	Clinic data, (43,48,58)
	Probability of 3HP initiation	0.77	0.70	0.85	Clinic data. (43,48–51)
	Proportion choosing TPT based on SDM				
	Among 10 years and above group				TB GAPS trial data, (32) (Pre-print version)
	Proportion of selecting 3HP	0.8	0.75	0.95	
	Probability of selecting 6H	0.17	0.05	0.25	
	Declining TPT	0.03	0.01	0.07	
Probability on AE	**Probability of experiencing any AE with 3HP**				(16,51,59–64)
	9 and below	0.08	0.05	0.22	
	Adolescent and adult	0.11	0.07	0.14	
	Probability of experiencing any AE with 6H				(64–69)
	9 and below	0.10	0.08	0.12	
	Adolescent and adult	0.20	0.15	0.35	
	Probability of experience serious AE 3HP				(16,51,59–64)
	9 and below	0.0020	0.0010	0.0030	
	Adolescent and adult	0.0060	0.0040	0.0070	
	Probability of experience serious AE 6H				(64–69)
	9 and below	0.0040	0.0030	0.0060	
	Adolescent and adult	0.0120	0.0080	0.0020	
Probability of TPT completion	Probability of completing 3HP with SOC	0.8	0.8	0.9	(16,42,50,70–74)

	Probability of completing 6H with SoC	0.56	0.41	0.77	(42,70,73,75,76)
	Percentage increment in completing 3HP and 6H with EAS	0.15	0.025	0.2	Assumption
Efficacy of TPT regimens	Efficacy of TPT	0.7	0.65	0.75	(16,42,58,70,77,78)
Natural progression of disease	**Annual progression of TB disease among PWH without TPT:** Year 1 and 2				(70,72,79)
	9 and below	0.1	0.03	0.18	
	Adolescent and adult	0.07	0.02	0.1	
	Annual progression of TB disease among PWH without TPT: Year 3 and beyond	0.02	0.01	0.04	
	Probability of death due to Tuberculosis on treatment	0.12	0.09	0.16	(80–83)
	Annual death rate form all other cause				(84,85)
	9 and below	0.044			
	Adolescent and adult	0.0088			
Probability of death among those who experience SAE	Probability of death from 3HP among those with SAE	0.0033	0.0004	0.01	(16,51,59–64,64–69)
	Probability of death from 6INH among those with SAE	0.0093	0.0003	0.02	
Cost (US$ 2024)	Cost of complete 3HP	$35	$21	$77	Empirical costing from TB GAPs

	Cost of complete INH for 10 and above	$34	$16	$89	
	Cost of complete INH among children	$32	$14	$88	
	Cost of active TB treatment	$141	$113	$169	
	Cost of active TB treatment (Children)	$148	$118	$178	
	Cost of EAS on 6H regimen	$19			
	Cost of EAS for HP regimen	$11			
	Cost of management of Mild to moderate AE	$35	$9	$113	(70,71)
	Cost of management of severe AE	$106	$53	$159	
	Cost of ART per year	$209	$183	$236	(43,71,86–89)
Disutility (DALY)	**PLHIV with ART**				(75,90–93)
	Healthy (no active TB)	0.05	0.03	0.08	
	Mild to moderate AE from TPT	0.20	0.08	0.36	
	Sever Adverse Event from TPT	0.62	0.13	0.91	
	Active TB disease	0.33	0.29	0.58	

Table 4.2: ICER per DALYs averted with 95% UR

Strategy	Average Cost (US$) per individual	Incremental Cost (US$)	Eff (DALYs)	DALYs Averted	ICER per DALYs averted (95% CI)
Strategy 1: SoC	$3,934		8.99		Reference
Strategy 2: 3HP all age group	$3,940	$6	8.93	0.06	$104 (Cost saving - $249)
Strategy 3: TPT with SDM	$3,944	$10	8.92	0.08	$125 ($77-$197)

Table 4.3. Lifetime TB cases and deaths per 1,000 people living with HIV under alternative TPT strategies

Strategy	TB Cases (per 1,000)	TB Cases Averted*	Incremental cost per TB case averted*	TB Death (per 1,000)	TB Death Averted*	Incremental cost per TB death averted*
Strategy 1: SoC	320	Reference	Reference	38	Reference	Reference
Strategy 2: 3HP all age group	302	18	$349	36	2	$2,908
Strategy 3: TPT with SDM	291	29	$334	35	3	$2,801

*Averted outcomes represent the absolute difference compared with the standard of care (SoC). Outcomes are expressed per 1,000 individuals over the lifetime horizon.

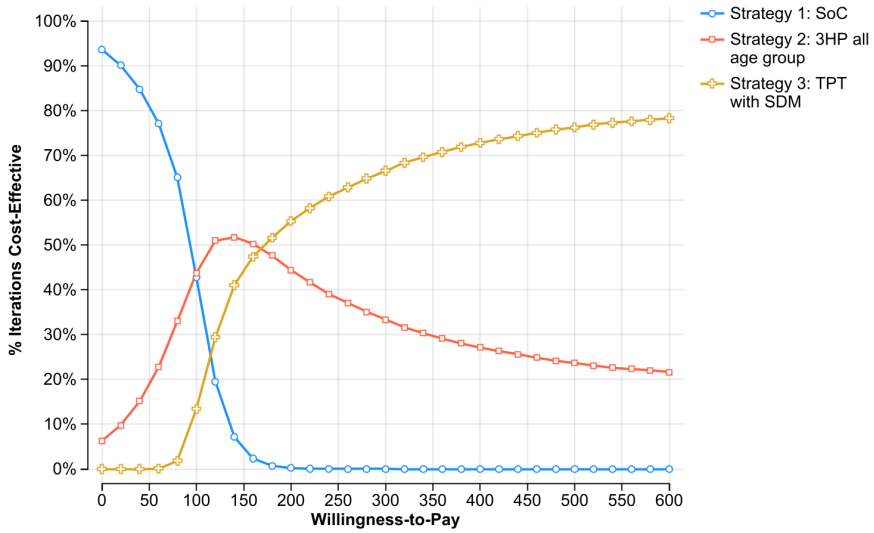


Figure 4.2: Cost-effectiveness acceptability curve of different TPT strategies: CE acceptability curve: Represents the proportion of simulations where it shows the strategy to consider cost-effective compared to SoC, at varying WTP thresholds. TPT: TB Preventive Treatment; SDM: Shared Decision Making; EAS: Enhanced Adherence Support; SoC: Standard of Care; CE: Cost Effectiveness; WTP: Willingness to Pay.

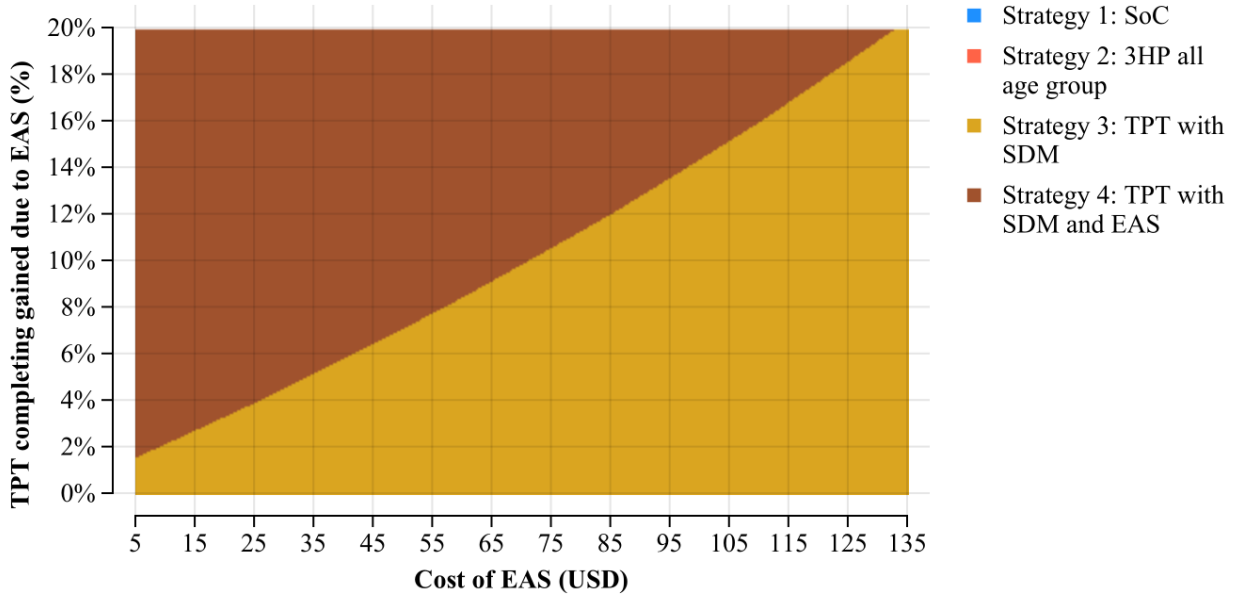


Figure 4.3: Two-way deterministic sensitivity analysis of EAS cost and completion gain at an opportunity cost–based willingness-to-pay threshold at $780 per DALYs averted. Net monetary benefit (NMB) was calculated at a willingness-to-pay threshold of $780 per DALY averted, corresponding to approximately 20% of Eswatini's GDP per capita and used as a proxy for the health opportunity cost. The figure displays the optimal strategy across combinations of enhanced adherence support (EAS) cost and incremental improvement in treatment completion. Regions indicate the strategy with the highest NMB at each parameter combination.

Table 4.4: Scenario analysis result when TPT is provided with SDM and EAS

Strategy	Average Cost (US$) per individual	Incremental Cost (US$)	Eff (DALYs)	DALYs Averted	ICER per DALYs averted (95% CI)	TB Cases (per 1,000)	TB Cases Averted*	Incremental cost per TB case averted*	Deaths (per 1,000)	Deaths Averted*	Incremental cost per TB death averted*
Strategy 1: SoC	$3,934		8.99		Reference	320		Reference	38		Reference
Strategy 4: TPT with SDM and EAS	$3,971	$37	8.84	0.15	$238 ($129 - $1,420)	259	61	604	31	7	5066

4.9 Supplemental

Supplemental Table 4.1: Description of TPT strategies

Strategy	Description	SoC Eswatini
Strategy 1 (Comparator): Standard of Care	TPT regimen according to country's current guidelines.	9 years and below: 6H 10 years and above: 3HP
Strategy 2: 3HP to all age group	3HP will be provided to all three-age group.	3HP to all age group
Strategy 3: TPT provided with SDM	Participants will be choosing their preferred TPT regimen	9 years and below: 6H 10 years and above: 3HP or 6H
Strategy 4: TPT provided with SDM and EAS (Hypothetical optimistic scenario)	Participants choose their preferred TPT regimen and will be enroll in EAS. EAS includes weekly bidirectional text messages for medication adherence and appointment reminders. Assuming an absolute optimistic TPT completion gain of 15% have been assumed.	9 years and below: 6H 10 years and above: 3HP or 6H

Notes: All strategies were evaluated using a combined decision tree and Markov state-transition model to estimate incremental costs, health outcomes, and cost-effectiveness. Enhanced adherence support (EAS) consisted of weekly bidirectional text messages for medication adherence and clinic appointment reminders. Strategy 1 served as the comparator.

Abbreviations: TPT: Tuberculosis Preventive Treatment; SoC: Standard of Care; SDM: Shared Decision-Making; EAS: Enhanced Adherence Support; 3HP = 3-month weekly isoniazid–rifapentine; 6H = 6-month isoniazid; 3RH = 3-month rifampicin–isoniazid.

Supplemental results:

Supplemental result on Sequential Analysis Results

In the sequential analysis (supplemental table 2), strategies were ordered by increasing cost. Compared with the SoC, Strategy 2 (3HP for all age groups) was associated with lower DALYs and an ICER of $105 per DALY averted. Strategy 3 (TPT with SDM) provided additional health gains relative to Strategy 2 and resulted in an ICER of $181 per DALY averted. No strategy was subject to simple or extended dominance in the base-case analysis, indicating that each strategy offered additional health benefits at increasing incremental cost along the efficiency frontier.

Supplemental Table 4.2: ICER per DALYs averted in sequential analysis.

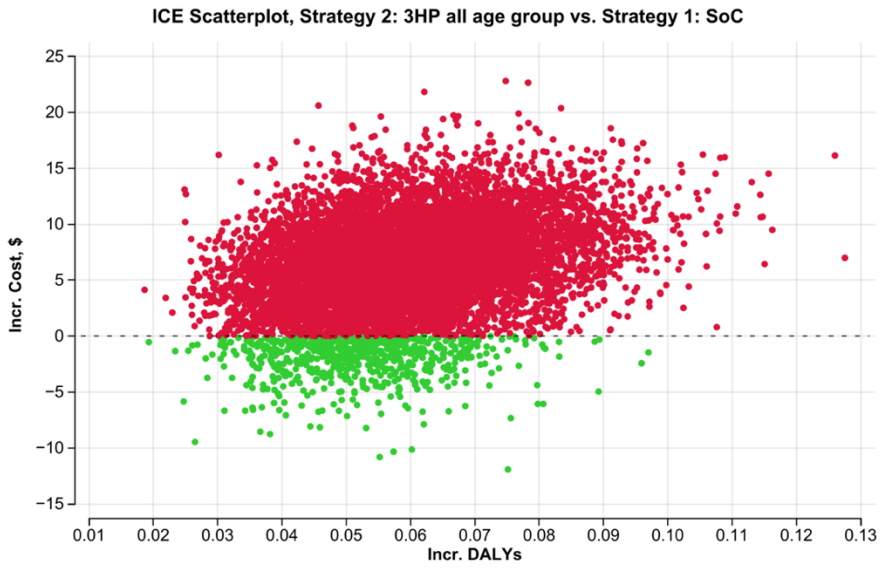
Strategy	Cost (US$)	Incr Cost (US$)	Eff (DALYs)	Incr Eff	ICER per DALYs averted
Strategy 1: SoC	$3,932		8.99		Reference
Strategy 2: 3HP all age group	$3,939	$6	8.93	0.06	$105
Strategy 3: TPT with SDM	$3,942	$4	8.92	0.02	$182

Supplemental results on Probabilistic sensitivity analysis:

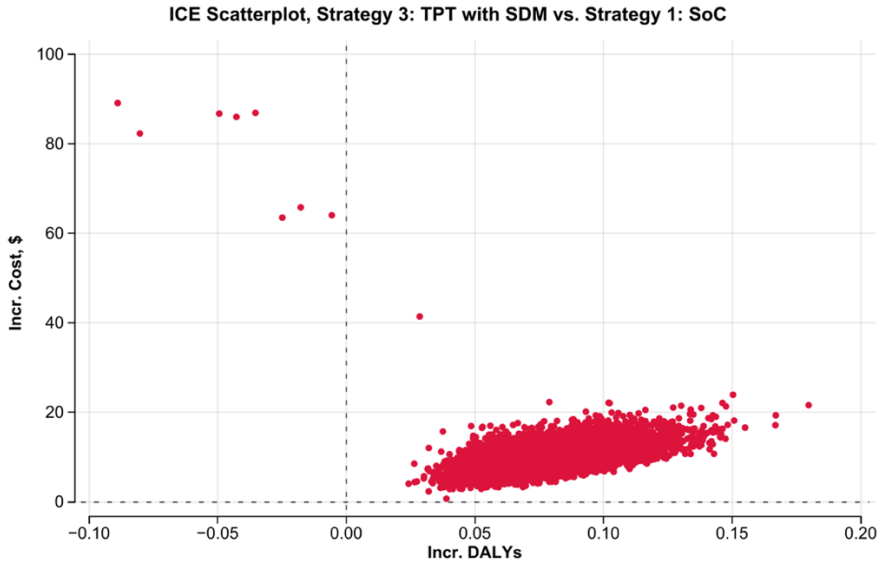
The incremental cost-effectiveness scatter plot for Strategy 2 (3HP for all age groups) compared with Standard of Care (supplemental figure 1a) shows that across simulations, incremental effectiveness remained consistently positive, indicating improved health outcomes relative to SoC. Incremental costs were generally small and clustered close to zero, with most simulations indicating slightly higher costs and a smaller proportion indicating cost savings.

Overall, the distribution of simulations suggests that Strategy 2 is likely to provide additional health benefits relative to SoC, with limited variability in incremental effectiveness and modest uncertainty in incremental costs.

The incremental cost-effectiveness scatter plot for Strategy 3 (TPT with SDM) compared with SoC (supplemental figure 1b) shows that the majority of simulations resulted in positive incremental effectiveness and increased costs. However, a smaller proportion of simulations yielded negative incremental effectiveness, indicating potential reductions in health benefit under certain parameter combinations.

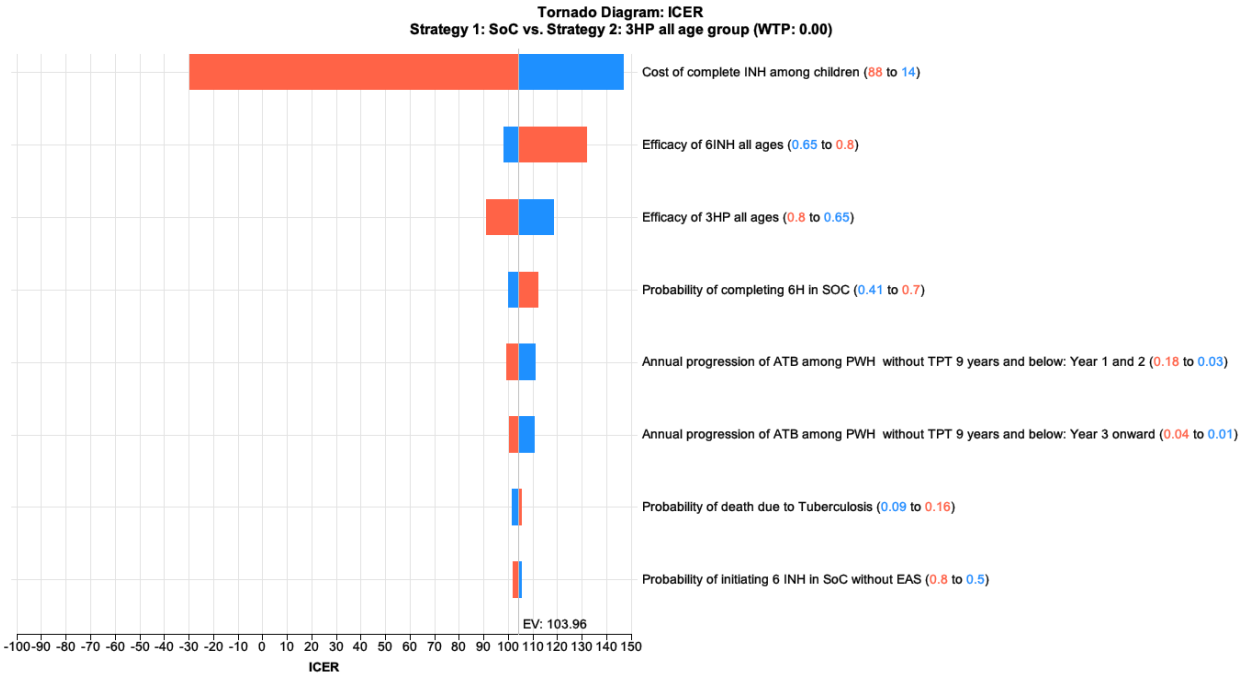


Supplemental Figure 4.1a: Incremental cost-effectiveness scattered plot for 3HP provided to all age group. Each scatterplot compares the ICER of strategy 2 versus SoC, showing incremental cost (X-axis) against incremental effectiveness in DALYs averted (Y-axis). Red dots represent 10,000 probabilistic simulations. TPT: TB Preventive Treatment; SDM: Shared Decision Making; EAS: Enhanced Adherence Support; SoC: Standard of Care; DALY: Disability-Adjusted Life Year; ICER: Incremental Cost-Effectiveness Ratio



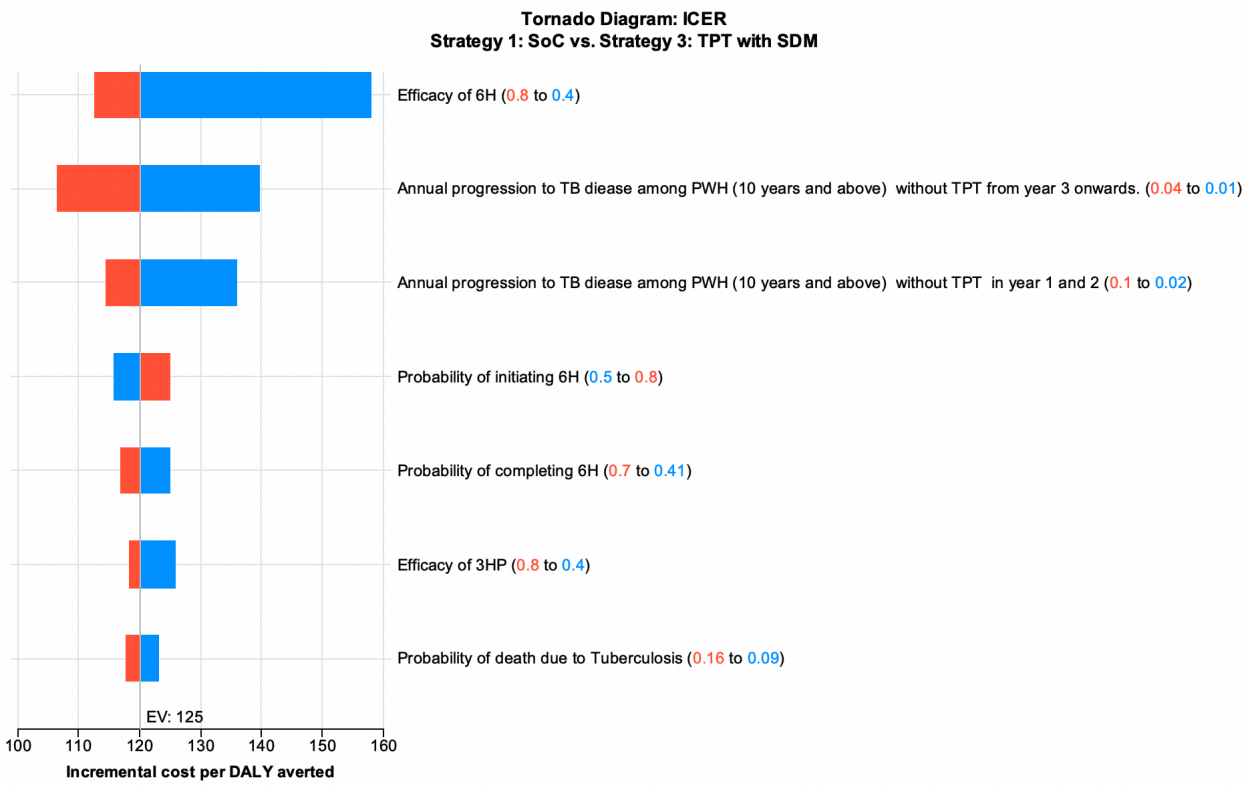
Supplemental Figure 4.1b: Incremental cost-effectiveness scattered plot for TPT provided with SDM. Each scatterplot compares the ICER of strategy 3 versus SoC, showing incremental cost (X-axis) against incremental effectiveness in DALYs averted (Y-axis). Red dots represent 10,000 probabilistic simulations. TPT: TB Preventive Treatment; SDM: Shared Decision Making; EAS: Enhanced Adherence Support; SoC: Standard of Care; DALY: Disability-Adjusted Life Year; ICER: Incremental Cost-Effectiveness Ratio

Supplemental results on deterministic sensitivity analysis:



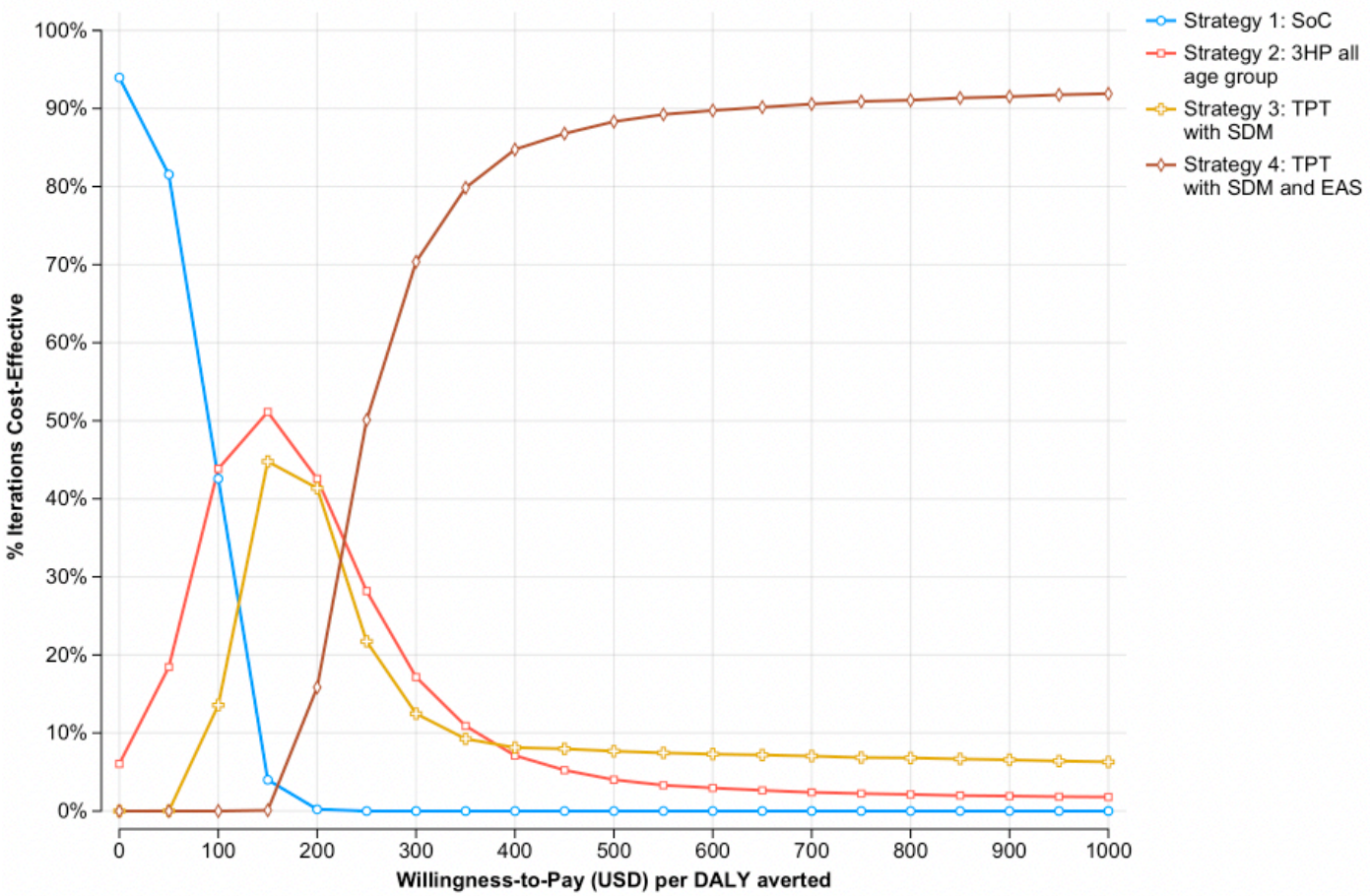
Supplemental Figure 4.2a. One-way sensitivity analysis of the ICER for Strategy 2 versus standard of care.

The tornado diagram illustrates the impact of varying key model parameters on the ICER of Strategy 2 (3HP provided to all age groups) compared with SoC. Each bar represents the range of ICER values obtained by varying one parameter at a time across its predefined lower and upper bounds while holding all other parameters constant. Parameters are ranked according to their influence on the ICER, with the most influential drivers shown at the top. **Abbreviations:** ICER, incremental cost-effectiveness ratio; SoC, standard of care; TPT, tuberculosis preventive treatment; PLHIV, people living with HIV



Supplemental Figure 4.2b. One-way sensitivity analysis of the ICER for Strategy 3 versus standard of care.

The tornado diagram illustrates the impact of varying key model parameters on the ICER of Strategy 3 (TPT provided with SDM) compared with SoC. Each bar represents the range of ICER values obtained by varying one parameter at a time across its predefined lower and upper bounds while holding all other parameters constant. Parameters are ranked according to their influence on the ICER, with the most influential drivers shown at the top. **Abbreviations:** ICER, incremental cost-effectiveness ratio; SoC, standard of care; TPT, tuberculosis preventive treatment; PLHIV, people living with HIV; SDM, shared decision-making; TB, tuberculosis.



Supplemental Figure 4.3: Cost-effectiveness acceptability curve with addition of hypothetical scenario analysis strategy 4 (TPT with SDM and EAS): CE acceptability curve: Represents the proportion of simulations where it shows the strategy to consider cost-effective compared to SoC, at varying WTP thresholds. TPT: TB Preventive Treatment; SDM: Shared Decision Making; EAS: Enhanced Adherence Support; SoC: Standard of Care; CE: Cost Effectiveness; WTP: Willingness to Pay.

Supplemental Table 4.3. Scenario Analysis Results: ICER per DALY Averted Under Alternative Assumptions on EAS Effectiveness and SDM Regimen Availability

Scenario	Strategy	ICER per DALYs averted
Base case	SoC	Reference
	3HP all age	$104
	TPT with SDM	$125
	TPT with SDM and EAS	$238

30% LTBI prevalence	SoC	Reference
	3HP all age	$152
	TPT with SDM	$172
	TPT with SDM and EAS	$339
Reduced first-two-year progression (3.5%)	SoC	Reference
	3HP all age	$106
	TPT with SDM	$135
	TPT with SDM and EAS	$268
Reduced 6H efficacy (60%)	SoC	Reference
	3HP all age	$96
	TPT with SDM	$133
	TPT with SDM and EAS	$258
No TPT protection after completion	SoC	Reference
	3HP all age	$743
	TPT with SDM	$708
	TPT with SDM and EAS	$1,244
5-year TPT protection	SoC	Reference
	3HP all age	$179
	TPT with SDM	$183
	TPT with SDM and EAS	$451
10-year TPT protection	SoC	Reference
	3HP all age	$142
	TPT with SDM	$152
	TPT with SDM and EAS	$326
20-year TPT protection	SoC	Reference
	3HP all age	$119
	TPT with SDM	$132
	TPT with SDM and EAS	$268
SDM for children ≤9 years	SoC	Reference
	3HP all age	$104
	TPT with SDM	$112
	TPT with SDM and EAS	$144
	SoC	Reference

Higher first-year progression risk	3HP all age	$110
	TPT with SDM	$119
	TPT with SDM and EAS	$203
Incomplete TB diagnosis/treatment	SoC	Reference
	3HP all age	$109
	TPT with SDM	$114
	TPT with SDM and EAS	$148
Undiscounted ICER	SoC	Reference
	3HP all age	$102
	TPT with SDM	$112
	TPT with SDM and EAS	$195

SoC = standard of care; TPT = tuberculosis preventive treatment; SDM = Shared decision making; 3HP = 3 months of isoniazid and rifapentine; 6H = 6 months of isoniazid; EAS = enhanced adherence support; DALY = disability-adjusted life year; ICER = incremental cost-effectiveness ratio.

Supplemental Table 4.4: CHEERS checklist for economic studies

Topic	No.	Item	Location where item is reported
Title			
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Title page
Abstract			
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Abstract
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Yes, background section
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Yes, methods section
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Yes, methods section

Topic	No.	Item	Location where item is reported
Setting and location	6	Provide relevant contextual information that may influence findings.	Yes, methods section
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Yes, methods section
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Yes, methods section
Time horizon	9	State the time horizon for the study and why appropriate.	Yes, methods section
Discount rate	10	Report the discount rate(s) and reason chosen.	Yes, methods section
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Yes, methods section
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Yes, methods section
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Yes, methods section
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Yes, methods section
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Yes, methods section
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Yes, methods section
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Yes, methods section
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Yes, methods section
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Yes, methods section
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Yes, methods section

Topic	No.	Item	Location where item is reported
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Not Applicable
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Yes, supplemental section
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Yes, results section
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Yes, results section
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Not Applicable
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Yes, discussion section
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Yes
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Yes

From: Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force. Value Health 2022;25. doi:10.1016/j.jval.2021.10.008

Chapter 5: General Discussion

Ending TB requires not only better technologies and shorter regimens, but delivery models that translate efficacy into real-world effectiveness under real-world budget and workforce constraints. This thesis examines three persistent gaps across the TB care and prevention cascade—gap in detection of drug-resistant TB, lack of realistic cost data for TPT delivery, and suboptimal TPT adherence- and evaluates whether innovative diagnostic and preventive interventions represent efficient uses of limited health system resources. Through three integrated studies, this thesis provides economic evidence that moves beyond isolated intervention assessment, but in line with WHO's End TB Strategy pillar of "integrated, patient-centred care and prevention".

5.1 Integrated studies summaries

Taken together, these three studies address different bottlenecks along the TB cascade: diagnosing drug-resistant TB, delivering preventive treatment affordably, and supporting adherence to complete TPT. Each study stands on its own, but together they show that ending TB requires attention to all three areas.

Improving DR-TB diagnosis with tNGS closes critical gaps in DST coverage, enabling earlier appropriate treatment. We examined the cost-effectiveness of targeted NGS for drug-resistance testing in high-burden settings. The value of tNGS was highly context dependent. In India, where phenotypic DST is often incomplete, tNGS dominated existing DST algorithms, improving DR-TB detection (beyond rifampicin alone) at lower cost. In South Africa, tNGS was cost-effective at conventional thresholds, due to faster, more comprehensive resistance profiling. By contrast, in Georgia, which already has broad DST coverage, tNGS added little benefit and did not meet cost-

effectiveness benchmarks. In all cases, universal phenotypic DST (if fully available) would outperform tNGS. The findings reinforce that incomplete DST beyond rifampicin remains a binding constraint in many high-burden settings, contributing to delayed initiation of appropriate DR-TB therapy and suboptimal outcomes. The value of tNGS lies not in replacing comprehensive phenotypic testing where it already exists, but in addressing diagnostic gaps where universal DST is operationally or financially infeasible. For national programs, this implies that tNGS should be targeted to settings with documented diagnostic gaps rather than adopted uniformly.

Understanding the real costs of TPT delivery and the cost drivers helps programs budget and plan. Our micro-costing analysis revealed substantial variation in TPT delivery costs across countries and regimens. Across all settings, drug costs and human resources emerged as the dominant cost drivers. Critically, treatment initiation, adherence counselling, and follow-up monitoring were identified as the most time-consuming and costly activities among all TPT-related tasks. These findings align with prior studies indicating that TB screening and preventive services are labour-intensive interventions. These findings have important implications for budget impact analyses and national TB program planning, particularly in resource-constrained settings where workforce capacity is already stretched. Importantly, identifying initiation and follow-up visits as the most time-consuming and costly components of TPT delivery suggests that improving service organization efficiency may be as critical as reducing medication prices. While recent global agreements have reduced the cost of rifapentine-based regimens, sustainable TPT scale-up will require parallel investments in workforce optimization and service integration.

Finally, addressing adherence through SDM and, where effective, EAS to improve completion rates can prevent more cases from progressing into active TB. We evaluated whether combining shorter regimens with patient-centred interventions improves TPT outcomes among people living with HIV. Shorter regimens such as 3HP improved outcomes compared with standard care, but the addition of SDM and EAS generated the largest modelled health gains by directly addressing adherence gaps. However, this result depends on an assumed 15% completion improvement from EAS, an assumption with limited TB-specific empirical support. Given the contradictory evidence (including a TB-specific trial finding no benefit from two-way SMS), national programs should first prioritize 3HP and SDM alone, which offer robust, evidence-backed improvements. SDM+EAS should be reserved for settings where adherence support can be delivered optimally and its impact measured locally. Together, these results point to a clear conclusion: efficient TPT scale-up requires expanding access to shorter regimens while simultaneously strengthening patient engagement and adherence mechanisms. This shifts the economic evaluation lens from simply which regimen to provide toward how to deliver it effectively, emphasizing that implementation design is just as important as technological innovation for reaching End TB targets.

We also want to emphasize that none of these findings alone is sufficient. A new diagnostic does not fix treatment adherence. A shorter regimen does not address delivery costs. And adherence support cannot compensate for missed diagnoses. But together, strategic investments in diagnostics, realistic costing, and patient-centred delivery can move us closer to ending TB. The challenge for decision-makers is to identify which bottleneck binds most tightly in their setting and invest accordingly, while not ignoring the others.

5.2 Policy implications

This thesis provides timely economic evidence to inform national and global TB policy. First, it supports the strategic adoption of tNGS as part of efforts to expand comprehensive drug susceptibility testing, particularly in settings with a high burden of drug-resistant TB. The economic evidence generated in this work directly contributed to global policy discussions through the World Health Organization Guideline Development Group (GDG) process in 2023, informing the WHO rapid communication (1) and subsequent 2024 consolidated guidelines recommending the use of tNGS for drug-resistance testing. (2) These guidelines conditionally recommend tNGS for people with bacteriologically confirmed TB and rifampicin-resistant TB to detect resistance to a broad range of first- and second-line drugs, including isoniazid, fluoroquinolones, and newer agents, as an alternative to culture-based phenotypic drug susceptibility testing. By enabling more comprehensive and rapid resistance profiling, tNGS supports earlier and more appropriate treatment decisions.

Beyond guideline development, the modelling framework developed in this thesis has been applied in subsequent analyses, including the study *"Cost-effectiveness of Targeted Next Generation Sequencing for TB drug-resistance testing as an alternative to the standard of care in South Africa,"* (3) which found that tNGS can be a cost-effective alternative to standard diagnostic approaches by improving detection of drug resistance and supporting more appropriate treatment at acceptable incremental cost. The model is also currently being adapted to support country-level decision-making in Kyrgyzstan and Tanzania through collaborations with KNCV as part of the DREAM Fund project.(4) These applications demonstrate the broader policy relevance and transferability of this work across diverse settings.

Second, this thesis highlights the importance of accounting for the full costs of TPT delivery. It provides comprehensive, activity-based cost estimates that capture all components of service delivery, including drugs, human resources, and overheads. These detailed cost estimates were subsequently used to inform the cost-effectiveness analysis within this thesis, ensuring that the evaluation of TPT strategies was grounded in realistic, programmatic cost data. In addition, the standardized data collection tools and costing templates developed in this work offer a practical resource for conducting similar costing studies in other settings, supporting cross-country comparisons and strengthening the evidence base for TPT scale-up.

Third, this thesis demonstrates that investments in adherence support and person-centred care can represent efficient uses of limited resources. The cost-effectiveness analysis shows that combining shorter TPT regimens with approaches such as shared decision-making and enhanced adherence support can improve treatment completion and maximize health gains. The modelling framework developed in this analysis is being extended to support ongoing cost-effectiveness evaluations in multiple high-burden settings, including Lesotho, Malawi, Uganda, and Tanzania. These applications will provide policy-relevant economic evidence for sub-Saharan Africa and other high TB–HIV burden settings, supporting national decision-making and program planning.

Crucially, the findings of this thesis must be interpreted within a rapidly shifting global health financing landscape. Recent funding contractions to the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), for instance, have introduced severe challenges for tuberculosis control efforts among PWH. PEPFAR has historically served as a financial cornerstone of HIV/TB integration in

high-burden settings, underwriting essential screening, treatment, and preventive services. Reductions in this external funding stream threaten to reverse hard-won gains in collaborative TB/HIV activities, particularly in countries where domestic health infrastructure remains heavily dependent on donor aid. (5)

In this volatile funding climate, the economic evidence generated by this thesis becomes even more critical. Demonstrating that person-centred TPT strategies and tNGS yield favourable incremental cost-effectiveness ratios provides an empirical safeguard to justify sustained investment even when budgets are tight. As domestic and international resource constraints tighten, policymakers require precise data to identify which interventions yield the highest return on investment; the robust ICERs presented herein provide exactly this evidence. Collectively, these findings align with the strategic pillars of the WHO End TB Strategy and the political commitments of the United Nations High-Level Meeting on TB. By offering actionable guidance on targeted diagnostic investments and efficient resource allocation, this work provides a framework for strengthening TB control resilience in an era of fiscal uncertainty.

5.3 Cross-cutting limitations:

Our conclusions should be interpreted with caution for several reasons. First, the economic estimates are highly context-dependent: they assume specific country settings for costs, TB incidence, and existing services. If conditions differ—for example, in DST coverage or workforce costs—cost-effectiveness would change, so local adaptation of our model is needed. Second, the analyses rely on model-based extrapolation where we projected long-term outcomes (like DALYs) from short-term trial data using assumptions about TB re-infection and how long protection lasts.

Third, a favorable ICER on paper does not always mean a strategy is affordable or feasible. Implementing new diagnostics like tNGS or preventive programs may require substantial upfront investment in equipment, supply chains, and specialized staff training. Budget constraints and health system capacity could prevent achieving the modeled impact. Finally, we took the healthcare system perspective, excluding patient's out-of-pocket costs and productivity losses. If we had included these societal factors, the net benefits of interventions, especially those that improve adherence and prevent illness, might look even more favourable. In short, these limitations mean our findings provide guidance but require careful local validation and consideration of real-world constraints.

5.4 Priorities for Future Research and Global Strategic Implications

5.4.1 Bridging the Implementation and Scalability Gap

While this thesis shows that tNGS and person-centred TPT are cost-effective, being cost-effective does not always mean they are affordable or easy to implement. Future research needs to test how these interventions work in decentralized setting for tNGS and when person-centered TPT is being delivered in smaller, rural clinics where supply chains are weaker, and staff training is more limited. Studies should also examine how the high upfront costs of sequencing machines can be spread across multiple diseases (like HIV or COVID-19) to improve value for money.

5.4.2 Equity Considerations and the Societal Perspective

The current analysis was conducted from a healthcare system perspective, which excludes indirect costs such as patient out-of-pocket expenses and productivity losses. Given that 50% of TB-affected households still face catastrophic costs, future research should adopt a societal

perspective to evaluate whether patient-centred models (such as SDM and shorter regimens) successfully reduce the financial hardship that drives treatment interruption. Furthermore, equity in digital adherence support must be examined; future studies should investigate whether reliance on digital EAS inadvertently excludes vulnerable populations with limited mobile access or low literacy, potentially widening health disparities.

5.4.3 Real-World Effectiveness and Long-Term Impact

This research relied on an optimistic 15% completion gain for EAS, which currently lacks strong TB-specific empirical support. Large-scale pragmatic trials are needed to quantify the real-world impact of bidirectional messaging and SDM specifically for TPT, moving beyond the HIV-centric evidence used in current models. Additionally, future research should integrate the findings of this thesis into transmission-dynamic models to evaluate how closing the diagnostic gap with tNGS impacts community-level TB incidence and the development of further drug resistance over decades.

5.4.4 Generalizability to Other High-Burden Settings

The findings of this thesis offer a strategic blueprint that informs TB control beyond the specific contexts of India, South Africa, Georgia and countries in sub-Saharan Africa. The finding that diagnostic innovation should be targeted to settings with documented diagnostic gaps rather than adopted uniformly is a universal lesson for any National TB Programme (NTP) with fragmented laboratory infrastructure. The standardized, activity-based micro-costing templates developed in this work provide a practical toolkit for NTPs in other resource-constrained settings (e.g., Southeast Asia) to move away from price-only budgeting toward realistic fiscal planning that

accounts for the 41-80% human resource burden of TPT delivery. The overarching conclusion is that implementation design is as critical as technological innovation. This mandate should guide global policy toward pairing every new tool with a robust, person-centred delivery framework to ensure that global investments translate into value for money and ultimate TB elimination.

5.5 Overall conclusion

In conclusion, this thesis demonstrates that achieving TB elimination requires not only effective diagnostic and preventive tools but also economically informed strategies that address diagnostic completeness, implementation affordability, and treatment adherence. By integrating economic evidence across the TB care cascade, this work contributes to a more comprehensive understanding of how limited resources can be deployed efficiently to accelerate progress toward the goals of the WHO End TB strategy.

5.6 Reference

1. Use of targeted next-generation sequencing to detect drug-resistant tuberculosis [Internet]. [cited 2026 Mar 17]. Available from: https://www.who.int/publications/i/item/9789240076372
2. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection. World Health Organization [Internet]. 2024 [cited 2026 Mar 17];1–184. Available from: https://www.who.int/publications/i/item/9789240089488
3. de Nooy A, Omar SV, Ockhuisen T, Zwerling A, Shrestha S, Suresh A, et al. Cost-effectiveness of Targeted Next-Generation Sequencing for Tuberculosis Drug-resistance Testing as an Alternative to the Standard of Care in South Africa. Clin Infect Dis. 2026 Feb 9;82(1). doi:10.1093/cid/ciaf495 PubMed PMID: 40920587.
4. Dream Fund project ‘No More Pandemics’ | KNCV Tuberculosis [Internet]. [cited 2026 Mar 17]. Available from: https://www.kncvtbplus.com/projects/dream-fund-project-no-more-pandemics

5. Olpengs D, Mamwa J. Sustaining HIV gains towards the UNAIDS 95 95 95 targets amid a shifting funding landscape in Sub Saharan Africa. Discover Public Health 2025 22:1. 2025 Dec 27;22(1):879-. doi:10.1186/S12982-025-01296-W