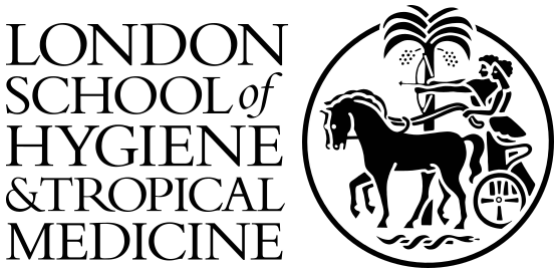

THE ECONOMIC BURDEN OF TUBERCULOSIS AND THE MITIGATION EFFECT OF SOCIAL PROTECTION: A POPULATION-BASED STUDY IN GHANA

Debora Pedrazzoli

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Department of Infectious Disease Epidemiology
Faculty of Epidemiology and Population Health

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

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Declaration of own work

I, Debora Pedrazzoli, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed: 

Date: 20th August 2020

Abstract

Background

Tuberculosis (TB), a major global public health concern, is known as a disease of the poor. However, evidence on the economic burden of TB is limited, and so is the literature on the impact of poverty alleviation strategies, such as social protection (SP), on financial protection for TB patients. This PhD aimed to contribute to the body of knowledge on the costs and affordability of TB care, and on the potential mitigation effect of SP on TB patient costs.

Conceptual analyses and empirical data I collected as part of a nationally representative TB patient cost survey in Ghana were used to address these objectives:

1) Provide evidence on the level, and composition, of costs incurred by TB-affected households and affordability of TB care;
2) Investigate determinants of costs, and the impact of National Health Insurance (NHIS) on costs;
3) Explore the potential impact of costs on TB treatment outcomes.

Results

This thesis showed that TB patients in Ghana face financial catastrophe and impoverishment due to the cost of TB care. The poorest and those with drug-resistant TB have increased odds of experiencing catastrophic costs. NHIS in its current form is not effective in defraying costs, and its expansion will not be effective to relieve the financial burden for TB-affected households. Further, this thesis did not find an effect of costs on treatment outcomes as, like most TB patient cost surveys, our study was not powered to detect such an association.

Conclusion

SP schemes require enhancement if they are to protect TB patients from financial catastrophe. Evidence generated from this thesis provides original insights into affordability of TB care, lending weight to policy recommendations on financial protection for TB patients. This PhD also shows both the potential and limitations of TB patient cost surveys to assess the impact of social protection strategies on costs, and of TB-related costs on treatment outcomes, thus calling for further methodological developments, and outlining a clear map for future research.

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Preface

The work of this PhD reflects my professional journey over the past five years. As a member of the World Health Organization's (WHO's) Global task force on TB patient cost surveys since its inception, I was involved in the development of the generic protocol and tool, and subsequently in their pilot in Ghana. The work undertaken for this PhD has fed into further methodological development of the WHO instrument, and in the handbook, which was eventually published in 2017. During my time working with the WHO, I provided technical assistance to a number of countries in sub-Saharan Africa, Asia and Europe during the design and implementation of their national surveys. Most importantly, I also had the unique opportunity to support Ghana in translating the findings presented in this thesis into policy and practice, that will help improve the lives of people living with TB.

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List of acronyms and abbreviations

CI	Confidence interval
DM	Diabetes Mellitus
GDP	Gross Domestic Product
HIV	Human Immunodeficiency Virus
LEAP	Livelihoods Empowerment Against Poverty Programme
LSHTM	London School of Hygiene and Tropical Medicine
MDR-TB	Multi-drug resistant tuberculosis
NHIS	National Health Insurance Scheme (Ghana)
NTP	National Tuberculosis Control Programme
OOP	Out-of-pocket (payments)
SD	Social determinant
SHI	Social Health Insurance
SP	Social protection
TB	Tuberculosis
TB-MAC	TB Modelling and Analysis Consortium
TREAT TB	Technology, Research, Education and Technical Assistance for Tuberculosis Project
UHC	Universal Health Coverage
USAID	United States Agency for International Development
WHO	World Health Organization

Chapter 1: Introduction

1.1 Background

1.1.1 Tuberculosis as an equity challenge

Much has been achieved in tuberculosis (TB) control since the World Health Organization (WHO) declared it a global emergency in the mid-nineties (1). Yet TB, with an estimated 10 million new cases and 1.4 million TB-related deaths in 2018, remains the leading cause of mortality from a single infectious agent (2).

TB is a communicable disease that is caused by the bacillus *Mycobacterium tuberculosis*, which is spread when people who are sick with TB expel bacteria into the air, for example, by coughing but also breathing and talking. It typically affects the lungs (pulmonary TB) but can also affect other sites in the body (extra-pulmonary TB) (2). About a quarter of the world's population is infected with *M. tuberculosis* and thus at risk of developing TB disease (3).

TB also represents an equity challenge. While TB is not solely a disease of the poor, poverty and inequity fuel the epidemic (4). Socio-economic factors have long been acknowledged as major drivers of TB (5). Poverty has been found to increase the risk of acquiring TB infection and developing the disease through more proximal risk factors such as malnutrition and overcrowded living conditions (6-8).

The poverty preference also affects access to care, particularly in low- and middle-income countries (LMICs), where health care financing is largely characterised by out-of-pocket (OOP) payments for the individual and a lack of prepayment mechanisms (e.g. taxation, health insurance) (9). Even when TB diagnosis and treatment are, in principle, provided free of charge, TB patients often incur transport, accommodation and time costs. Costs can be a deterrent to accessing diagnosis and care in the first place (10), and for those who do seek care, costs reduce available income making them more vulnerable and driving them further into poverty. This means that TB patients may struggle to adhere to treatment and fail to complete it (11), thus leading to increased TB transmission in the household and community, and exacerbating morbidity and mortality (12). This is a particular concern for patients with multi-drug resistant (MDR)-TB which requires lengthy treatment (13).

1.1.2 Towards zero families incurring catastrophic costs due to TB

The financial hardship that many households face due to TB is often catastrophic. This is mainly driven by income losses and non-medical expenses rather than the direct charges of medical care (13).

The End TB Strategy therefore includes a target of preventing any TB patient from incurring catastrophic costs due to TB by 2025, defined as total TB-related (i.e. non-medical direct costs of illness and income losses) exceeding 20% of pre-illness annual household income (14). To monitor progress towards this milestone, the WHO Global TB Programme convened a task force of experts in 2015 to develop a field-testing protocol and survey instrument for nationally representative, health facility-based surveys of costs faced by TB patients and their households ("TB patient cost surveys") (15).

The concepts and related measurement that underlie the End TB Strategy indicator of 'zero catastrophic costs' due to TB provide the framework for the PhD, which, as a first step, reviews costs and affordability, discusses the standard methods for measuring these constructs in the Universal Health Coverage (UHC) monitoring framework, and contrast them with how they are measured in TB patient cost surveys (**Research gap 1**).

After field testing and experience in pathfinding countries that conducted the first surveys, the WHO refined and expanded the methodology, and developed a handbook in 2017 (16). Countries, and particularly high TB burden countries, are expected to adapt and implement these surveys (i) to document the magnitude and main drivers of costs incurred by TB patients (and their households); (ii) to assess the proportion of TB patients who incur catastrophic costs as a result of the cost of care, and to monitor this metric over time. Findings from these surveys should also help identify entry points for developing policies to ensure better financial and social protection for TB patients (16).

As of July 2019, national TB patient cost surveys had been completed in 14 countries, and were underway in further 9 countries. Results from 12 of the completed surveys show that the proportion of TB patients and their households experiencing catastrophic costs ranged from 27% (95% CI: 21–32%) in Kenya to 83% (95% CI: 80–86%) in Timor-Leste, and this figure was consistently higher for drug-resistant patients. The composition of costs varied across countries. Medical costs, despite "free TB care" policies, were high in some countries; non-medical costs

were the largest cost component in most countries, followed by income losses associated with loss of employment or time lost while seeking or staying in care (2).

Despite the growing body of evidence on costs incurred by TB patients since the endorsement of the End TB Strategy, at the time this PhD was conceived evidence on affordability of TB care was limited (**Research gap 2**): the majority of studies looking at TB patient costs were outdated, suffered from small sample sizes or focussed on specific sub-populations, and employed heterogeneous methodologies (17-19). Further, most studies did not report costs as a proportion of income, nor did they measure affordability of TB care (13).

1.1.3 Social protection as a means to ensure effective and equitable TB care

While Universal Health Coverage (UHC), defined as affordable access to effective care for all (20), is critical to ensure access to quality TB diagnosis and treatment without facing financial hardship, interventions designed to defray or mitigate non-medical costs and income loss (beyond medical expenses) are equally key (21).

Aligned with the Sustainable Development Goals (SDGs) and appreciating that TB disproportionally affects poor households, the WHO's End TB Strategy considers pro-poor initiatives such as social protection (SP) a key instrument for preventing TB-affected households from incurring catastrophic costs, and ensuring equitable access to TB care.

Social protection is defined as a set of poverty alleviation initiatives and policies that aim to provide protection to the poor and vulnerable against livelihood risks and achieve sustainable and inclusive economic growth (22) (Table 1).

Social transfers are increasingly popular components of SP (particularly in South American and African countries), which deliver cash ("cash transfers") or welfare/in-kind transfers to the poor and thereby seek to reduce income inequalities, alleviate poverty and improve health and development outcomes. Common to many such schemes are "conditions" where recipients of transfers are required to undertake activities (such as infant vaccination) seen as beneficial for themselves and the whole country, usually focused on health and education (in this case, transfers are called conditional or targeted) (23).

In TB care, besides cash transfers, SP strategies to TB patients may include food rations or

nutritional support (24), transport vouchers, payment of health insurance premium and access to social benefits such as the Disability Grant in South Africa (25).

Table 1: Social protection: summary of key definitions and examples

	Definition	Examples	Reference/ Source
Social protection	A set of initiatives that secure protection aimed at preventing or alleviating poverty, livelihood risks and social exclusion	-	Devereux, 2004 (22)
Social insurance or Social security	An initiative to provide transfers to households in the event of adverse economic events, conditional on prior contributions and participation in the labour market	Sickness benefits, unemployment benefits, disability benefits and survivor's benefits	ILO, 2013 (26)
Social health insurance	A form of social insurance. Health insurance schemes with public stewardship and at least some insurance premium contributions from the insured	Ghana (National Health Insurance Scheme); The Philippines (PhilHealth); Kenya (National Hospital Insurance Fund)	Wells, 2019 (27)
Social assistance or Safety nets	An initiative to provide transfers to deprived households unconditional on previous payments or contributions	Cash transfers, in-kind transfers, food-based programmes (e.g., food stamps) non-contributory social pensions, and fee waivers and exemptions for health care, schooling, utilities	Ivashenko, 2018 (28)
Cash transfer	A form of social assistance scheme/safety net which provides cash to families living in poverty subject to the condition that they fulfil specific behavioural requirements (conditional cash transfer). These conditions oblige individuals to satisfy some action associated with human development goals (e.g. school attendance, utilisation of basic preventative nutrition and health care services).	Livelihood Empowerment Against Poverty, LEAP (Ghana); Cash Transfer Programme for Orphans and Vulnerable Children, CT-OVC (Kenya)	ILO, 2013 (26) Bastagli, 2016 (29)
TB-specific social protection	Interventions targeted at TB-affected households/individuals with the aim to improve TB prevention, care and support	Vouchers intervention (South Africa)	Boccia, 2016 (30)
TB-sensitive social protection	Interventions that can potentially affect TB prevention, care and control by targeting people who are at high risk of TB and/or are susceptible to the consequences of TB	Bolsa Familia Programme (Brazil)	Boccia, 2016 (30)

Evidence from a systematic review indicates that cash transfers have the potential to reduce monetary poverty, increase school attendance, improve the use of health services, dietary diversity and anthropometric measures, and, finally, can stimulate household savings (29).

Whilst limited, evidence points to the potential of cash transfers to contribute to disease prevention, and improve health outcomes for affected populations (31, 32).

Evidence for the potential of social protection to improve TB outcomes (TB prevention, care and support) is also limited. Table 2 provides a summary of the current evidence. To my knowledge, the studies summarised in Table 2 and in the following paragraphs constitute all the available evidence on this topic and no similar studies exist, either published or unpublished, that present negative or null results.

Two studies support evidence for the impact of social protection on TB prevention. A modelling study shows that achieving SDG1 through ending extreme poverty and expanding social protection could have a considerable impact on the global burden of TB (33). Another modelling study used Bolsa Familia, the national conditional cash transfer programme in Brazil, as a test case to demonstrate that social protection can reduce TB prevalence by improving household income and therefore the nutritional status of their members (34).

The body of evidence for the impact of social protection on TB care, and particularly on treatment outcomes, has recently grown. One systematic review and meta-analysis concludes that patients in LMICs who receive cash transfers during treatment for active pulmonary TB are more likely to have a positive clinical outcome (35). Another review found an association between social protection and TB treatment success, with cure of patients, and with a reduction in the risk of defaulting treatment (36). Findings from two recent studies in Brazil suggest that TB treatment outcomes improved among beneficiaries of a governmental cash transfer programme (37, 38). Research from Argentina among socio-economically disadvantaged TB patients shows that those who registered to receive the conditional cash transfer programme had significantly higher treatment success rates and lower treatment abandonment compared to those who were not in the programme (39).

Evidence for the potential of social protection to protect households from experiencing financial hardship in response to TB is limited (**Research gap 3)**. Evidence from a trial among MDR-TB patients in Peru demonstrates the effectiveness of a non-governmental cash transfer intervention in reducing the likelihood of incurring catastrophic costs (40). A cross-sectional study in Rio de Janeiro, Brazil, shows that households affected by MDR-TB that uptake social protection are less likely to experience financial hardship (41). Finally, an economic modelling study indicates that providing cash transfers to defray TB-related costs was effective in

preventing catastrophic costs (34).

Table 2: The impact of social protection on TB: a summary of the evidence

Author/Year	Country	Study design	Implementation model[a]		Impact findings[b]		
			TB-specific	TB-sensitive	Prevention[c]	Care[d]	Support[e]
Lutge /2013 (42)	South Africa	Pragmatic two arm cluster randomised controlled trial	●			+/-	
Ciobanu/2014 (43)	Moldova	Retrospective cohort study	●			++	
Sripad /2014 (44)	Ecuador	Cohort study		●		++	
Reeves /2014 (45)	Multi-country	Ecological		●	++		
Wingfield /2014 (46)	Peru	Community randomised controlled trial	●				++
Siroka/2015 (47)	Multi-country	Ecological analysis		●	+	+	
Wingfield /2016 (40)	Peru	Community randomised controlled trial	●		++	+	
Torrens/2016 (48)	Brazil	Retrospective cohort study		●		++	
Nery/2017 (49)	Brazil	Ecological analysis		●	++		
Rudgard/2017 (34)	Multi-country	Economic modelling	●	●			+
Durovni/2017 (50)	Brazil	Retrospective cohort study		●		++	
Rudgard/2018 (41)	Brazil	Cross-sectional study		●			+
Carter/2018 (33)	Brazil	Quasi-experimental study		●		++	
Boccia/2018 (51)	Brazil	Mathematical Modelling		●	+		
Carter/2018 (33)	Multi-country	Ecological analysis		●	++		
Reis-Santos/2019 (37)	Brazil	Cohort study		●		+	
Klein/2019 (39)	Argentina	Cohort study		●		++	

Oliosi/2019 (38)	Brazil	Cohort study	●	+

a. Implementation model. TB-specific: Interventions targeted at TB-affected households/individuals with the aim to improve TB prevention, care and control. TB-sensitive: Interventions that can potentially affect TB prevention, care and control by targeting people who are at high risk of TB and/or are susceptible to the consequences of TB (Table 1) (30)
b. Impact: ++ Strong positive impact; + Modest positive impact (either significant or not); +/- No impact in either direction; - Negative impact.
c. Prevention includes impact on TB incidence and prevalence.
d. TB care includes impact TB treatment outcomes.
e. TB support includes mainly the mitigation effect of social protection on TB-related costs.

Another component of SP that has recently attracted growing attention in LMICs is the adoption of health insurance schemes as a means for protecting populations from the cost of care seeking, improving equity, expanding access, and ensuring quality of care (52).

Health insurance has been defined as "a way to distribute the financial risk associated with the variation of individuals' health care expenditures by pooling costs over time through prepayment and over people by risk pooling" (53). Insurance can be mandatory or voluntary; national insurance (NHI, or social health insurance, SHI) is generally mandatory covering specific sections of the population (e.g., public/formal sector) and has a single risk pool; voluntary insurance can be private or community-based insurance (CBHI). SHI differs from a tax-based system, where government revenues are the main source for health care expenditures (54). This thesis focuses on SHI.

Evidence from two systematic reviews of studies conducted in LMICs in Africa and Asia suggests that (national or social) health insurance has a weak impact on changes in health status, but can improve financial protection by reducing out-of-pocket expenditures among the general population (52, 53). However, there are ongoing concerns that national health insurance programmes with premiums may not be able to protect the most vulnerable groups in society, who may not be able to afford the premium, or may live in peripheral or rural areas with limited access to health services (55).

Given the epidemiology of TB and its concentration in LMICs, many of the countries that are adopting SHI schemes are countries with a high burden of TB. Initial assessments have focused on the integration (or potential for) of TB services into the service delivery package of NHI programmes. Case studies demonstrate that the inclusion of TB services in SHI can enhance access to services and utilisation, and their quality (56). Evidence for the potential of health insurance to provide financial protection to TB patients is lacking (**Research gap 3**).

1.1.4 Financial hardship and TB treatment outcomes

While the body of evidence on the impact of social protection on TB treatment outcomes has recently grown, evidence on the effect of costs on TB treatment outcomes remains limited (**Research gap 4)**: a study among MDR-TB patients in Peru found a relationship between costs and unfavourable treatment outcomes (46), and a study in China between costs and treatment adherence (57). Although the 20% catastrophic cost threshold endorsed by WHO was eventually

set through expert opinion voting, it was initially influenced by the by the study in Peru, which showed that above this threshold, patients with TB were nearly twice as likely to experience adverse treatment outcome (odds ratio, OR = 1.7 [95% CI = 1.1–2.6], *P-value*=0.01). The WHO handbook on TB patient cost surveys recommends assessing the potential impact of costs on TB treatment outcomes as part of national TB patient cost surveys to help validate or change the threshold endorsed by WHO (16).

1.2 Rationale for this PhD

In light of the existing knowledge and research gaps listed above, the importance of this thesis is threefold. First, while work has been done in assessing costs for TB patients, there remain critical gaps as TB-related costs are still under studied. The End TB Strategy target of zero TB-affected families facing financial hardship is a first important step in broadening metrics of financial protection to account for demand-side barriers to accessing TB care and to treatment adherence. However, while there have been previous assessments of TB patient costs in LMICs (including in Ghana), most studies did not report costs as a proportion of income, nor did they measure affordability of TB care.

At the time this PhD was conceived, the protocol and survey instrument developed by the WHO needed field testing, and further methodological development and data to inform them. The work of this PhD constitutes the first study to adopt and adapt the WHO tools in sub-Saharan Africa.

Second, little is known about the potential of social protection initiatives to protect TB-affected households from experiencing financial hardship. Using Ghana as a case study, this PhD aimed to inform the design and implementation of policies and interventions to ensure financial risk protection to TB patients. In doing so, this work also wanted to set an example for countries to evaluate the potential of social protection strategies to defray costs as a second step following the assessment of affordability.

Third, while it is plausible to hypothesise that costs related to TB care incurred by patients may have an impact on treatment outcomes, the evidence supporting such an association is very limited. This thesis aimed to provide evidence on the potential impact of catastrophic costs for TB on TB treatment outcomes within the context of a national TB patient cost survey based on the WHO methodology.

1.3 Aim and research objectives of the thesis

Aim

This PhD aimed to contribute to the body of knowledge on the costs and affordability of TB care, and on the potential impact of SP strategies to mitigate TB-related costs.

Objectives

This thesis addressed the four knowledge gaps identified through the following four objectives:

1) Summarise key measurable concepts for TB patient cost surveys, notably the types of costs that are captured and related affordability measures, and contrast them with the standard methods for measuring these constructs in the UHC framework.
2) Provide further evidence on the level, and composition, of costs incurred by TB-affected households and affordability of TB care.
3) Investigate drivers and determinants of costs incurred by TB patients, and the potential impact of social protection on mitigating these costs.
4) Explore the potential impact of catastrophic payments for TB care on TB treatment outcomes, and discuss the relevance and appropriateness of this analysis.

The research gaps identified by the thesis, the objectives and methods employed by this PhD are summarised in Table 3.

Table 3: Synopsis of the research gaps addressed by the thesis, its objectives, methods, and corresponding chapter and research paper

Research gap	PhD Objective	Method	Chapter # Research paper #
1. Lack of a comprehensive overview of key concepts for TB patient cost surveys, and how they are measured in the End TB Strategy *vs*. the UHC framework.	1. Summarise key measurable concepts for TB patient cost surveys, notably the types of costs that are captured and related affordability measures, and contrast them with the standard methods for measuring these constructs in the UHC framework.	Conceptual review of cost measurement and affordability metrics for the indicator of "catastrophic total costs due to TB" and "catastrophic spending on health"	Chapter 2 Research paper 1
2. Limited evidence on detailed costs, on costs as a proportion of income, and on	2. Provide further evidence on the level, and composition of costs incurred by TB-affected households and	a) Survey among TB experts on availability and cost of chest-radiography	Chapter 3 & 4 Research paper 2 & 3

	affordability of TB care.		affordability of care.	b) Nationally representative TB patient cost survey in Ghana	
3.	Limited knowledge on determinants of TB patient costs and on the potential impact of social protection on TB patient costs.	3.	Investigate drivers and determinants of costs incurred by TB patients, and the potential impact of social protection on mitigating these costs.	Using data from the Ghana survey: a) Regression models were used to determine drivers of costs and affordability. b) Inverse Probability of Treatment Weighting Analysis was used to investigate the effect of enrolment into NHIS on costs	Chapter 5 Research paper 4
4.	Limited evidence on the potential impact of TB related costs on TB treatment outcomes	4.	Explore the potential impact of catastrophic payments for TB care on TB treatment outcomes, and discuss the relevance and appropriateness of this analysis.	Analysis of data from completed national TB patient cost surveys, including the Ghana survey.	Chapter 6 Research paper 5

1.4 Structure and methodological approach of the thesis

This thesis is structured in a research paper style and is comprised of five different papers, along with introductory and linking material.

The second chapter provides the framework for the PhD, and reviews and defines core concepts of relevance to this thesis: costs and their measurement, and affordability. It discusses the standard methods for measuring these constructs in the UHC framework and contrast them with how they are measured in TB patient cost surveys (**Objective 1; Research paper 1**). The paper included as supplementary material complements this conceptual review with a reflection on the potential of TB patient cost surveys to inform changes to health service delivery and financing towards patient-centred care to eliminate TB patient costs, as well as to enhance social protection measures.

Objective 2 was addressed through two independent pieces of work. The first (**Research paper 2**) is a case study on the cost of chest-radiography as part of TB diagnosis and care, which is a major contributor to the medical costs incurred by TB patients. This was investigated through a survey among TB experts in a number of countries worldwide, which provided a snapshot of

current availability and accessibility of chest x-rays to TB patients and presumptive TB patients. The second piece of work entailed conducting a nationally representative facility-based survey of costs incurred by TB patients in Ghana. Using the data from this survey, **Research paper 3** examined affordability of TB care using catastrophic and impoverishment measures.

For **Objective 3**, this thesis analysed data from the Ghana TB patient cost survey to investigate drivers and determinants of costs. It also undertook a quasi-experimental analysis to investigate the role of enrolment into Ghana's National Health Insurance Scheme in greater depth (**Research paper 4**).

The last chapter of this thesis addresses **Objective 4** through a reflection on the relevance of analysing the potential impact of costs on TB treatment outcomes, and presents an analysis to illustrate the current methodological limitations of TB patient cost surveys to detect an association between costs incurred by TB patients and treatment outcomes (**Research paper 5**).

The paper in the Appendix presents work done as part of a TB Modelling and Analysis Consortium (TB-MAC) expert meeting on modelling the social and structural determinants of TB, and reflects the renewed interest in measuring the socio-economic impact of disease on patients and their households.

In addition to the published or submitted manuscripts, some sections have been expanded to include additional analyses or methodological considerations that could not feature in detail in the publications.

Finally, in Chapter 7 I summarise the findings from the thesis, its methodological limitations, discuss the contribution of this work to policy, and identify areas that warrant further research.

1.5 References

1. Nunn P, Reid A, De Cock KM. Tuberculosis and HIV Infection: The Global Setting. Journal of Infectious Diseases. 2007;196(Supplement 1):S5-S14.
2. World Health Organization. Global Tuberculosis Report 2019. Geneva, Switzerland; 2019.
3. Houben RM, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLoS medicine. 2016;13(10):e1002152.
4. Dubos RJ, Dubos J. The white plague: tuberculosis, man, and society: Rutgers University Press; 1952.

5. Janssens JP, Rieder HL. An ecological analysis of incidence of tuberculosis and per capita gross domestic product. The European respiratory journal. 2008;32(5):1415-6.
6. Weiss KB, Addington WW. Poverty's Penalty. Am J Respir Crit Care Med. 1998;157:1011.
7. Lienhardt C. From exposure to disease: the role of environmental factors in susceptibility to and development of tuberculosis. Epidemiologic reviews. 2001;23(2):288-301.
8. Oxlade O, Murray M. Tuberculosis and poverty: why are the poor at greater risk in India? PloS one. 2012;7(11):e47533.
9. McIntyre D, Garshong B, Mtei G, Meheus F, Thiede M, Akazili J, et al. Beyond fragmentation and towards universal coverage: insights from Ghana, South Africa and the United Republic of Tanzania. Bulletin of the World Health Organization. 2008;86(11):871-6.
10. Cambanis A, Yassin MA, Ramsay A, Squire SB, Arbide I, Cuevas LE. Rural poverty and delayed presentation to tuberculosis services in Ethiopia. Tropical medicine & international health : TM & IH. 2005;10.
11. Long Q, Smith H, Zhang T, Tang S, Garner P. Patient medical costs for tuberculosis treatment and impact on adherence in China: a systematic review. BMC Public Health. 2011;11(1):393.
12. Ukwaja KN, Alobu I, Lgwenyi C, Hopewell PC. The high cost of free tuberculosis services: patient and household costs associated with tuberculosis care in Ebonyi State, Nigeria. PloS one. 2013;8(8):e73134.
13. Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. The European respiratory journal. 2014;43.
14. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM. WHO's new End TB Strategy. Lancet. 2015;385.
15. Pedrazzoli D, Borghi J, Viney K, Houben R, Lonnroth K. Measuring the economic burden for TB patients in the End TB Strategy and Universal Health Coverage frameworks. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2019;23(1):5-11.
16. World Health Organization. Tuberculosis patient cost surveys: a handbook. Geneva, Switzerland2017.
17. Ukwaja KN, Modebe O, Igwenyi C, Alobu I. The economic burden of tuberculosis care for patients and households in Africa: a systematic review. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2012;16(6):733-9.
18. Barter DM, Agboola SO, Murray MB, Barnighausen T. Tuberculosis and poverty: the contribution of patient costs in sub-Saharan Africa--a systematic review. BMC Public Health. 2012;12:980.
19. Laurence YV, Griffiths UK, Vassall A. Costs to Health Services and the Patient of Treating Tuberculosis: A Systematic Literature Review. PharmacoEconomics. 2015;33(9):939-55.
20. World Health Organization. Tracking Universal Health Coverage. Washington, DC: World Health Organization; 2017.
21. Lonnroth K, Glaziou P, Weil D, Floyd K, Uplekar M, Raviglione M. Beyond UHC: monitoring health and social protection coverage in the context of tuberculosis care and prevention. PLoS medicine. 2014;11.
22. Devereux S S-WR. Transformative social protection. Brighton: Institute of Development Studies, University of Sussex: Institute of Development Studies, University of Sussex; 2004.
23. Adato M, Bassett L. Social protection to support vulnerable children and families: the potential of cash transfers to protect education, health and nutrition. Aids Care. 2009;21(S1):60-75.

24. Pedrazzoli D, Houben RM, Grede N, de Pee S, Boccia D. Food assistance to tuberculosis patients: lessons from Afghanistan. Public Health Action. 2016;6(2):147-53.
25. Richter LM, Lonnroth K, Desmond C, Jackson R, Jaramillo E, Weil D. Economic support to patients in HIV and TB grants in rounds 7 and 10 from the global fund to fight AIDS, tuberculosis and malaria. PloS one. 2014;9(1):e86225.
26. Office IL. Social protection assessment based national dialogue: A good practices guide: Approaches and tools developed in East and South-East Asia from 2011 to 2013. 2013.
27. Wells W, Stallworthy G, Balsara Z. How tuberculosis programs can navigate the world of social health insurance. The International Journal of Tuberculosis and Lung Disease. 2019;23(1):26-37.
28. Ivaschenko O, Alas CPR, Novikova M, Romero C, Bowen TV, Zhu L. The state of social safety nets 2018: World Bank Group; 2018.
29. Bastagli F, Hagen-Zanker J, Harman L, Barca V, Sturge G, Schmidt T, et al. Cash transfers: what does the evidence say. A rigorous review of programme impact and the role of design and implementation features London: Overseas Development Institute. 2016.
30. Boccia D, Pedrazzoli D, Wingfield T, Jaramillo E, Lönnroth K, Lewis J, et al. Towards cash transfer interventions for tuberculosis prevention, care and control: key operational challenges and research priorities. BMC Infectious Diseases. 2016;16:307.
31. Rasella D, Aquino R, Santos CA, Paes-Sousa R, Barreto ML. Effect of a conditional cash transfer programme on childhood mortality: a nationwide analysis of Brazilian municipalities. The lancet. 2013;382(9886):57-64.
32. Cluver L, Boyes M, Orkin M, Pantelic M, Molwena T, Sherr L. Child-focused state cash transfers and adolescent risk of HIV infection in South Africa: a propensity-score-matched case-control study. The Lancet Global Health. 2013;1(6):e362-e70.
33. Carter DJ, Glaziou P, Lönnroth K, Siroka A, Floyd K, Weil D, et al. The impact of social protection and poverty elimination on global tuberculosis incidence: a statistical modelling analysis of Sustainable Development Goal 1. The Lancet Global Health. 2018;6(5):e514-e22.
34. Rudgard WE, Evans CA, Sweeney S, Wingfield T, Lönnroth K, Barreira D, et al. Comparison of two cash transfer strategies to prevent catastrophic costs for poor tuberculosis-affected households in low- and middle-income countries: An economic modelling study. PLoS medicine. 2017;14(11):e1002418.
35. Richterman A, Steer-Massaro J, Jarolimova J, Nguyen LBL, Werdenberg J, Ivers LC. Cash interventions to improve clinical outcomes for pulmonary tuberculosis: systematic review and meta-analysis. Bulletin of the World Health Organization. 2018;96(7):471.
36. Andrade KVFd, Nery JS, Souza RAd, Pereira SM. Effects of social protection on tuberculosis treatment outcomes in low or middle-income and in high-burden countries: systematic review and meta-analysis. Cadernos de Saúde Pública. 2018;34.
37. Reis-Santos B, Shete P, Bertolde A, Sales CM, Sanchez MN, Arakaki-Sanchez D, et al. Tuberculosis in Brazil and cash transfer programs: a longitudinal database study of the effect of cash transfer on cure rates. PloS one. 2019;14(2).
38. Oliosi JGN, Reis-Santos B, Locatelli RL, Sales CMM, da Silva Filho WG, da Silva KC, et al. Effect of the Bolsa Familia Programme on the outcome of tuberculosis treatment: a prospective cohort study. The Lancet Global Health. 2019;7(2):e219-e26.
39. Klein K, Bernachea MP, Irribarren S, Gibbons L, Chirico C, Rubinstein F. Evaluation of a social protection policy on tuberculosis treatment outcomes: A prospective cohort study. PLoS medicine. 2019;16(4).
40. Wingfield T, Tovar MA, Huff D, Boccia D, Montoya R, Ramos E, et al. The economic effects of supporting tuberculosis-affected households in Peru. European Respiratory Journal. 2016.

41. Rudgard WE, Nancy S, Gayoso R, Barreto ML, Boccia D, Smeeth L, et al. Uptake of governmental social protection and financial hardship during drug-resistant tuberculosis treatment in Rio de Janeiro, Brazil. Eur Respiratory Soc; 2018.
42. Lutge E, Lewin S, Volmink J, Friedman I, Lombard C. Economic support to improve tuberculosis treatment outcomes in South Africa: a pragmatic cluster-randomized controlled trial. Trials. 2013;14:154.
43. Ciobanu A, Domente L, Soltan V, Bivol S, Severin L, Plesca V, et al. Do incentives improve tuberculosis treatment outcomes in the Republic of Moldova? Public health action. 2014;4(2):S59-S63.
44. Sripad A, Castedo J, Danford N, Zaha R, Freile C. Effects of Ecuador's national monetary incentive program on adherence to treatment for drug-resistant tuberculosis. The International journal of tuberculosis and lung disease. 2014;18(1):44-8.
45. Reeves A, Basu S, McKee M, Stuckler D, Sandgren A, Semenza J. Social protection and tuberculosis control in 21 European countries, 1995–2012: a cross-national statistical modelling analysis. The Lancet Infectious Diseases. 2014;14(11):1105-12.
46. Wingfield T, Boccia D, Tovar M, Gavino A, Zevallos K, Montoya R, et al. Defining catastrophic costs and comparing their importance for adverse tuberculosis outcome with multi-drug resistance: a prospective cohort study, Peru. PLoS medicine. 2014;11(7):e1001675.
47. Siroka A, Ponce NA, Lönnroth K. Association between spending on social protection and tuberculosis burden: a global analysis. The Lancet Infectious Diseases. 2016;16(4):473-9.
48. Torrens AW, Rasella D, Boccia D, Maciel EL, Nery JS, Olson ZD, et al. Effectiveness of a conditional cash transfer programme on TB cure rate: a retrospective cohort study in Brazil. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2016;110(3):199-206.
49. Nery JS, Rodrigues LC, Rasella D, Aquino R, Barreira D, Torrens AW, et al. Effect of Brazil's conditional cash transfer programme on tuberculosis incidence. The international journal of tuberculosis and lung disease. 2017;21(7):790-6.
50. Durovni B, Saraceni V, Puppin MS, Tassinari W, Cruz OG, Cavalcante S, et al. The impact of the Brazilian Family Health Strategy and the conditional cash transfer on tuberculosis treatment outcomes in Rio de Janeiro: an individual-level analysis of secondary data. Journal of Public Health. 2017;40(3):e359-e66.
51. Boccia D, Rudgard W, Shrestha S, Lönnroth K, Eckhoff P, Golub J, et al. Modelling the impact of social protection on tuberculosis: the S-PROTECT project. BMC Public Health. 2018;18(1):786.
52. Spaan E, Mathijssen J, Tromp N, McBain F, ten Have A, Baltussen R. The impact of health insurance in Africa and Asia: a systematic review. Bulletin of the World Health Organization. 2012;90(9):685-92.
53. Acharya A VS, Taylor F, Masset E, Satija A, Burke M and Ebrahim S. Impact of national health insurance for the poor and the informal sector in low- and middle-income countries. London: EPPI-Centre, Social Science Research Unit, Institute of Education, University of London; 2012.
54. Wagstaff A. Social Health Insurance vs. Tax-Financed Health Systems—Evidence from the OECD. Washington, DC, USA: The World Bank; 2009.
55. Fiestas Navarrete L, Ghislandi S, Stuckler D, Tediosi F. Inequalities in the benefits of national health insurance on financial protection from out-of-pocket payments and access to health services: cross-sectional evidence from Ghana. Health policy and planning. 2019;34(9):694-705.
56. Smith-Arthur A KN, Matji R. Synthesis report: inclusion of TB in national insurance programs. Chevy Chase, MD, USA: TB CARE II; 2013.
57. Sun B, Wang W, Jiao J, Zhu F, Dan Y, Dong Q, et al. Research of TB treatment compliance and socio-economic and clinical factors influencing it in Guanyun County. Chinese Primary Health Care. 2007;21(1):58-60.

Chapter 2: Measuring the economic burden for TB patients in the End TB Strategy and Universal Health Coverage frameworks

2.1 Preamble

In line with Objective (1) of this thesis, this chapter provides the framework for this PhD, by reviewing and defining core concepts of relevance to this thesis: costs and their measurement, and affordability. It also discusses the standard methods for measuring these constructs in the Universal Health Coverage (UHC) framework and contrasts them with how they are measured in TB patient cost surveys. In doing so, the paper that makes up this chapter addresses the first knowledge gap identified by the PhD: the lack of a comprehensive description of the concepts and measurements that underlie the End TB Strategy indicator of 'zero catastrophic costs' due to TB, in relation to approaches used in the UHC monitoring framework.

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2.2 Cover sheet

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London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

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2.3 Summary

Tuberculosis (TB) is a disease of poverty. Ensuring access to health care without risk of financial hardship due to out-of-pocket health care expenditures (Universal Health Coverage; UHC) is essential for providing accessible care for underprivileged populations, but it is not enough.

The End TB Strategy promotes both patient-centred TB services and social protection measures, which aim to mitigate economic hardship on TB patients and their households due to direct medical and non-medical expenditures, as well as lost income. The strategy includes a target that no families should face catastrophic total costs due to TB. The indicator linked to this target aims to capture the total economic burden linked to TB care, and thus differs from the "catastrophic expenditure on health" indicator, a key component of the UHC monitoring framework, aligned with the Sustainable Development Goals.

Countries, and particularly high TB-burden countries, are expected to conduct nationally representative TB patient cost surveys to establish baseline measurements for the catastrophic costs indicator. Findings from these surveys should also help identify entry points to develop policies to ensure better financial and social protection for TB patients. In this paper, we define the key measurable concepts for TB patient cost surveys, notably the types of costs that are captured and related affordability measures. We discuss methods for measuring these notions in the UHC framework and contrast them with how they are measured in TB patient cost surveys.

2.4 Manuscript

2.4.1 Introduction

Tuberculosis (TB) remains a major threat to global public health (1). Poor people in resource-constrained settings are most at risk of the disease and its devastating economic consequences (2). In low- and middle-income countries (LMICs), health care financing is heavily reliant on out-of-pocket payments. Despite basic TB care being officially free of charge, usually partly through vertical funding mechanisms, TB patients often struggle to afford TB care, and they incur costs considered to be "catastrophic" (3-5).

Universal Health Coverage (UHC), whereby everyone can access the quality health services they need without financial hardship (6), has long been on the global TB control agenda. Free diagnosis and treatment have been the cornerstone of global TB control strategies since 1994 (7). The DOTS Strategy emphasises the use of low-cost, cost-effective tools and interventions to enable affordable access to quality TB care, which has resulted in 53 million lives saved. Yet, this

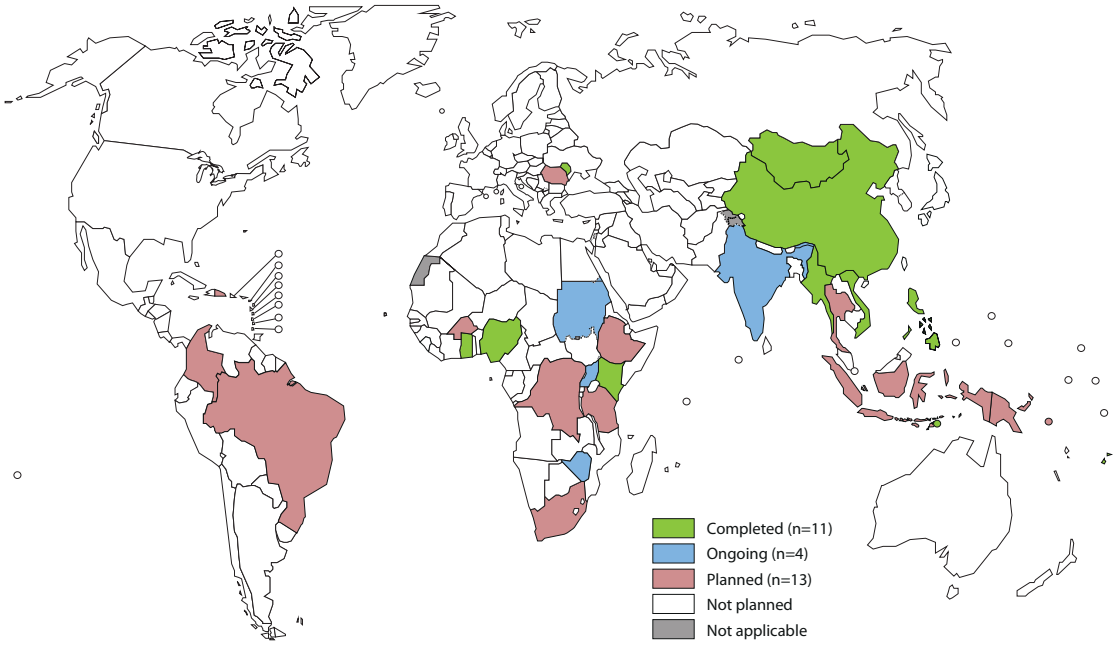
has been shown to be insufficient in mitigating economic consequences, as non-medical costs and income losses, which account for a large part of the economic burden for households, are not accounted for within the UHC monitoring framework (8-10).

Aligned with the Sustainable Development Goals (SDGs), the World Health Organization´s (WHO's) End TB Strategy has an increased focus on poverty alleviation strategies and social protection initiatives that cover costs beyond medical expenses, including income security. It also includes as a target that no TB-affected families should suffer from catastrophic total costs due to the disease (10, 11). To monitor progress towards this target, the WHO Global TB Programme convened a task force of experts in 2015 to develop a field-testing protocol and survey instrument for nationally representative, health facility-based surveys of costs faced by TB patients and their households ("TB patient cost surveys"), building upon the Tool to Estimate Patients' Costs (12). After field testing, the WHO developed a handbook for TB patient cost surveys (11). Countries, and particularly high TB burden countries, are expected to adapt and implement these surveys to document the magnitude and main drivers of costs incurred by TB patients (and their households) and the proportion of TB patients who incur catastrophic costs as a result of the cost of care, and to monitor these metrics over time. Findings from these surveys should also help identify entry points to develop policies to ensure better financial and social protection for TB patients (8).

As of July 2018, eleven countries had conducted a TB patient cost survey using the WHO instrument and methodology (13), four surveys were ongoing or near completion, and thirteen countries were planning and mobilising funding to conduct such surveys (Figure 1).

Figure 1: Global implementation of TB patient cost surveys following the WHO methodology, as of July 2018

Source: WHO Global TB Programme, July 2018 (12) TB=tuberculosis; WHO=World Health Organization.



In the present paper, we describe the key notions that are measured using these TB patient cost surveys, notably the types of costs that are captured, and measures of the affordability of these costs in relation to household income, expressed as occurrence of catastrophic costs and impoverishment. We discuss the standard methods for measuring these concepts and how they have been adapted in the TB patient cost survey handbook, and conclude by highlighting areas for consideration for those implementing TB patient cost surveys going forward.

2.4.2 Defining economic burden for patients and households

At the heart of the UHC paradigm is the concept that families should not face undue financial hardship in accessing health care. This is referred to as financial protection, and it builds on the notion of affordability of care (14, 15).

The WHO and the World Bank track financial protection through two indicators: high (or catastrophic) health spending and impoverishment (6). Catastrophic health spending quantifies the proportion of the population whose resources would be catastrophically reduced by spending on health care (16). When health care expenditures exceed a given proportion of available income (or expenditure capacity), they are considered "catastrophic". The impoverishment approach estimates the proportion of the population that would be pushed below a defined poverty line due to seeking and receiving care (17). Catastrophic spending and

impoverishment rates are generally calculated using household level data captured through population-based surveys.

2.4.3 Measuring catastrophic health spending

When measuring catastrophic health spending, there are two key variables underlying this approach: 1) total household out-of-pocket payments for health care (numerator, see Sections "Measuring and Valuing household costs" and "Generating a ratio of health care costs to a measure of ability to pay"); and 2) a measure of household resources (denominator, see Section on "Measuring ability to pay"). A ratio of health care costs to a measure of ability to pay can then be generated (see on Section on 'Generating a ratio of health care costs to a measure of ability to pay'), which is compared to a threshold (see Section on "Defining thresholds for catastrophic payments").

2.4.3.1 Measuring and valuing household costs

While the UHC indicator uses household surveys to capture health care expenditures (medical costs) for all conditions, the TB indicator aims to capture instead the total economic burden related to one diagnosed health condition only, i.e., TB. The UHC indicator focuses on direct out-of-pocket medical costs only.

TB patient cost surveys measure three types of cost: **direct medical costs**, **direct non-medical costs** and **income loss (indirect costs** or **opportunity costs)**. Direct medical costs represent the money actually spent out of pocket by the patient on medical services such as prescribed medications, consultation fees, hospitalisation and laboratory tests. These costs are the same as the direct medical costs measured in the UHC framework.

Patients (and their carer) often incur other direct costs associated with the utilisation of health care, such as transport costs to and from the health facility, and costs for accommodation and food, which are referred to as **direct non-medical costs.** Direct costs are valued by asking patients to recall their actual expenditure.

When seeking care and when sick, individuals also incur costs associated with lost productivity due to illness/disability and time spent seeking care, or looking after a patient instead of working (i.e. carers). These opportunity costs are referred to as **indirect costs** in the End TB monitoring framework. Two approaches are typically employed to value indirect costs to households: the human capital approach and the output-based approach (18).

The human capital approach involves valuing an individual's time by multiplying the number of hours spent seeking and receiving care/caring for by their reported or estimated hourly wage rate (19). If based on reported income, this method can have equity concerns, as it then implicitly values the time of more productive (higher income) individuals more highly and does not take into account the value of time lost by individuals who are performing unpaid work or are unemployed or retired (20). This can be corrected by using a standard estimated income for these individuals (e.g., the mean for the lower quintiles based on national statistics or the minimum civil servant wage).

The output-based approach considers reported changes in income/production (21). This approach is recommended by WHO for settings predominately characterised by formal economies, where individuals can reliably report income in monetary terms.

The WHO's generic instrument for TB patient cost surveys collects data that allow the valuation of both indirect costs using the human capital approach and the output-based approach (Table 4) (13). The End TB Strategy indicator is generally computed on the basis of the output-based approach, with the human capital approach used in sensitivity analyses. The reason for capturing these data in TB patient cost surveys is to encourage the valuation of TB-related indirect costs, as such evidence is currently limited (13, 22-24). To date, researchers have generally employed the human capital approach to value productivity losses associated with TB, with varying levels of precision in the estimations of time and income. However, more than a third of studies included in one recent systematic review that presented indirect costs did not clearly explain the methods that were used to calculate them (25).

Table 4: Summary of recommended and additional approaches, metrics and valuation methods for TB patient cost surveys based on the World Health Organization methodology (13)

Approach/valuation method/metric			Recommended	Additional
Costs	Direct	Cost disaggregation (medical/non-medical)	•	
	Indirect	Human capital approach	•	
		Output-related approach	•	
Measure of living standard	Income	Reported individual and household income pre and post-TB diagnosis	•	
		Asset-based income	•	
	Consumption expenditure		•	
Measures of financial protection	Catastrophe	Catastrophic Payment Headcount	•	
		Catastrophic payment gap		•
	Impoverishment	Incidence of impoverishment		•
		Depth of poverty		•
Threshold	Catastrophe	20% threshold	•	
		Sensitivity analysis with different percentages of income threshold	•	
	Impoverishment	International poverty lines (e.g. US$ 1.25-a-day in 2005 PPPs)		•
		National/locally defined relevant poverty lines		•

The economic burden of illness can be measured at the individual level, but it is perhaps more practical to look at the economic impact on the whole household, particularly as other household members also contribute to direct expenditures and may take time off work to care for the ill person or take their children out of school to contribute to the household income (25). The affordability of TB costs is also analysed at the household level due to the impact that TB potentially has on households, as discussed below.

2.4.3.2 Measuring ability to pay

Ability to pay is usually measured in terms of income, consumption or expenditure. Income refers to earnings from employment and sale of assets and receipt of transfers. Consumption refers to spending on resources (goods and services) consumed by the household. Expenditure

excludes consumption that is not based on market transactions (e.g. home production), and refers to goods or services purchased but not immediately consumed by the household (27).

While reported income is the gold standard measure of ability to pay, in low-income settings, where employment is mainly outside the formal sector and income is hard to measure reliably, consumption expenditure is often believed to be a more valid measure of economic resources than income. However, both remain difficult and costly to collect (28-31).

In the UHC framework, consumption expenditure is often used rather than income to measure catastrophic expenditure and impoverishment (6). It can be argued that deducting food spending from consumption (non-food expenditure) can better capture a household's ability to pay for health expenditures (6). Alternatively, no deduction for necessities is made.

TB patient cost surveys capture either income or consumption expenditure, or both. The TB indicator is computed using the measure of income that is more robust in the specific country setting. For countries collecting more than one measure, the more robust will be used for main analysis and the alternative measures in sensitivity analysis.

2.4.3.3 Generating a ratio of health care costs to a measure of ability to pay

When computing catastrophic spending within the UHC monitoring framework, the numerator is restricted to direct medical costs (32), and does not measure direct non-medical and indirect costs, as UHC is mainly about moving towards progressive and equitable health care financing, and national financing schemes (tax or insurance-based) covering direct medical costs.

The End TB monitoring framework, on the other hand, is designed to also collect data that can guide policies on patient-centred service delivery models that can reduce both direct and indirect costs, as well as social protection schemes for income security and social support. A key element of innovation of the End TB Strategy "zero catastrophic costs" indicator is thus that the numerator comprises direct medical, non-medical and indirect costs. In TB care, indirect costs have been found to account for a sizeable proportion of total costs (on average 60% of total costs, range: 16-94%) in LMICs (33); these are therefore important elements for capturing all care-related expenditures and the economic impact on TB patients, from the onset of symptoms to the end of anti-tuberculosis treatment. The denominator is further defined as annual household income or annual household consumption expenditure, as outlined in the section "Measuring ability to pay" (33). The resulting ratio is then compared to the thresholds defined below to determine whether spending is catastrophic.

2.4.3.4 Defining thresholds for catastrophic payments

The catastrophic payment threshold is set as a proportion of income, i.e., households should not spend more than a pre-specified proportion of their income on health care. When a household's healthcare payments exceed that pre-defined threshold, they are defined as catastrophic (16). The choice of the threshold is so far arbitrary. Various thresholds have been used in the literature: 10% (35), 15% (36) of household annual income, or 40% of household non-food expenditure (32, 37). The WHO and World Bank now track catastrophic spending on the basis of out-of-pocket expenditures exceeding 10% or 25% of household total income or consumption (6).

For global monitoring of the End TB Strategy "zero catastrophic costs" indicator, in 2017, the WHO chose to use a threshold of 20% of annual household income (13), which was set through expert opinion voting in the task force. This is the threshold that is currently used by National TB Programmes (NTPs) that implement TB patient cost surveys whose results are annually reported to the WHO (1, 38). Countries that conduct national TB patient cost surveys are encouraged to undertake sensitivity analyses whereby the 20% threshold is altered so that the proportion of patients facing catastrophic costs can be assessed at different thresholds, and potentially inform a review of the threshold in the future (Table 4).

The threshold can be used to help define two measures of catastrophic health spending, in both the UHC and End TB Strategy framework. The ***catastrophic payment headcount*** measures the incidence of catastrophic health care costs (i.e., the number, or fraction, of individuals who have been exposed to catastrophic expenses). The ***catastrophic payment gap*** (or excess) measure is used to assess the intensity or severity of catastrophic spending by looking at the extent to which health care costs exceed the pre-defined threshold (16) (Table 5).

The proportion of patients incurring catastrophic costs due to TB is derived from the number of TB patients with catastrophic costs divided by the number of all TB patients treated at NTP facilities. This means that the sampling frame is notified patients on treatment rather than all people with TB in the community, or households in a country. This is selected for practical reasons, as the only available sampling frame is notified TB patients, and household surveys would require a large sample size to include a sufficient number of prevalent TB cases.

2.4.4 Measuring impoverishment

An additional measure of the affordability of care used for UHC monitoring is ***impoverishment***, or whether health care costs push households into poverty (or more deeply into poverty). In this case, the threshold is absolute and set in terms of a poverty line. If health care payments cause household income/consumption expenditure to fall below the poverty line, they are considered "impoverishing". The widely used international dollar-a-day poverty line proposed by the World Bank to allow international comparability, was replaced by USD 1.25/day in 2009, at 2005 purchasing power parity (39). Countries also have their own national poverty lines which may be relevant for comparing impoverishment over time within a country.

The ***incidence of impoverishment*** measures the increase in poverty due to health care spending. The ***poverty gap*** is the shortfall from the poverty line. While these are not included in the End TB Strategy monitoring, countries can include them in the analyses of TB patient cost surveys. Table 5 provides a summary of the key measures presented in this section and in the Section, "Defining thresholds for catastrophic payments".

Table 5: Summary of key measures of catastrophic health spending and impoverishment for general Universal Health Coverage monitoring (source: adapted from (40).

Indicator	What it is measuring
Concept of catastrophic health expenditure: key indicators	
Catastrophic payment headcount *(or incidence of catastrophic health expenditure)*	Proportion of households in a population who face catastrophic health expenditure
Catastrophic payment gap *(or excess or mean positive catastrophic overshoot)*	Percentage points by which household spending on health exceeds the threshold for catastrophic health expenditure
Concept of impoverishment due to health spending: key indicators	
Incidence of impoverishment	Proportion of households in a population who fall into poverty due to health care spending
Poverty gap *(or increase in the depth of poverty)*	Percentage points by which a household falls further into poverty due to health care spending

2.4.5 Towards zero families facing catastrophic costs due to TB: areas for consideration

The End TB Strategy target is a first important step in broadening the concept and measurement of affordability to account not only for medical costs but also for the broader economic impact of TB, including non-medical and indirect costs.

However, as described above, the application of the concepts and standard methods of financial protection requires further development in the End TB Strategy. The WHO recently published a handbook based on the experiences and data from the first round of surveys between 2016 and 2017, which provides comprehensive guidance for conducting facility-based cross-sectional surveys to assess TB patient costs (13). This would benefit from periodic methodological updates based on multi-country analyses of survey findings and strengthen collaboration with health economists, NTPs and policy makers. These updates include methods for calculating confidence intervals for key survey indicators adjusted for the sampling design, a regression-based approach for imputing missing costs, recommendations on the design of a household expenditure questionnaire (to derive a household income measure based on expenditure), and adaptation of the survey instrument to high-income settings.

There are a number of areas for consideration for those implementing TB patient cost surveys going forward, including descriptive analyses of costs that unpack direct medical and non-medical costs, and indirect costs, as they can provide valuable information to identify entry points for appropriate polices and interventions to minimise these costs; the use of both the human capital and the output-based approach to value indirect costs for comparison and correlation; and measuring and comparing income and consumption expenditure to compute financial protection measures. Approaches and metrics in addition to the standard End TB Strategy framework methodology include measuring impoverishment, computing the catastrophic payment gap, and sensitivity analyses with different proportions of income thresholds (Table 4).

Finally, it is important to bear in mind that the cross-sectional study design for a TB patient cost survey recommended by the WHO inevitably focuses on the economic consequences of TB by using a measure at one point in time. It therefore fails to capture the long-term economic consequences of the disease for the household, including the impact on reduced labour supply and productivity, and household resilience. Coping mechanisms were originally explored as part of the development of the TB indicator as they were deemed to be potentially less labour intensive to collect and easier to integrate in routine surveillance. However, as coping mechanisms differ in different cultures and societies, it is difficult to consider them as a proxy for catastrophic payments.

Several research studies that have adapted the WHO generic protocol to a longitudinal design, including for long-term follow-up after anti-tuberculosis treatment, are now ongoing. These studies will be helpful for the validation and interpretation of cross-sectional TB patient cost

survey data. Separate studies of non-notified TB patients, such as those in private care, are required to measure costs in situation where user charges for clinical care are often higher than in facilities linked to NTPs. However, other studies sampling people with TB who are not under treatment at the time of the study are also needed as the current methodology only includes TB patients who remain in care. Such studies can be conducted in the context of tracing patients who are lost to follow-up (e.g., initial loss to follow-up or loss to follow-up during treatment) by reconnecting them with treatment and explore reasons for loss to follow-up. The assessment of costs incurred by such patients may shed light on costs related to the disease and disability that are not linked to care seeking, and costs of living with TB without getting proper care.

2.4.6 Conclusions

In this paper, we have described economic burden and affordability concepts and measurements that underlie the End TB Strategy indicator of "zero catastrophic costs" due to TB, and have highlighted the novel elements of this indicator in relation to approaches used in the UHC monitoring framework. Further findings from national TB patient surveys, multi-country analyses and research using alternative approaches will be important in providing further evidence to refine metrics and methodology for country-level implementation and global monitoring.

The conventional concepts and measurement of "financial protection" of the UHC monitoring framework have been taken a step forward in the End TB Strategy to ensure metrics are able to capture the total economic burden of TB on patients and families. This approach has the potential to inform the design of financing and implementation of both health care and social protection policies that aim to prevent both direct and indirect costs of care, and ultimately ensure that TB care is truly affordable for TB patients.

2.4.7 Acknowledgments

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2.4.8 References

1. World Health Organization. Global Tuberculosis Report 2016. 2017.
2. Dubos RJ, Dubos J. The white plague: tuberculosis, man, and society: Rutgers University Press; 1952.
3. McIntyre D, Garshong B, Mtei G, Meheus F, Thiede M, Akazili J, et al. Beyond fragmentation and towards universal coverage: insights from Ghana, South Africa and the United Republic of Tanzania. Bulletin of the World Health Organization. 2008;86(11):871-6.
4. Ukwaja KN, Alobu I, Lgwenyi C, Hopewell PC. The high cost of free tuberculosis services: patient and household costs associated with tuberculosis care in Ebonyi State, Nigeria. PloS one. 2013;8(8):e73134.
5. Mauch V, Bonsu F, Gyapong M, Awini E, Suarez P, Marcelino B. Free tuberculosis diagnosis and treatment are not enough: patient cost evidence from three continents. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2013;17.
6. World Health Organization. Tracking Universal Health Coverage. Washington, DC: World Health Organization; 2017.
7. Dye C, Floyd K. Tuberculosis. In: Jamison D T, Breman J G, Measham A R, et al., eds. Disease control priorities in developing countries. Chapter 16. 2nd ed. Washington, DC, USA: The International Bank for Reconstruction and Development & The World Bank, 2006. https://www.ncbi.nlm.nih.gov/books/NBK11724/ Accessed November 2017.
7. Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. The European respiratory journal. 2014;43.
8. Lonnroth K, Glaziou P, Weil D, Floyd K, Uplekar M, Raviglione M. Beyond UHC: monitoring health and social protection coverage in the context of tuberculosis care and prevention. PLoS medicine. 2014;11.
9. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM. WHO's new End TB Strategy. Lancet. 2015;385.
10. Lönnroth K, Glaziou P, Weil D, Floyd K, Uplekar M, Raviglione M. Beyond UHC: Monitoring Health and Social Protection Coverage in the Context of Tuberculosis Care and Prevention. PLoS medicine. 2014;11(9):e1001693.
11. KNCV Tuberculosis Foundation. Tool to estimate patients' costs. The Netherlands: 2008.
12. World Health Organization. Tuberculosis patient cost surveys: a handbook. Geneva, Switzerland2017.
13. McIntyre DI, Thiede M, Birch S. Access as a policy-relevant concept in low- and middle-income countries. Health Economics, Policy and Law. 2009;4(2):179-93.
14. McIntyre D, Thiede M, Dahlgren G, Whitehead M. What are the economic consequences for households of illness and of paying for health care in low- and middle-income country contexts? Social science & medicine (1982). 2006;62.
15. Wagstaff A, Doorslaer E. Catastrophe and impoverishment in paying for health care: with applications to Vietnam 1993–1998. Health Econ. 2003;12.
16. Niëns L. Affordability in Health Care: Operationalizations and Applications in Different Contexts [Ph.D. thesis]: Erasmus University Rotterdam; 2014.
17. Drummond MF, McGuire A. Economic evaluation in health care: merging theory with practice: OUP Oxford; 2001.
18. World Health Organization. Protocol for survey to determine direct and indirect costs due to TB and to estimate proportion of TB-affected households experiencing catastrophic total costs due to TB

http://www.who.int/tb/advisory_bodies/impact_measurement_taskforce/meetings/tf6_background_5a_patient_cost_surveys_protocol.pdf2015

19. Lensberg BR, Drummond MF, Danchenko N, Despiégel N, François C. Challenges in measuring and valuing productivity costs, and their relevance in mood disorders. ClinicoEconomics and Outcomes Research: CEOR. 2013;5:565-73.
20. World Health Organization. WHO guide to identifying the economic consequences of disease and injury; 2009. Geneva: WHO Available from URL: http://www/ who int/choice/publications/discussion_papers/en/index html (Accessed 4 June 2010).
21. Foster N, Vassall A, Cleary S, Cunnama L, Churchyard G, Sinanovic E. The economic burden of TB diagnosis and treatment in South Africa. Social science & medicine (1982). 2015;130:42-50.
22. Mauch V, Woods N, Kirubi B, Kipruto H, Sitienei J, Klinkenberg E. Assessing access barriers to tuberculosis care with the tool to Estimate Patients' Costs: pilot results from two districts in Kenya. BMC Public Health. 2011;11:43.
23. Sinanovic E, Floyd K, Dudley L, Azevedo V, Grant R, Maher D. Cost and cost-effectiveness of community-based care for tuberculosis in Cape Town, South Africa. The international journal of tuberculosis and lung disease. 2003;7(9):S56-S62.
24. Laurence YV, Griffiths UK, Vassall A. Costs to Health Services and the Patient of Treating Tuberculosis: A Systematic Literature Review. PharmacoEconomics. 2015;33(9):939-55.
25. Russell S. The economic burden of illness for households in developing countries: a review of studies focusing on malaria, tuberculosis, and human immunodeficiency virus/acquired immunodeficiency syndrome. The American journal of tropical medicine and hygiene. 2004;71(2 Suppl):147-55.
26. ILO. Household income and expenditure statistics. Geneva: International Labour Organization, 2003.
27. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 1). Journal of Epidemiology and Community Health. 2006;60(1):7-12.
28. Howe LD, Galobardes B, Matijasevich A, Gordon D, Johnston D, Onwujekwe O, et al. Measuring socio-economic position for epidemiological studies in low- and middle-income countries: a methods of measurement in epidemiology paper. International Journal of Epidemiology. 2012;41(3):871-86.
29. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 2). Journal of Epidemiology and Community Health. 2006;60(2):95-101.
30. O'Donnell O, van Doorslaer, Eddy, Wagstaff, Adam, Lindelow, Magnus. Analyzing Health Equity Using Household Survey Data: World Bank Institute Development Studies; 2007.
31. Ke X. Distribution of health payments and catastrophic expenditures methodology. Geneva: WHO Discussion Paper No. 2. 2005.
32. Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low-and middle-income countries: a systematic review. European Respiratory Journal. 2014;43(6):1763-75.
33. Ataguba JE, Akazili J, McIntyre D. Socioeconomic-related health inequality in South Africa: evidence from General Household Surveys. Int J Equity Health. 2011;10:48.
34. Ranson MK. Reduction of catastrophic health care expenditures by a community-based health insurance scheme in Gujarat, India: current experiences and challenges. Bulletin of the World Health Organization. 2002;80(8):613-21.
35. Wyszewianski L. Financially catastrophic and high-cost cases: definitions, distinctions, and their implications for policy formulation. Inquiry. 1986:382-94.

36. Kawabata K, Xu K, Carrin G. Preventing impoverishment through protection against catastrophic health expenditure. Bulletin of the World Health Organization. 2002;80(8):612.
37. World Health Organization. Tuberculosis country profiles http://www.who.int/tb/country/data/profiles/en/2017
38. Ravallion M, Chen S, Sangraula P. Dollar a Day Revisited. The World Bank Economic Review. 2009;23(2):163-84.
39. Saksena P, Hsu J, Evans DB. Financial risk protection and universal health coverage: evidence and measurement challenges. PLoS medicine. 2014;11(9):e1001701.

2.5 Supplementary material

2.5.1 Preamble

This article complements Chapter 2 with a reflection on the potential of TB patient cost surveys to inform changes to health service delivery and financing towards patient-centred care to eliminate TB patient costs, as well as to enhance social protection measures. This article was written in reply to the letter to the Editor by Timire et al. *Eliminating tuberculosis by 2035: tackling the financial barriers at all stages of the cascade of care* (1) in the International Journal of Tuberculosis and Lung Disease, and it was published in the same journal as:

Citation

Pedrazzoli D, Houben R, Viney K, Lonnroth K, Beyond measurement: taking bold multisector actions towards zero catastrophic costs and suffering due to TB, Int J Tuberc Lung Dis., 2019 Nov 1;23(11):1236. doi: 10.5588/ijtld.19.0282.

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2.5.3 Manuscript

We agree with Timire and colleagues that all financial barriers faced by people with TB at all stages of the care cascade should be addressed if we are to achieve the ambitious targets set by the End TB Strategy and the Sustainable Development Goals. Further evidence on economic hardship during pathways to care, and also after treatment completion, is warranted. Several studies are ongoing, including "TBSequel", which tracks costs after completed TB treatment in four African countries (2).

Although national TB patient cost surveys focus on diagnosed TB patients, they also aim to capture retrospective information about pre-diagnosis costs related to seeking care (3). In addition, the survey instrument can be incorporated into patient pathway analyses, prospective studies and trials and thereby provide important complementary information.

The design and sampling strategy are as important as the choice of the instrument. Even studies with inception during the diagnostic pathway will inevitably miss those that never seek or receive any care, or do so at facilities that are not captured in the study design. Prospectively collecting patient costs from symptomatic individuals as part of a TB prevalence survey is an attractive design, but challenging to implement, due for instance to the geographical spread of small numbers of untracked patients.

We welcome the suggestion from Timire and colleagues for more evaluations of different social protection interventions. Findings from ongoing or planned intervention studies in e.g. Vietnam, Nepal, Uganda and Mozambique, aiming to improve completion of the care pathway through different modalities of socio-economic support will contribute important evidence. Several of these studies are linked to the Social Protection Action Research & Knowledge Sharing (SPARKS) (4), an international interdisciplinary research network on social protection, aiming to facilitate networking and knowledge sharing between academia, public health practitioners, international organizations and civil society. Government-led schemes such as the Direct Benefit Transfer in India may encourage people to engage with care, thus addressing another gap that is not tackled by looking at individuals who are lost to follow-up pre-treatment. This potential needs rigorous evaluation.

TB patient cost surveys provide important information on how health service delivery and financing can be changed towards patient-centred care to eliminate TB patient costs, as well as

enhancing social protection measures (3). They are a powerful tool to draw focus towards eliminating the financial plight and barriers for presumptive and TB patients, through collaboration with relevant stakeholders within and across the health sector.

For example, addressing pre-diagnosis medical costs involves streamlining the TB patient pathway, expanding access to rapid molecular testing and digital X-rays, intensifying contact investigation and case finding (5), looking for synergies with programmes on HIV, nutrition, diabetes.

Ghana, the first country in Africa to conduct a national TB patient cost survey (6), recently developed a national roadmap to eliminate financial catastrophe for TB patients through a broad multi-sectoral agenda. The first policy action of this roadmap has led to the decision of the Ghana National Health Service and National Health Insurance Authority to enrol all TB patients in the National Health Insurance Scheme free of charge. This should serve as an example and reminder to other countries and technical partners that ongoing efforts to measure TB-related costs can, and should lead to even greater concerted efforts to take bold actions towards zero catastrophic costs due to TB, zero TB suffering and ultimately TB elimination.

2.5.4 References

1. Timire C, Sandy C, Harries A. Eliminating tuberculosis by 2035: tackling the financial barriers at all stages of the cascade of care. The international journal of tuberculosis and lung disease. 2019;23(11):1235-.
2. Rachow A, Ivanova O, Wallis R, Charalambous S, Jani I, Bhatt N, et al. TB sequel: incidence, pathogenesis and risk factors of long-term medical and social sequelae of pulmonary TB - a study protocol. BMC Pulm Med. 2019;19(1):4.
3. World Health Organization. Tuberculosis patient cost surveys: a handbook. Geneva, Switzerland2017.
4. Health and Social Protection Action Research & Knowledge Sharing (SPARKS) Network. Rationale, Objectives and Work Plan. Report from the first SPARKS consultation 15-16 December, 2016. 2017.
5. Morishita F, Yadav RP, Eang MT, Saint S, Nishikiori N. Mitigating Financial Burden of Tuberculosis through Active Case Finding Targeting Household and Neighbourhood Contacts in Cambodia. PloS one. 2016;11(9):e0162796.
6. Pedrazzoli D, Siroka A, Boccia D, Bonsu F, Nartey K, Houben R, et al. How affordable is TB care? Findings from a nationwide TB patient cost survey in Ghana. Tropical medicine & international health: TM & IH. 2018;23(8):870-8.

Chapter 3: Can tuberculosis patients in resource constrained settings afford chest radiography?

3.1 Preamble

In line with Objective (2) of this thesis, in this chapter I present the first piece of work I undertook to address the second knowledge gap identified by the PhD, namely the limited evidence on the affordability of TB care. This is a case study on the cost of chest-radiography as part of TB diagnosis and care, which is a major contributor to the medical costs incurred by TB patients, as found by many national TB patient cost surveys. This was investigated through a survey among TB experts in a number of countries worldwide, which provided a snapshot of current availability and cost of chest x-rays to TB patients and presumptive TB patients. The paper was published in the European Respiratory Journal in 2017, and it is reproduced as follows with no revisions or adaptation from the published manuscript.

Citation

Pedrazzoli D, Lalli M, Boccia D, Houben R, Kranzer K, Can tuberculosis patients in resource-constrained settings afford chest radiography? Eur Respir J. 2017 Mar 22;49(3).

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3.3 Manuscript

3.3.1 Background

To the Editors:

Even when tuberculosis (TB) care is free, impoverished patients, and their households, continue to incur unmanageable costs due to seeking and staying in care for the full duration of anti-tuberculosis treatment (1). By aggravating household vulnerability, these costs can prevent or delay diagnosis, treatment and successful outcome, leading to increased TB transmission, morbidity and mortality (2-4). The new World Health Organization (WHO)'s End TB Strategy places greater emphasis on ensuring universal free access to care, and it includes a target of elimination of associated catastrophic costs for TB patients and their households by 2020 (5).

Data from prevalence surveys has led to a renewed interest in chest radiography as a triage test and a tool for active case finding (6, 7). Today chest radiography is employed in many settings both for screening and as part of the diagnostic algorithm and follow-up. If, however, chest radiography is not provided free of charge to the patient, there is a risk that these may aggravate costs incurred by patients during their path to a TB diagnosis.

We sought to provide a snapshot of current accessibility of chest radiography to TB patients and patients accessing care with symptoms suggestive of TB (presumptive TB cases (8)) both geographically and financially. We consulted experts from 44 low- and middle-income countries (of these, 12 are from the 30 high TB burden and 10 from the 30 countries deemed to have a high burden of multi-drug resistant (MDR-)TB (Figure 2), using an online survey with open and multiple-choice questions. The questionnaire was sent *via* email to staff working in National TB Programmes (NTPs) or consultants and researchers working closely with NTPs. We received a response from 27 of them (61.4%).

The survey asked about the availability and cost of chest radiography in public health facilities, role of chest radiography in the country's diagnostic algorithm, provision of health insurance or other forms of social protection to TB patients and presumptive TB cases (Table 6).

Table 6: Main topics and domains covered by the survey questionnaire

Question	Domain
Where can patients get a chest radiography, e.g. public hospital, private provider?	Coverage and access of chest radiography
Is chest-radiography free in the public service?	Access and cost of chest radiography
If chest radiography is not provided free of charge, how much does it cost?	Cost of chest radiography
Are there certain circumstances when chest radiography is provided free of charge, e.g. for children?	Cost of chest radiography
Is chest radiography part of the diagnostic algorithm in your country?	Role of chest radiography in diagnostic algorithm
Is smear microscopy provided free of charge in the public service in your country?	Cost of diagnosis by smear microscopy
Are TB patients in your country covered by a national health insurance scheme or other forms of social protection (e.g. cash transfer to cover the cost of TB diagnosis and treatment)?	Availability of social protection/health insurance in the country
If so, does the national health insurance cover the cost of chest radiography for TB patients?	Coverage of TB patients by health insurance

3.3.2 Findings

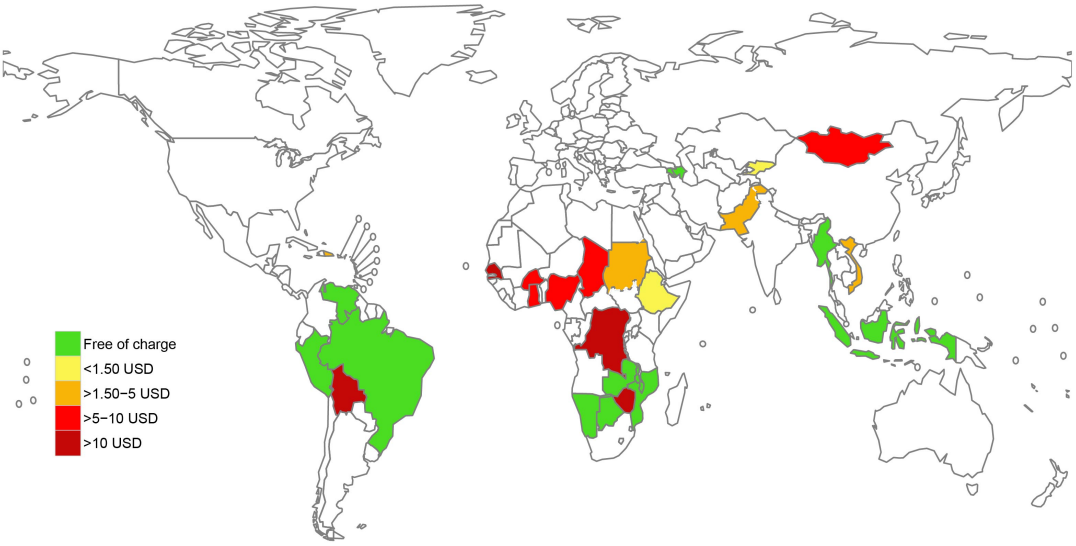
In most countries (19/27), chest radiography is part of the routine diagnostic algorithm and follow-up. In over half of the countries (15/27, 55%) patients have to pay for a chest radiography examination in the public service. The cost for a chest radiograph varies between USD 1.5 and USD 42 (median USD 7.8). The highest costs were reported from African countries (Figure 2). Costs were reported to vary even within countries: prices ranged between USD 8.4 and 42 in Senegal, and between USD 5 and USD 20 in Zimbabwe, dependent on the facility and the region. Some patients were exempt from payment: MDR-TB patients (Bolivia, Burkina Faso, Senegal), patients co-infected with HIV (Ghana, Burkina Faso), children < 5 years (Bolivia, Burkina Faso, Vietnam), patients categorised as very poor by their *kebele* ("neighbourhood") leaders (Ethiopia) and patients under follow-up (Kyrgyz Republic). In contrast, sputum smear microscopy is provided free of charge in all countries. In countries where chest radiographs are also employed for monitoring progress during treatment, this exposes patients to even higher costs as they must pay for diagnostic chest radiography and also for follow-up chest radiography examinations.

TB diagnostics and treatment is free of charge with the exception of chest radiographs in most low-income countries without a national health insurance scheme (such as Zimbabwe). The same holds true for middle-income countries (Vietnam, Dominican Republic, Indonesia, Peru). However, those countries often have health insurance schemes covering the costs of chest radiographs. Health insurance schemes based on a contributory model (such as in Ghana) are only accessible to individuals employed in the formal sector. Hence the poorest, who are at greatest risk of TB, are left out of the health insurance scheme and are unable to access chest radiography free of charge.

Figure 2: Costs of tuberculosis (TB). a) Cost of chest radiography; b) inclusion by the World Health Organization on list of high-burden countries (HBC) for TB and multidrug-resistant (MDR)-TB for the period 2016–2020 (11).

#: World Bank country classification by income: low-income economies are defined as those with a gross national income (GNI) per capita, calculated using the World Bank Atlas method, of ⩽USD 1025 in 2015; lower middle-income economies are those with a GNI per capita of USD 1026–4035; and upper middle-income economies are those with a GNI per capita of USD 4036–12475.

a)



b)

World Bank income classification#	Country included in the survey	TB HBC List	MDR-TB HBC List
Low-income economies	Burkina Faso		
	Chad		
	Congo, Dem. Rep.	•	
	Ethiopia	•	•
	Malawi		
	Mozambique	•	•

	Senegal		
	Zimbabwe	•	•
Lower middle-income economies	Armenia		
	Bolivia		
	Ghana		
	Indonesia	•	•
	Kyrgyzstan		•
	Mongolia		
	Myanmar	•	•
	Nigeria	•	
	Pakistan	•	•
	Sudan		
	Vietnam	•	•
	Zambia	•	
Upper middle-income	Azerbaijan		•
	Botswana		
	Brazil	•	
	Dominican Republic		
	Namibia	•	
	Peru		•
	Venezuela		

3.3.3 Discussion

Our analysis has limitations. It is likely that we underestimated the costs of chest radiography for patients as we only considered direct medical costs, but hidden direct "out of pocket" costs such as transport costs (especially when chest radiography facilities are not on site) and food, as well as indirect costs due to loss of productivity, tend to account for a sizable proportion of expenditure on seeking and receiving care (1). Patient costs surveys that are currently under way will provide useful insights and more comprehensive estimates.

We focused on the public sector only. The private sector often represents the first point of care for most TB patients in many Asian countries (8). Data reported from Pakistan show that chest radiography costs in the private sector can be up to four times higher than in public health facilities (USD 2.5-8.0 *versus* USD 1.5-2.0).

Our survey is not representative of the global level, nor was it intended to be. However, we covered 12 of the 30 high TB burden and 10 of the 30 high MDR-TB burden countries. Furthermore, we included countries from the three most affected continents (Figure 2).

As prevalence surveys have shown, expanding the use of chest radiography has a great potential as a screening/triage tool and can contribute to achieving the ambitious targets set in the End TB Strategy (6). However, the TB community needs to be aware that widespread use of chest radiography might potentially aggravate costs for patients and presumptive TB cases. chest radiography, similar to sputum smear microscopy and Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), should be easily accessible and free of charge if employed for TB diagnosis and follow-up. A recently published WHO policy document on chest radiography aptly states that chest radiography should be free of charge and/or fully reimbursed by health insurance (9). Additionally, practical approaches to mitigate patient costs should also be provided to NTPs. Harmonisation within and across countries and donors will be necessary. Another potential avenue to reducing the costs for patients is the extension of social protection interventions (such as cash transfers and health insurance) to cover all costs associated with TB diagnosis and treatment. This will require strong political commitment and dedicated resources, and it will be difficult to implement in the near future.

3.3.4 Conclusion

In conclusion, the direct costs of chest radiography for patients are high. In many of the countries participating in this survey a large proportion of their population lives on < USD 1.9 per day (10). Efforts are made to reduce financial barriers for patients by providing smear microscopy, Xpert/MTBRIF and treatment free of charge. A similar approach is necessary if chest radiographs become part of the diagnostic algorithms.

3.3.5 Acknowledgments

The authors thank all the country experts that contributed information to this study. We additionally would like to thank Andrew Codlin (Stop TB Partnership) and Andrew Siroka (WHO/Global TB Programme) for their help with providing contacts in countries.

3.3.6 References

1. Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low-and middle-income countries: a systematic review. European Respiratory Journal. 2014;43(6):1763-75.
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3. Ukwaja KN, Alobu I, Lgwenyi C, Hopewell PC. The high cost of free tuberculosis services: patient and household costs associated with tuberculosis care in Ebonyi State, Nigeria. PloS one. 2013;8(8):e73134.
4. Wingfield T, Boccia D, Tovar M, Gavino A, Zevallos K, Montoya R, et al. Defining catastrophic costs and comparing their importance for adverse tuberculosis outcome with multi-drug resistance: a prospective cohort study, Peru. PLoS medicine. 2014;11(7):e1001675.
5. The End TB Strategy. Geneva, Switzerland: World Health Organization, 2015.
6. Chest radiography for tuberculosis detection http://www.who.int/tb/publications/Radiography_TB_factsheet.pdf?ua=1: World Health Organization, 2016.
7. WHO. Tuberculosis prevalence surveys: a handbook. Geneva: 2011.
8. Hazarika I. Role of Private Sector in Providing Tuberculosis Care: Evidence from a Population-based Survey in India. Journal of Global Infectious Diseases. 2011;3(1):19-24.
9. WHO. Chest radiography in tuberculosis detection - Summary of WHO recommendations and guidance on programmatic approaches. Geneva: World Health Organization, 2016". Geneva: 2016.
10. Poverty and equity data: World Bank; 2016 [Available from: http://povertydata.worldbank.org/poverty/home/
11. WHO. Use of high burden country lists for TB by WHO in the post-2015 era. Geneva, Switzerland: 2015.

Chapter 4: How affordable is TB care? Findings from a nationwide TB patient cost survey in Ghana

4.1 Preamble

In line with Objective (2) of this thesis, this chapter aimed to provide further evidence on the affordability of TB care, and therefore addressed the second research gap identified by this PhD. In the paper that makes up this chapter, I describe the main findings from the nationally representative facility-based survey of costs incurred by TB patients which I undertook in Ghana, and which constitutes the fieldwork of this PhD. In doing so, in this chapter I applied the concepts reviewed and defined in Chapter 2 to the analyses of the data gathered during the survey. The article was published in the Tropical Medicine and International Health Journal in 2018, and it is reproduced as follows with no revisions or adaptation from the published manuscript.

Citation

Pedrazzoli D, Siroka A, Boccia D, Bonsu F, Nartey K, Houben R, Borghi J, How affordable is tuberculosis care? Findings from a nationwide TB patient cost survey in Ghana, Tropical Medicine and International Health. 2018 May 31.

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Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was first author on this paper. I developed the survey protocol and questionnaire, led and oversaw data collection in Ghana. I analysed the data, drafted the manuscript and then incorporated feedback from the co-authors. I oversaw the manuscript submission process, and revised the manuscript, as necessary, to respond to input from peer review.

SECTION E

Student Signature	[redacted]
Date	10/08/2020

Supervisor Signature	[redacted]
Date	17/08/2020

4.3 Abstract

Objectives: Tuberculosis (TB) is known as a disease of the poor. Despite TB diagnosis and care usually being offered for free, TB patients can still face substantial costs, especially in the context of multi-drug resistance (MDR). The End TB Strategy calls for zero TB-affected families incurring "catastrophic" costs due to TB by 2025.

This paper examines, by MDR status, the level and composition of costs incurred by TB-affected households during care seeking and treatment; assesses affordability of TB care using catastrophic and impoverishment measures; and describes coping strategies used by TB-affected households to pay for TB care.

Methods: A nationally representative survey of TB patients at public health facilities across Ghana.

Results: We enrolled 691 patients (66 MDR). The median expenditure for non-MDR TB was US$ 429.6 during treatment, *vs.* US$ 659.0 for MDR patients (*P-value*=0.001). Catastrophic costs affected 64.1% of patients. MDR patients were pushed significantly further over the threshold for catastrophic payments than DS patients. Payments for TB care led to a significant increase in the proportion of households in the study sample that live below the poverty line at the time of survey compared to pre-TB diagnosis. Over half of patients undertook coping strategies.

Conclusion: TB patients in Ghana incur substantial costs, despite free diagnosis and treatment. High rates of catastrophic costs and coping strategies in both non-MDR and MDR patients show that new policies are urgently needed to ensure TB care is actually affordable for TB patients.

4.4 Manuscript

4.4.1 Introduction

Much has been achieved in tuberculosis (TB) control since the World Health Organization (WHO) declared it a global emergency in the mid-nineties (1). Yet TB, with an estimated 10.4 million new cases and 1.7 million TB-related deaths globally in 2016, is now the leading cause of mortality from a single infection (2).

TB also represents an equity challenge. While TB is not solely a disease of the poor, poverty and inequity fuel the TB epidemic (3, 4). Poverty increases the risk of acquiring TB infection and developing the disease through more proximal risk factors such as malnutrition and

overcrowded living conditions (5-7). Poverty also limits access to care for TB patients, particularly in low- and middle-income countries (LMICs), where health care financing is characterised by a heavy reliance on out-of-pocket (OOP) payments and the limited coverage of prepayment mechanisms (e.g., taxation, health insurance) (8). Even when TB diagnosis and treatment are provided free of charge, TB patients often incur transport, accommodation and time costs associated with care seeking (9). Costs can be a deterrent to accessing diagnosis and care in the first place for those with constrained incomes (10), and where patients do seek care, costs reduce available income making the patient and their household more vulnerable to financial hardship (11). Where households struggle to afford care, TB patients will be less likely to adhere to treatment and may fail to complete it (12), thus leading to increased TB transmission in the household and community, as well as exacerbating individual morbidity and mortality (13). Affordability is a particular concern for treatment of multi-drug resistant (MDR)-TB which often lasts for more than 18 months (14, 15).

Recognising this challenge, the WHO's End TB Strategy for the 2015-2035 era includes a target of preventing any TB patient from incurring "catastrophic" costs due to TB, or ensuring that costs do not exceed 20% of annual household income (16, 17).

However, while there have been previous assessments of TB patient costs in LMICs (18) (including in Ghana, (19)), most studies did not report costs as a proportion of income, nor did they measure affordability of TB care (14). To enhance the evidence base on the costs and affordability of TB care, WHO developed a survey tool to enable rigorous measurement of TB patient costs and their share of household income (20).

Here, we report findings from a nationwide representative sample of TB patients in Ghana, the first study to use this survey tool in sub-Saharan Africa (SSA). This paper examines the level and composition of costs incurred by TB-affected households during care seeking and treatment, by MDR status; assesses affordability of TB care using catastrophic and impoverishment measures; and describes coping strategies used by TB-affected households to pay for TB care.

4.4.2 Methods

Study setting

Despite positive economic growth over the past two decades and consequent reduction in poverty levels (21), 24.2% of people in Ghana still live below US$1.90/day and economic and health inequalities persist and have worsened (22).

TB incidence in Ghana was estimated at about 160 per 100,000 population in 2016 (2). A prevalence survey was conducted in 2013, which also highlighted barriers to accessing and adhering to TB care. Diagnostics and treatment for TB are officially offered free of charge by public providers to all presumptive patients and individuals diagnosed with TB disease, with the exception of chest radiography (23).

Data collection

In late 2016, we conducted a nationally representative survey with random cluster sampling among TB patients at health facilities within the National TB Programme network, using an adapted and expanded version of the WHO patient cost tool. 25 districts (clusters) across Ghana were sampled using a probability proportional to size approach, where each district's chance of being selected was relative to the number of TB patients notified in that district in 2015.

Eligibility for the study was restricted to TB patients registered for treatment, attending a health facility within a sampled cluster, who had received at least two weeks of intensive or continuation phase treatment, and who consented to the study. In total, 734 individuals were interviewed; of these, 691 (94%) were eligible and consented to take part in the study. We collected information on TB-related costs incurred by respondents, as well as on their clinical, demographic, and socio-economic characteristics.

Costs incurred by TB-affected households

The survey collected data on direct medical (consultation fees, drugs, laboratory tests) and non-medical (e.g. transport and food) costs, and indirect costs (the time lost by a patient seeking and receiving care), up to the time of interview. To value time, we employed the output-related approach, by which the value of time is defined as the difference in household annual income pre and post-TB diagnosis (24). To minimise recall bias, data were collected only for the treatment phase the patient was in at the time of interview (i.e. intensive or continuation phase).

To estimate patient costs for the entire TB episode, including costs for all phases of treatment, we extrapolated costs based on data from patients in other phases of illness. We used the approach recommended by WHO, whereby missing cost data were replaced by the median cost of the phase of illness among those in that phase with available data (20).

Affordability of TB care

We computed four summary metrics of affordability of health care: i) the *catastrophic payment headcount, ii) catastrophic payment gap*), iii) *impoverishment incidence* and iv) *poverty gap* (25).

For the *catastrophic payment headcount ratio,* consistent with the approach adopted by WHO for the "zero TB-affected families facing catastrophic costs due to TB" indicator, costs were defined as "catastrophic" if a household incurred total TB-related costs (direct and indirect) exceeding 20% of their pre-disease annual household income (20). The *catastrophic payment gap* represents the amount by which households exceed this threshold (26).

The *impoverishment incidence* measures the increase in poverty resulting from households incurring costs for TB care. The World Bank US$ 1.90/day international poverty line is used in this study (27). The *poverty gap* is the short-fall from this poverty line (28).

Income was measured as self-reported individual and household income where available (n=553). If missing, income estimates were based on self-reported household assets (e.g. composition of floor or ownership of a mobile phone) using a regression-based approach (n=134) (20) (Annex A), or minimum reported income where only one asset was reported (n=4). Metrics were computed using the best available measure of income for each household.

We used a Pen's parade chart to plot two income distributions (gross income and income net of payments for TB) using a cumulative proportion of individuals ranked according to their gross household income, to show the potential decrease in household welfare due to payments for TB care and consequent reduction in household income (29).

Coping mechanisms

We also computed a complementary metric ("coping") if households undertook any of the following: borrowing (having taken a loan), selling household items or assets (e.g. livestock), and use of savings.

Data analyses

We report descriptive analysis of the level (median and interquartile range, IQR) and composition of costs. We used median values of costs and time as opposed to means due to the skewed distributions of both costs and time spent seeking care. Given the higher costs reported in previous studies for MDR-TB *vs.* drug susceptible (DS) patients, results are presented by MDR status (14, 15).

Comparisons between costs for DS and MDR patients were made using chi-square and Wilcoxon Rank Sum test. All analyses were run in Stata v13.0 (StataCorp, College Station, TX). Costs were converted to United States Dollars (US$) using the average annual exchange rate during study enrolment of US$1=4.15 Ghanaian cedis (oanda.com).

Sensitivity analyses

For estimating missing costs, we employed a regression-based approach, by estimating costs for that patient and treatment phase using a set of variables conceptually linked to incurring costs (sex, age, occupation, rural/urban residence). We also varied the 20% threshold for catastrophic costs to see how this would affect the proportion of households deemed as facing catastrophic costs. Additional thresholds we considered were 10%, 40% and 50% that have been previously used in the healthcare literature (30-33). The catastrophic payment headcount was also computed using consumption expenditure instead of income as a robustness check (34), because in settings where employment is mainly outside the formal sector, consumption expenditure is often believed to be a more valid measure than income (35-37). Finally, we also looked at how taking into account only direct costs would impact on the proportion of households confronting financial catastrophe.

Ethics

The study was approved by the research ethics committees of the London School of Hygiene and Tropical Medicine (REF:11240) and Ghana Health Service (GHS-ERC 14/06/16) (Appendix 5 and 6).

4.4.3 Findings

Half the sampled patients had a secondary level education and were non-salaried employees (Table 7). Three-quarters of respondents lived in an urban setting. Sixty-six (9.6%) respondents were being treated for MDR-TB at the time of survey, and about a tenth had already been treated for TB in the past (Table 7). Ninety respondents were new cases in their intensive phase of treatment and reported on average a delay of four weeks between experiencing symptoms and diagnosis. The characteristics of DS and MDR patients did not differ significantly overall, although DS patients were more likely to be newly diagnosed and have larger household size.

Table 7: Descriptive statistics and selected socio-demographic and economic characteristics of the study population, by MDR status and overall

Characteristic	DS-TB N= 625	MDR-TB N= 66	*p-value*	All N= 691
Sex, N (%)				
Male	423 (67.7%)	42 (63.6%)	0.51	465 (67.3%)
Female	202 32.3%)	24 (36.4%)		226 (32.7%)
Age in years, Median [IQR]	41 [29-52]	43 [29-50]	0.88	41 [29-52]
Phase, N (%)				
Intensive	210 (33.6%)	22 (33.3%)	0.10	232 (33.6%)
Continuation	415 (66.4%)	44 (66.7%)		459 (66.4%)
Recorded HIV Status, N (%)				
Positive	121 (19.4%)	8 (12.1%)		129 (18.7%)
Negative	431 (69.0%)	32 (48.5%)	0.78	463 (67.0%)
Unknown	73 (11.7%)	26 (39.4%)		99 (14.3%)
Retreatment status, N (%)				
New	560 (89.6%)	55 (83.3%)	0.08	615 (89%)
Retreatment/Relapse	65 (10.4%)	11 (16.7%)		76 (11%)
Diagnosis delay (weeks), Median (SD)	4 (16.2)	6 (12.9)		4 (15.9)
N (%)	80 (44.2%)	10 (52.6%)	0.48	90 (45%)
Patient's education status, N (%)	623	66		689
No education	125 (20.1)	11 (16.7)	0.24	136 (19.7)
Primary school	122 (19.6)	8 (12.1)		130 (18.9)
Secondary school / High school	350 (56.2)	42 (63.6)		392 (56.9)
University and higher	26 (4.2)	5 (7.6)		31 (4.5)
Occupation pre-disease (by main categories), N (%)	525	59		691
Salaried	70 (13.3)	9 (15.4)	0.16	79 (13.5)
Not salaried	269 (51.2)	36 (61.0)		305 (52.2)
Not employed / In school	186 (35.4)	14 (23.7)		200 (34.3)
Place of residence, N (%)	621	66		687
Urban	444 (71.5)	47 (71.2)	0.96	491 (71.5)
Rural	177 (28.5)	19 (28.8)		196 (28.5)
Household size, Median [IQR]	6 [4;11]	4 [3;9]	0.01	6 [4;11]
Monthly household income in US$ [IQR] †	144.6 [79.5-241.0]	154.7 [96.4-241.0]	0.34	144.6 [84.3-241.0]

† Pre-TB diagnosis

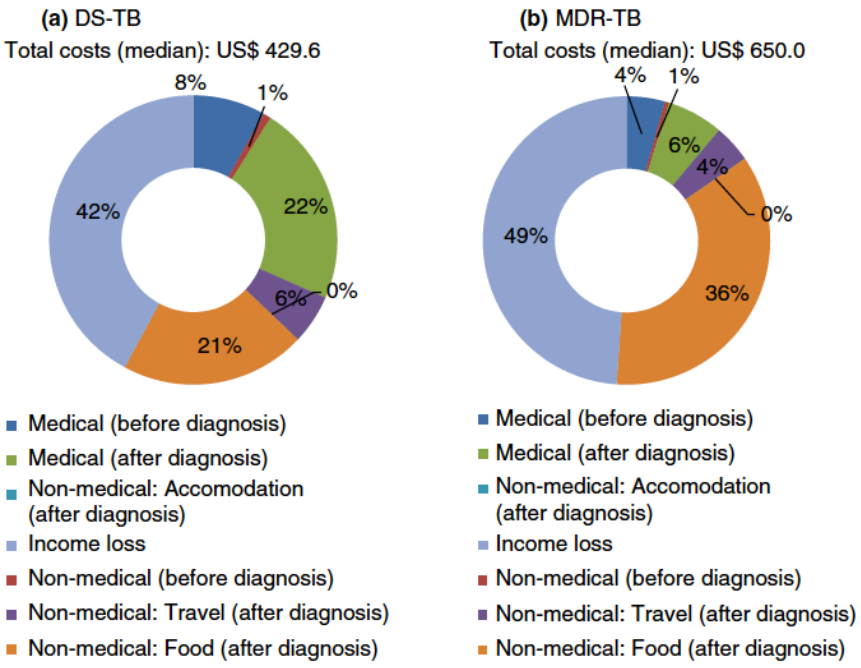
Costs incurred by TB-affected households

The median (IQR) costs that TB patients incurred as a result of TB was US$ 455 (159.2-1059.2). MDR-TB patients incurred significantly higher costs than DS patients: the median expenditure for DS-TB patients was US$ 429.6 (154.0-981.2), and for MDR-TB patients was US$ 659.0 (93.2-1680.3) (*P-value*=0.001).

Costs after diagnosis were most significant at 93% of total. This was largely driven by non-medical costs, notably income loss (42% for DS and 49% for MDR patients). Median lost income was US$ 0.0 (0.0-195.2) for DS patients and US$ 0.0 (0.0-216.9) for MDR-TB (*P-value*=0.38). The median percentage of household income lost due to TB was US$ 0.0% (0.0%-14.6%) for DS and US$ 0.0% (0.0%-14.2%) for MDR-TB patients (*P-value*=0.43).

Although there was no difference in median costs between DS and MDR before diagnosis, the median costs after diagnosis were almost three times greater for the MDR group (*P-value*<0.0001) (US$ 1276 *vs.* US$ 481), due to higher levels of non-medical costs among the MDR group (supplementary Table A1). Food and/or nutritional supplements outside the patient's normal diet were the largest contributors to non-medical expenses and these were significantly higher for MDR than for DS patients (36% *vs.* 21% of total costs) (Figure 3).

Figure 3: Composition of costs pre and post-TB diagnosis, by MDR status. a) DS-TB; b) MDR-TB



Affordability of TB care

The median percentage of household income spent on TB was 32.3% (IQR: 11.7%-61.2%), which was significantly higher for MDR compared to DS patients (48.8% *vs.* 31.3%, *P-value*=0.0016).

The proportion of patients incurring catastrophic costs at a 20% threshold of annual household income was 64.1% (443/691) (95% confidence interval: 60.5%-67.6%) (*catastrophic payment*

headcount ratio). This ratio was estimated at 72.7% (CI: 60.5%-82.3%) for MDR patients *vs.* 63.2% (CI: 59.3%-66.9%) for DS individuals – a difference which was not statistically significant (*P-value*=0.125).

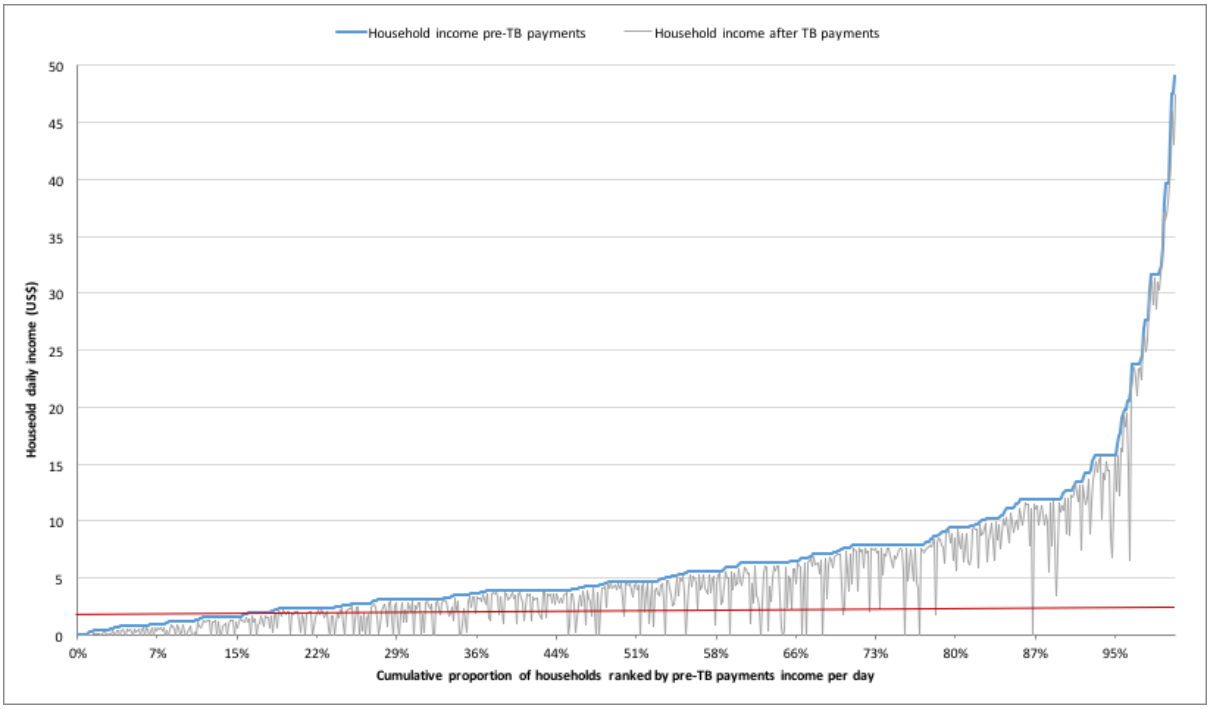
For the *catastrophic payment gap*, patients overshot the 20% threshold by an average of 39.2 percentage points overall. This indicator was significantly higher for MDR patients (59.2%) than for DS patients (37.1%) (*P-value*=0.005).

Payments for TB care led to a significant increase in the proportion of households in the study sample that live below the poverty line (PPP US$ 1.90/day) (*P-value*<0.001), from 45.6% before TB diagnosis to 59.8% at the time of the survey *(poverty headcount ratio)*. There was no statistical difference between the levels of poverty pre-diagnosis nor of the proportions shifted below the poverty line between MDR and DS patients.

The *poverty gap*, the short-fall from the international poverty line*,* increased from 60.8% (61.8% for DS and 50.7% for MDR, *P-value*=0.012) to 67.0% at the time of survey (68.4% for DS and 56.0% for MDR, *P-value*=0.026), a relative increment of 10%, which did not significantly differ by MDR status.

The "paint drips" in the Pen's chart suggest that payments for TB care led to a decrease in household income and therefore to a decrease in household welfare. It is primarily households in the middle and lower half of the income distribution that are pushed below the poverty line or further into poverty by payments for TB (Figure 4).

Figure 4: Pen's parade of household income gross and net of payments for TB (red line represents the poverty line at US$ 2.02 PPP (2015) *)



* US$ 2.02 PPP (2015) =US$ 1.90 PPP (2011), which is equal to 2.79 Ghanaian cedis (December 2016, oanda.com).

Coping mechanisms

Over half (51.5%) of patients were unable to pay for TB-treatment from existing income alone, and had to rely on savings, borrowing or selling assets (collectively termed: coping strategies) to pay for TB-related care (Table 8). This did not significantly differ by MDR status (*P-value*=0.4).

Table 8: Reported dissaving mechanisms by MDR status

Coping strategies	DS, % (N)	MDR, % (N)	All, % (N)
Loan	27.0 (169/625)	30.3 (20/66)	27.4 (189/691)
Use of savings	29.4 (184/625)	16.7 (11/66)	28.2 (195/691)
Sale of assets	10.7 (67/625)	15.2 (10/66)	11.1 (77/691)
Any of the three above	52.0 (325/625)	47.0 (31/66)	51.5 (356/691)

Productivity loss

Nearly three-quarters (73.7%) of patients lost days of work due to TB diagnosis and treatment, and this proportion was significantly higher for DS patients (75.3%) than for DS patients (59.7%) (*P-value*<0.008). The median number of working days of income lost was 54 (IQR: 0-150), and

this was significantly higher for DS patients (56 days; IQR: 1-150) than for MDR patients (24.5 days: IQR: 0-90) (*P-value*=0.008). The median number of days lost by patients in the formal sector was 30 (IQR: 0-120), versus 60 days (IQR: 14-150) for patients in the informal sector. More than forty percent (41.0%) of patients reported that they lost their job as a result of TB. This was not significantly different by MDR status (*P-value*=0.186).

Sensitivity analyses

Using the regression-based approach to impute costs instead of the median cost approach, the level of costs incurred decreased by 18.2%, leading to lower estimates of catastrophic costs which significantly differed by MDR status (53.1% for DS and MDR 72.7%; *P-value*=0.002) (supplementary Table A2 and A3).

When we used annual household consumption expenditure instead of income, the proportion of households incurring catastrophic costs was fairly consistent (61.8%) and the difference between DS and MDR patients remained statistically insignificant (61.2% versus 67.7%, *P-value*=0.305).

As the income threshold increases, the catastrophic payment headcount ratio decreases accordingly, but even at a 40% threshold of annual household income 42.3% of patients would be still considered to incur catastrophic costs (supplementary Figure 1A). This ratio was significantly different for DS and MDR patients (40.6% versus 57.6%, *P-value*=0.008).

When we took into account only direct costs in the numerator, 49.1% of patients incurred financial catastrophe, and the difference between DS and MDR patients was significant (47.6% for DS and 63.6% MDR, *P-value*=0.013).

4.4.4 Discussion

Our findings show that despite policies of free TB care in the public sector in Ghana, TB patients lack financial protection, with two-thirds of TB-affected households facing financial catastrophe, an additional 14.2% pushed into poverty due to the disease, and half undertaking coping strategies to finance costs. The increase in the poverty gap means that not only is the number of TB-affected households in Ghana that experience catastrophic health payments high, but these households (and especially MDR affected families) also substantially exceed this threshold.

Median costs that TB patients incurred in Ghana are higher than what was found in the systematic review by Tanimura *et al.* (US$ 379), and in a previous study conducted by Mauch *et al.* in two regions of Ghana in 2009 (US$ 202) (14, 19). Although it is hard to directly compare our findings to those from these studies due to the different methodologies employed, it is possible to draw similar conclusions pointing to the financial catastrophe and impoverishment faced by TB patients in Ghana due to TB.

The proportion of TB patients living below the poverty line is greater than in the general population (45.6% *vs.* 24.2%) (38). This means that TB patients are more vulnerable and policies that can effectively defray costs incurred by TB patients are warranted. As direct medical expenditures only account for 18.2% of total costs, universal health coverage is unlikely to impact on the number of families facing catastrophic costs. Income loss and food and/or nutritional supplements are the largest cost components. This calls for social protection interventions aimed at income replacement or food assistance programmes, such as the provision of food packages, specifically targeting TB patients (39).

Findings from our study clearly show that to address the devastating economic burden of TB care on TB-affected households, multi-sectoral actions are needed. Eliminating direct medical cost requires thorough review of TB service delivery including streamlined access to quality TB diagnostics and care. To mitigate direct non-medical costs and indirect costs, social support and protection measures need to be enhanced and integrated with TB care. As many patients lost their job as a result of TB, labour protection for TB patients needs to be endorsed and implemented effectively.

Costs incurred pre-diagnosis only account for 7.0% of total costs. The difference in costs between DS and MDR lies primarily in post-diagnosis costs. This is consistent with other surveys that followed the WHO methodology (40), but considerably differs from the findings from the systematic review by Tanimura *et al.* (14), where costs incurred before treatment initiation represented half of total costs. This is likely due to the fact that studies included in this review employed heterogeneous data collection methods. It can also be argued that TB programmes may now be able to link people to care earlier by, for example, further decentralising diagnostic facilities or implementing more systematic case finding activities. This would lead to lower pre-diagnosis costs.

As in previous studies, we found that MDR patients face substantially higher costs than DS-TB which is driven by non-medical expenditures. While there was no statistical difference in the

proportion of patients incurring catastrophic expenditures by MDR status, MDR patients were pushed significantly further over the threshold for catastrophic payments than DS patients. To our knowledge, this is the first study to find this. However, when the numerator for catastrophic expenditures is limited to direct costs as is the case conventionally for financial protection measurement, the MDR patients were more likely to incur catastrophic expenditures than DS patients. The impoverishing effects of the disease did not significantly differ by MDR status. The long-term care of the disease makes this group particularly at risk of catastrophic costs and this requires special consideration in TB control programming.

Further, though the evidence on the effects of costs on TB treatment outcomes remains scanty, it may be reasonable to assume that higher costs associated with seeking and adhering to treatment may lead to worse outcomes by reducing household resources available for food and worsening living conditions. Therefore, the importance of assessing costs may also be clinically relevant.

This study has several limitations. Firstly, it only focused on Ghana, which has low HIV and MDR prevalence, hence our estimate of TB-related costs may be lower compared to other SSA settings with higher TB-HIV and MDR rates.

Second, this survey was conducted in health facilities in the NTP network, in line with the WHO protocol; however, the 2013 prevalence survey found that 38.5% of patients in Ghana seek care at private facilities. As we do not know if these patients are wealthier or poorer than those in the general population (41), we cannot determine whether the exclusion of the private sector has led to overestimating or underestimating TB-related costs.

In addition, the prevalence survey found little evidence to suggest strong geographical heterogeneity. If the TB epidemic is truly generalised, then districts with low notification rates can be a sign that cases are either not seeking care when needed, have limited access (perhaps geographically) to healthcare or are seeking care, but are being missed by the health system. Our findings may underestimate costs because we overlooked the financial impact on individuals that forgo medical care because they cannot afford to pay (e.g. to reach the health facility). This is a limitation of the sampling methodology which tends to select districts with high notifications and, therefore, possibly with better off patients.

This was a cross-sectional study. A major limitation to the estimation of costs incurred by patients is recall bias, i.e., patients not accurately remembering the amount of time or money

they spent in seeking care for their TB diagnosis and treatment. We attempted to minimise recall bias by asking patients only about the treatment phase they were in, and extrapolating costs to the entire episode using two different approaches. While this assumes that every patient successfully completes treatment, it is difficult to determine how patients who fail and/or re-start treatment or die while being treated affect our estimates of costs. We found some sensitivity based on the regression-based approach, but this did not affect the main findings and still meant that over half the respondents face financial catastrophe. This remained true when we considered only direct costs.

Finally, this analysis only focuses on the one period consequences of TB, but the effects of coping mechanisms, and the impoverishing and catastrophic consequences of the disease for the household span well beyond the TB episode by reducing labour supply and productivity.

4.4.5 Conclusions

Although TB diagnosis and treatment are provided free of charge, TB patients in Ghana incur substantial costs and lack financial protection. As non-medical and indirect costs account for the majority of these costs, free TB care is clearly not enough.

High rates of catastrophic costs and coping in both non-MDR and MDR patients show that new policies beyond providing free TB care are urgently needed to offset non-medical and indirect costs, and ensure TB care is actually affordable for TB patients. It is therefore essential that countries undertaking TB patient cost surveys follow up on the survey findings by conducting, for example, national consultations with key stakeholders to discuss policy and practice implications, and effectively translate these findings into concrete action.

4.4.6 Acknowledgements

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4.4.7 References

1. Nunn P, Reid A, De Cock KM. Tuberculosis and HIV Infection: The Global Setting. Journal of Infectious Diseases. 2007;196(Supplement 1):S5-S14.
2. World Health Organization. Global Tuberculosis Report 2016. 2017.
3. Dubos RJ, Dubos J. The white plague: tuberculosis, man, and society: Rutgers University Press; 1952.
4. Janssens JP, Rieder HL. An ecological analysis of incidence of tuberculosis and per capita gross domestic product. The European respiratory journal. 2008;32(5):1415-6.
5. Weiss KB, Addington WW. Poverty's Penalty. Am J Respir Crit Care Med. 1998;157:1011.
6. Lienhardt C. From exposure to disease: the role of environmental factors in susceptibility to and development of tuberculosis. Epidemiologic reviews. 2001;23(2):288-301.
7. Oxlade O, Murray M. Tuberculosis and poverty: why are the poor at greater risk in India? 2012.
8. McIntyre D, Garshong B, Mtei G, Meheus F, Thiede M, Akazili J, et al. Beyond fragmentation and towards universal coverage: insights from Ghana, South Africa and the United Republic of Tanzania. Bulletin of the World Health Organization. 2008;86(11):871-6.
9. Laokri S, Weil O, Drabo KM, Dembelé SM, Kafando B, Dujardin B. Removal of user fees no guarantee of universal health coverage: observations from Burkina Faso. Bulletin of the World Health Organization. 2013;91(4):277-82.
10. Cambanis A, Yassin MA, Ramsay A, Squire SB, Arbide I, Cuevas LE. Rural poverty and delayed presentation to tuberculosis services in Ethiopia. Tropical medicine & international health : TM & IH. 2005;10.
11. McIntyre D, Thiede M, Dahlgren G, Whitehead M. What are the economic consequences for households of illness and of paying for health care in low- and middle-income country contexts? Social Science & Medicine. 2006;62(4):858-65.
12. Long Q, Smith H, Zhang T, Tang S, Garner P. Patient medical costs for tuberculosis treatment and impact on adherence in China: a systematic review. BMC Public Health. 2011;11(1):393.
13. Ukwaja KN, Alobu I, Lgwenyi C, Hopewell PC. The high cost of free tuberculosis services: patient and household costs associated with tuberculosis care in Ebonyi State, Nigeria. PloS one. 2013;8(8):e73134.
14. Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. The European respiratory journal. 2014;43.
15. Wingfield T, Boccia D, Tovar M, Gavino A, Zevallos K, Montoya R, et al. Defining catastrophic costs and comparing their importance for adverse tuberculosis outcome with multi-drug resistance: a prospective cohort study, Peru. PLoS medicine. 2014;11(7):e1001675.
16. Lonnroth K, Glaziou P, Weil D, Floyd K, Uplekar M, Raviglione M. Beyond UHC: monitoring health and social protection coverage in the context of tuberculosis care and prevention. PLoS medicine. 2014;11.
17. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM. WHO's new End TB Strategy. Lancet. 2015;385.
18. Barter DM, Agboola SO, Murray MB, Barnighausen T. Tuberculosis and poverty: the contribution of patient costs in sub-Saharan Africa--a systematic review. BMC Public Health. 2012;12:980.

19. Mauch V, Bonsu F, Gyapong M, Awini E, Suarez P, Marcelino B. Free tuberculosis diagnosis and treatment are not enough: patient cost evidence from three continents. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2013;17.
20. World Health Organization. Tuberculosis patient cost surveys: a handbook. Geneva, Switzerland2017.
21. World Development Indicators: World Development Indicators. http://data.worldbank.org/data-catalog/world-development-indicators.
22. Ghana Statistical Service. Ghana Poverty Mapping Report - Ghana Statistical Service. 2015.
23. Pedrazzoli D, Lalli M, Boccia D, Houben R, Kranzer K. Can tuberculosis patients in resource-constrained settings afford chest radiography? The European respiratory journal. 2016.
24. World Health Organization. WHO guide to identifying the economic consequences of disease and injury; 2009. Geneva: WHO Available from URL: http://www/ who int/choice/publications/discussion_papers/en/index html (Accessed 4 June 2010).
25. Saksena P, Hsu J, Evans DB. Financial risk protection and universal health coverage: evidence and measurement challenges. PLoS medicine. 2014;11(9):e1001701.
26. Wagstaff A, Doorslaer E. Catastrophe and impoverishment in paying for health care: with applications to Vietnam 1993–1998. Health Econ. 2003;12.
27. Ravallion M, Chen S, Sangraula P. Dollar a Day Revisited. The World Bank Economic Review. 2009;23(2):163-84.
28. Haughton J, Khandker SR. Handbook on poverty+ inequality: World Bank Publications; 2009.
29. O'Donnell O, van Doorslaer, Eddy, Wagstaff, Adam, Lindelow, Magnus. Analyzing Health Equity Using Household Survey Data: World Bank Institute Development Studies; 2007.
30. Ranson MK. Reduction of catastrophic health care expenditures by a community-based health insurance scheme in Gujarat, India: current experiences and challenges. Bulletin of the World Health Organization. 2002;80.
31. Wyszewianski L. Financially catastrophic and high-cost cases: definitions, distinctions, and their implications for policy formulation. Inquiry. 1986:382-94.
32. Ke X. Distribution of health payments and catastrophic expenditures methodology. Geneva: WHO Discussion Paper No. 2. 2005.
33. Kawabata K, Xu K, Carrin G. Preventing impoverishment through protection against catastrophic health expenditure. Bulletin of the World Health Organization. 2002;80(8):612.
34. ILO. Household income and expenditure statistics. Geneva: International Labour Organization, 2003.
35. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 1). Journal of Epidemiology and Community Health. 2006;60(1):7-12.
36. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 2). Journal of Epidemiology and Community Health. 2006;60(2):95-101.
37. Howe LD, Galobardes B, Matijasevich A, Gordon D, Johnston D, Onwujekwe O, et al. Measuring socio-economic position for epidemiological studies in low- and middle-income countries: a methods of measurement in epidemiology paper. International Journal of Epidemiology. 2012;41(3):871-86.
38. World Bank. Poverty & Equity 2015 [Available from: http://povertydata.worldbank.org/poverty/country/GHA.
39. Boccia D, Pedrazzoli D, Wingfield T, Jaramillo E, Lönnroth K, Lewis J, et al. Towards cash transfer interventions for tuberculosis prevention, care and control: key operational challenges and research priorities. BMC Infectious Diseases. 2016;16:307.

40. Fuady A, Houweling TAJ, Mansyur M, Richardus JH. Catastrophic total costs in tuberculosis-affected households and their determinants since Indonesia's implementation of universal health coverage. Infectious diseases of poverty. 2018;7(1):3.
41. Montagu D, Sudhinaraset M, Lwin T, Onozaki I, Win Z, Aung T. Equity and the Sun Quality Health Private Provider Social Franchise: comparative analysis of patient survey data and a nationally representative TB prevalence survey. International Journal for Equity in Health. 2013;12(1):5.
42. Government of Ghana. Ghana - Demographic and health survey 2014 2014 [Available from: http://microdata.worldbank.org/index.php/catalog/2373.

4.4.8 Annex A

Table A 1: Summary of costs before and after diagnosis, by MDR status and overall (US$)

Cost component	DS-TB (N=625)		MDR-TB (N=66)		All (N=691)	
	Median	IQR	Median	IQR	Median	IQR
Costs before diagnosis	31.6	30.2-35.9	32.8	31.4-37.3	31.7	30.2-35.9
Medical costs	26.7	26.7-26.7	27.7	27.7-27.7	26.7	26.7-26.7
Non-medical costs	2.9	2.9-2.9	2.9	2.9-2.9	2.9	2.9-2.9
Costs after diagnosis	481.7	220.1-1032.8	1276.3	442.7-2456.2	519.3	232.3-1161.2
Medical costs	74	55.8-77.0	40.7	8.3-101.3	70.0	55.8-77.5
Non-medical costs	140.6	31.0-427.6	427.6	112.1-1061.3	149.3	32.3-524.0
Travel	18.3	8.1-49.2	27.1	8.1-131.2	18.3	8.1-51.3
Accommodation	0.0	0.0-0.0	0.0	0.0-0.0	0.0	0.0-0.0
Food/nutritional supplements	68.4	9.7-327.5	227.9	18.9-708.4	78.2	10.1-360.1
Caregiver's time	0.0	0.0-0.74	0.0	0.0-20.5	0.0	0.0-0.56
Income loss	0.0	0.0-195.2	0.0	0.0-216.9	87.3	0.0-506.0
Total costs	429.6	154.0-981.2	659	393.2-1680.3	455.0	159.2-1059.2

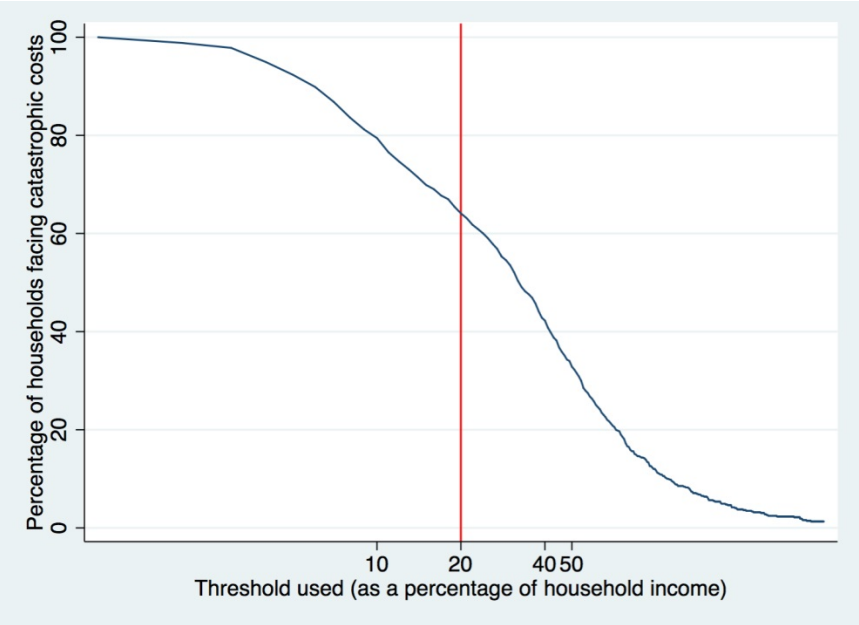
Table A 2: Sensitivity analysis (regression-based method): Summary of costs before and after diagnosis, by MDR status and overall (US$)

Cost component	DS-TB (N=625)		MDR-TB (N=66)		All (N=691)	
	Median	IQR	Median	IQR	Median	IQR
Costs before diagnosis	19.2	17.9-27.6	12	10.4-17.2	12.4	10.5-19.1
Medical costs	15.7	15.7-15.7	8.4	8.4-8.4	8.4	8.4-8.4
Non-medical costs	1.2	1.2-1.2	1.2	1.2-1.2	1.2	1.2-1.2
Costs after diagnosis	404.6	150.9-958.8	1250.8	431.9-2405.9	454.1	163.2-1083.5
Medical costs	0.0	0.0-14.4	0.0	0.0-86.7	0.0	0.0-20-6
Non-medical costs	129.5	19.3-484.0	425.2	109.6-1051.7	139.7	21.7-516.0
Total costs	341.9	67.5-893.1	634.5	354.2-1630.0	372.7	73.4-971.4

Table A 3: Sensitivity analysis (regression-based method): Catastrophic payments due to TB at the 20% threshold, by MDR status and living standard measure employed

Living standard measure employed	Households facing catastrophic costs		
	DS, % (N)	MDR, % (N)	All, % (N)
Income	53.1 (332/625)	72.7 (48/66)	55.0 (380/691)
Consumption expenditure	49.8 (296/595)	66.2 (43/65)	51.4 (339/660)

Figure A 1: Sensitivity analysis of catastrophic costs threshold



Prediction of household annual income based on asset ownership/dwelling characteristics

We selected all of the asset variables from the 2014 Ghana Demographic and Health Survey dataset (42), which measures both asset ownership and household income. Variables included household characteristics (e.g., the type of flooring material, availability of electricity, the number of rooms used for sleeping, place for cooking, type of cooking fuel), and household possessions (e.g. household effects such as radio, colour television, mobile/non-mobile telephone, refrigerator; means of transport, including bicycle, animal drawn cart, car/truck, boat with a motor; ownership of agricultural land and farm animals). We then employed a multi-variable linear regression model to predict household income. We selected those variables that were most strongly associated with income by looking at those with the smallest p-values or largest test statistics from the resulting regression. This list of selected assets was included in

the survey questionnaire.

This method may be useful in countries like Ghana with a large informal sector and where a validated set of questions on asset ownership or dwelling characteristics exists, as recommended in the WHO's "Tuberculosis Patient Cost Surveys: A Handbook" (20).

Chapter 5: Does Ghana's National Health Insurance Scheme provide financial protection to tuberculosis patients and their households?

5.1 Preamble

In line with Objective (3) of this thesis, this chapter aimed to investigate drivers and determinants of costs, thus complementing the analyses presented in Chapter 4. In addition, the paper that makes up this chapter aimed to investigate the role of enrolment into Ghana's National Health Insurance Scheme in greater depth through a quasi-experimental analysis. In doing so, this chapter addresses the third research gap identified by the thesis: the limited knowledge on determinants of TB patient costs and on the potential impact of social protection on TB patient costs. The paper was submitted to Social Science & Medicine at the time of submission of the thesis.

5.2 Cover sheet

The Research Paper Cover Sheet is enclosed on the following pages.

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

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Student ID Number	212722	**Title**	Ms
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Surname/Family Name	Pedrazzoli		
Thesis Title	The economic burden of tuberculosis and the mitigation effect of social protection: a population-based study in Ghana		
Primary Supervisor	Dr Rein Houben		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was first author on this paper. I drafted the manuscript, and analysed the data with D. Carter. I incorporated input from the co-authors, and I submitted the manuscript for publication.

SECTION E

Student Signature	[redacted]
Date	10/08/2020

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Date	17/08/2020

5.3 Abstract

Financial barriers are a key limitation to accessing health services, such as tuberculosis (TB) care in resource-poor settings. In Ghana, the National Health Insurance Scheme (NHIS), established in 2003, officially offers free TB care to those enrolled. Using data from the first Ghana's national TB patient cost survey, we address two key questions 1) what are the key determinants of costs and affordability for TB-affected households, and 2) what would be the impact on costs for TB-affected households of expanding NHIS to all TB patients?

We reported the level of direct and indirect costs, the proportion of TB-affected households experiencing catastrophic costs, and potential determinants of costs, stratified by insurance status. Regression models were used to determine drivers of costs and affordability. The effect of enrolment into NHIS on costs was investigated through Inverse Probability of Treatment Weighting Analysis.

Higher levels of education and income, a bigger household size and an MDR-TB diagnosis were associated with higher costs. Being in a low wealth quintile, living in an urban setting, losing one's job and having MDR-TB increased the odds of experiencing catastrophic costs. There was no evidence to suggest that enrolment in NHIS defrayed medical, non-medical, or total costs, nor mitigated income loss. Even if we expanded NHIS to all TB patients, the analyses suggest no evidence for any impact of insurance on medical cost, income loss, or total cost.

An expansion of the NHIS programme will not be effective to relieve the financial burden for TB-affected households. Social protection schemes require enhancement if they are to protect TB patients from financial catastrophe.

5.4 Manuscript

5.4.1 Introduction

Universal health coverage (UHC) means that people should receive the health services they need without risking financial hardship (1). Globally, at least half of the world's population still do not have access to effective and affordable health care (1). Tuberculosis (TB), one of the tracer indicators to monitor progress towards UHC in terms of coverage of essential health services (1), is a classic disease of poverty and the world's deadliest infection (2).

In line with the Sustainable Development Goals (SDGs) and policy efforts towards achieving UHC

(3), the World Health Organization's (WHO's) End TB Strategy calls for multi-sectoral interventions that address social and economic development, and that span beyond the TB sector to complement the biomedical response to the TB epidemic. Nested in its vision of "zero suffering" from the disease, the Strategy aims to prevent TB-affected households from incurring catastrophic costs due to TB (4). To this end, based on available evidence, WHO developed a methodology and instrument to rigorously measure the magnitude, nature and drivers of TB-related costs (5).

Financial barriers are a key limitation to accessing health services in low- and middle-income countries (LMICs), where health sector financing is often characterised by out-of-pocket payments (user fees) for the individual and limited prepayment mechanisms (e.g., taxation, health insurance) (6). Generally, basic TB diagnosis and care are officially offered free of charge to presumptive TB cases and TB patients, often financed through special vertical funding mechanisms, that supplement domestic resources. Yet, the TB care pathway remains long and complex, and consequently implies various risks of excessive financial burden on households and patients. The direct and indirect costs associated with TB care seeking often lead to financial distress and impoverishment among low-income households (7) (Table 9). The reasons for the substantial cost burden for TB are still not fully understood and documented, but it is possible that TB patients pay for services in the private sector, or they may have to pay for adjuvant medicines, hospitalisation or unofficial fees (7).

One approach that many countries have adopted to protect their populations from the costs of care seeking, is the introduction of national health insurance schemes. Such schemes typically start by enrolling the formal sector, and involve compulsory pre-payment of premiums by beneficiaries which are often matched by employers. The informal sector can sometimes opt in to such schemes. Health insurance can improve equity, expand access, and enhance quality of care, and it has also been found to reduce the likelihood of occurrence of catastrophic health expenditure and provide financial protection (8-12). An increasing number of African countries are implementing national insurance schemes as a means to provide financial protection against out-of-pocket expenditure and, ultimately, achieve UHC (13). As many of these countries have a high TB burden, their national TB programmes (NTPs) are starting to consider the relevance of national health insurance for their operations (14).

Table 9: Patient cost and social protection: key terminology and definitions used in this paper

	Definition	Examples
Direct medical cost	The money actually spent out of pocket by the patient on medical services	Consultation fees, prescribed medications, hospitalisation and laboratory tests
Direct non-medical cost	Direct costs associated with the utilisation of health care	Transport costs to and from the health facility, and costs for accommodation and food
Indirect cost (or opportunity cost)	Costs associated with lost productivity due to illness/disability and time spent seeking care, or looking after a patient instead of working	
Catastrophic cost	Total TB-related costs (direct and indirect) incurred by a household exceeding 20% of their pre-disease annual household income	
Catastrophic health expenditure	The UHC indicator that measures health care expenditures (direct out-of-pocket medical costs) for all conditions. In this paper, this indicator is computed using direct medical costs related to TB care, and it is also referred to as "conservative".	
Social protection	A set of initiatives that secure protection aimed at preventing or alleviating poverty, livelihood risks and social exclusion	-
Social insurance or Social security	An initiative to provide transfers to households in the event of adverse economic events, conditional on prior contributions and participation in the labour market	Sickness benefits, unemployment benefits, disability benefits and survivor's benefits
Social health insurance	A form of social insurance. Health insurance schemes with public stewardship and at least some insurance premium contributions from the insured	Ghana (National Health Insurance Scheme); The Philippines (PhilHealth); Kenya (National Hospital Insurance Fund)

Ghana was the first country in sub-Saharan Africa to introduce a National Health Insurance Scheme (NHIS) in 2003. NHIS covers both formal and informal sector workers. Currently, about 40% of Ghana's population is enrolled with a valid membership card (15). Children under the 18 years constituted the largest proportion (46.5%) of active NHIS members, followed by the informal sector (33.6%) (16). Beneficiaries can obtain healthcare from all public healthcare providers, faith-based, and private health facilities that have been accredited and operate under contract with the National Health Insurance Authority (NHIA). The benefit package covers about 95% of reported health problems, including TB (17). Table 10 provides an overview of the main features of the NHIS.

Table 10: Summary of the current main features and operational principles of the NHIS (17, 18)

Feature	Description
Stated mission	"To ensure equitable universal access for all residents of Ghana to an acceptable quality of essential health services without out-of-pocket payment being required at the point of service use" (Ghana Ministry of Health, 2004a).
Membership	All Ghanaians, from both the formal and informal sectors, are in principle required to enrol
Funding	▪ 2.5% VAT. ▪ 2.5% SSNIT contribution. ▪ Money allocated to the NHIF by Parliament. ▪ Income from investments. ▪ Premium from non-SSNIT contributors, registration and administrative fees. ▪ Donations from non-governmental organisation and individuals.
Benefit package	▪ 95% of diseases reported in health facilities in Ghana are covered, including a wide range of outpatient services with associated drugs and lab tests, inpatient care, treatment of cervical and breast cancers, basic oral health services, eye care, maternal care, and all emergency conditions. ▪ No coinsurance, co-payment, or deductible is required at the point of service.
Premium	Non-SSNIT contributors are expected to pay an income adjusted premium of between GH₵22 (about US$10) and GH₵48 (about US$22) per adult per annum.
Exemptions from paying premium	▪ People over age 70 ▪ Children under 18 whose parents both enrol ▪ The "core poor," defined as being unemployed with no visible source of income, no fixed residence, and not living with someone employed and with a fixed residence. ▪ All pregnant women (since July 2008). ▪ Mentally challenged individuals (since 2012).
Administration	▪ DHISs are centrally administered by the NHIA but day-to-day administration is decentralised to the districts. ▪ NHIA functions as the insurer; provides NHIS cards and accreditation to service providers, negotiates benefit packages, cost of care, ensures quality service and pays service providers.
Supervision	▪ The NHIA regulates premium and registration fees. ▪ Health facilities submit quarterly reports to the NHIA. ▪ DHISs submit annual reports to the NHIA who audits their accounts.
Payment to service providers	- Payment to service providers within four weeks of claim submission to DHISs.

Abbreviations: DHISs, district health insurance schemes; NHIA, National Health Insurance Authority; VAT, value added tax; SSNIT, Social Security and National Insurance Trust; NHIF, National Health Insurance Fund; NHIS, National Health Insurance Scheme; NHIF, National Health Insurance Fund.

Through NHIS, government and donor funds, TB care is intended to be free of charge to every individual at every level of service delivery in Ghana, i.e., direct payments for medical costs are supposed to be reduced to zero, regardless of whether someone is insured or not. Yet, strikingly the first nationwide cost survey conducted in 2016 among TB patients at health facilities within

the NTP's network across Ghana (described elsewhere) found that the majority of TB patients cannot afford TB care (19): total costs incurred due to an episode of TB were three times greater than the reported average monthly household income, and they were significantly higher for patients with multi-drug resistant (MDR) TB, who require a longer treatment compared to drug-susceptible patients (2). Medical and non-medical costs (e.g., transport and food) represented 18.2% and 47.4% of total costs respectively, while income loss accounted for the remaining 34.1%. About two-thirds (64.1%) of TB patients faced costs deemed catastrophic, defined as total TB-related costs exceeding 20% of annual household income.

Few studies assessed the impact of NHIS on out-of-pocket health expenditure in Ghana, and showed that the scheme has a protective effect against the financial burden of health care among the general population (15, 17). One study found that NHIS had a protective (although non-significant) effect on the cost of malaria treatment incurred by patients (20). To our knowledge, no study so far has looked at the impact of health insurance on costs and affordability of TB care in Ghana nor elsewhere.

The WHO End TB Strategy has formally recognised social protection strategies such as health insurance as a key instrument for preventing TB-affected households from experiencing financial hardship (21). However, evidence on this potential remains limited, thus preventing the swift translation of these recommendations into policy. Given the high coverage of NHIS and the availability of data on cost and affordability of TB care on a nationally representative population sample, Ghana is therefore a good case study to examine whether the strides made towards UHC translate into financial protection for TB patients.

The present paper aims to answer two key questions about TB patient costs and enrolment in the NHIS: 1) what are the key drivers of costs and affordability for TB-affected households, and 2) if NHIS is a driver, what would be the impact on costs of expanding the national health insurance scheme to all TB patients?

5.4.2 Methods

Study population and design

To approach these questions, this study used data from the above mentioned 2016 Ghana's national survey of costs faced by TB patients. Detailed methods are described elsewhere (19). Using an adapted and expanded version of the WHO TB patient cost tool (5), the survey collected information on the clinical, demographic and socio-economic characteristics of respondents, as well as on TB-related costs incurred by them over the entire TB episode. These costs

included direct medical (consultation fees, drugs, laboratory tests) and non-medical (e.g., transport and food) costs, and indirect costs or income loss (the time lost by a patient seeking and receiving care). Time was valued using the output-related approach, by which the value of time is defined as the difference in household annual income pre and post-TB diagnosis (22), thus measuring the effect of TB on income. Respondents were also asked about enrolment in the NHIS.

Descriptive analysis

We compared the total incurred costs (disaggregated by medical costs, non-medical costs, and income loss) and the proportion of TB-affected households experiencing catastrophic costs across the insured and the uninsured. We also compared the characteristics of the insured and uninsured on variables that are likely to be associated with cost. Potential determinants examined were age, sex, education level, occupation, job loss, place of residence, household income quintile, presence of MDR-TB, place of diagnosis, retreatment status, and enrolment in NHIS.

Consistent with the approach adopted by WHO for the 'zero TB-affected families facing catastrophic costs due to TB' indicator, costs were defined as 'catastrophic' if a household incurred total TB-related costs (direct and indirect) exceeding 20% of their estimated pre-diagnosis annual household income (5). As health insurance is intended to mainly offset/defray direct medical costs, we also computed the catastrophic health expenditure indicator used for UHC monitoring, which only includes direct medical expenditure in the numerator. We assessed differences in costs, experience of catastrophic costs, and potential determinants of costs (listed above) using chi-square and two-sample Wilcoxon Rank Sum tests.

Determinants of cost and affordability

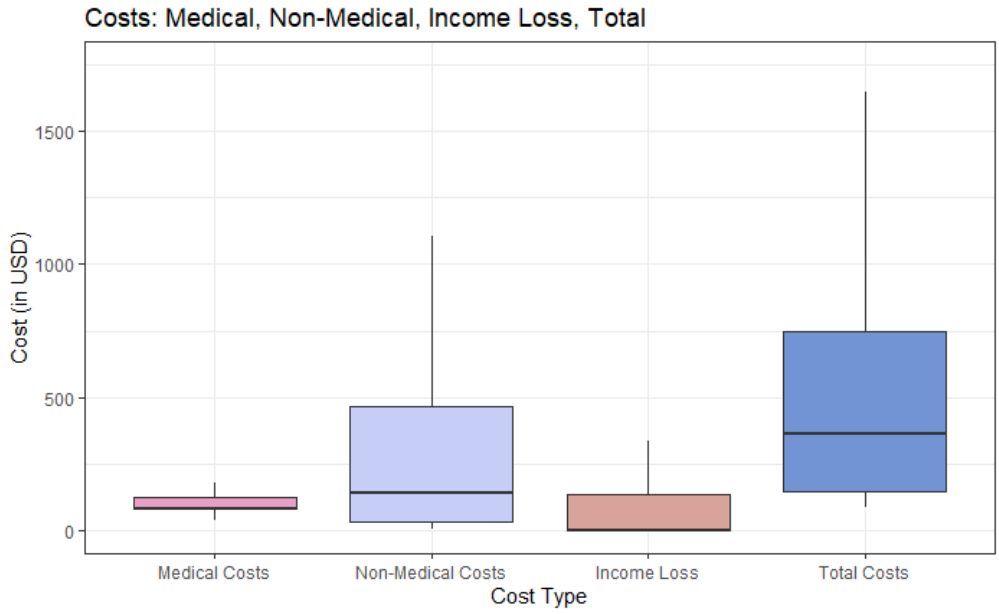
We sought to determine determinants of costs and affordability through the use of linear and logistic regression models.

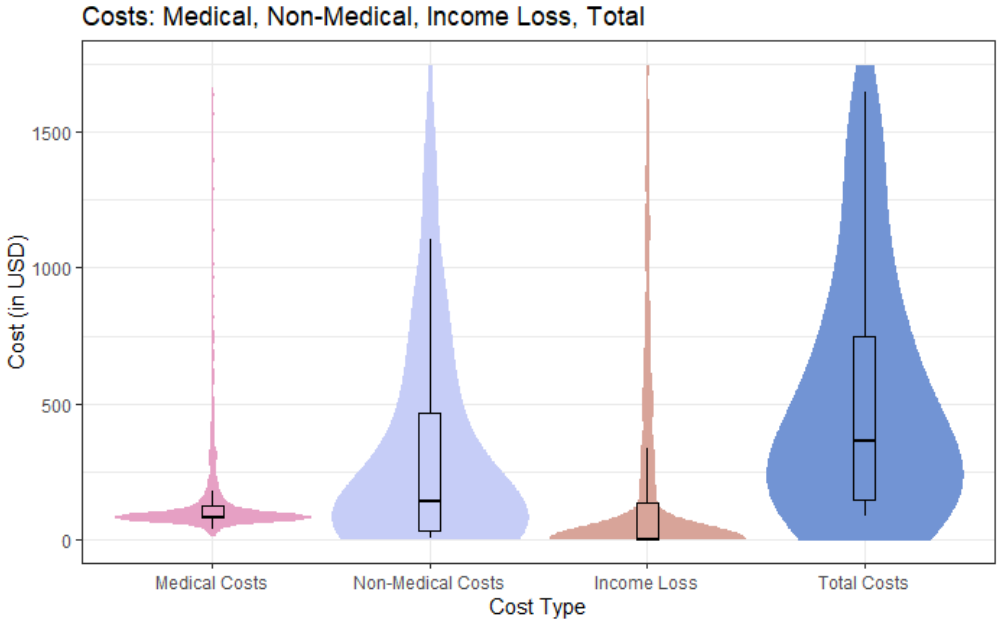
Six outcome variables and six corresponding regression models were fit. Linear regression was used to examine drivers of total cost, medical cost, non-medical cost, and income loss, while logistic regression was used to examine drivers of catastrophic costs and expenditure. Cost data are often right skewed and left censored (zeros) and thus may violate the assumption of normality required for standard linear regression techniques (23). A logarithmic transform is often suggested as a method for handling skewed data but the resulting estimate is not interpretable as a mean cost, even with back-transformation. The number of zero costs in the

data also are suggestive that a log transformation is unlikely to be a suitable model (Figure 5). We thus fit three gamma-distributed generalised linear models with a log link as alternative estimators of total cost, medical cost, non-medical cost and income loss to account for the right skew of data. Gamma models were not fit for income loss models due to the presence of a large number of zeros in the data which is not compatible with a gamma model.

Figure 5: Costs incurred by TB patients by type of cost – boxplots and violin plots

These plots inform the rationale for fitting the gamma models in addition to the linear models; they also show that non-medical costs are the biggest contributors to total costs.





Impact of NHIS on costs

To measure the effect of NHIS on costs, we used propensity score weighting (24). We considered enrolment into NHIS as the main exposure on each of the six cost and affordability outcomes.

A logistic regression model was fit to predict the propensity score. The propensity score is the probability of being enrolled in the NHIS given a set of covariates, regardless of whether an individual was actually enrolled or not. We then weighted participants using the inverse of their propensity to be enrolled with the intention of creating a pseudo-population theoretically balanced on their measured covariates (Figure 6 and 7). In the weighted sample, we calculated the difference in mean costs and the difference in the proportions experiencing catastrophic costs between the insured and uninsured, the average treatment effect (ATE).

Figure 6: Overlap in estimated propensity scores between TB patients enrolled in NHIS and those not enrolled, demonstrating good overlap on the propensity score

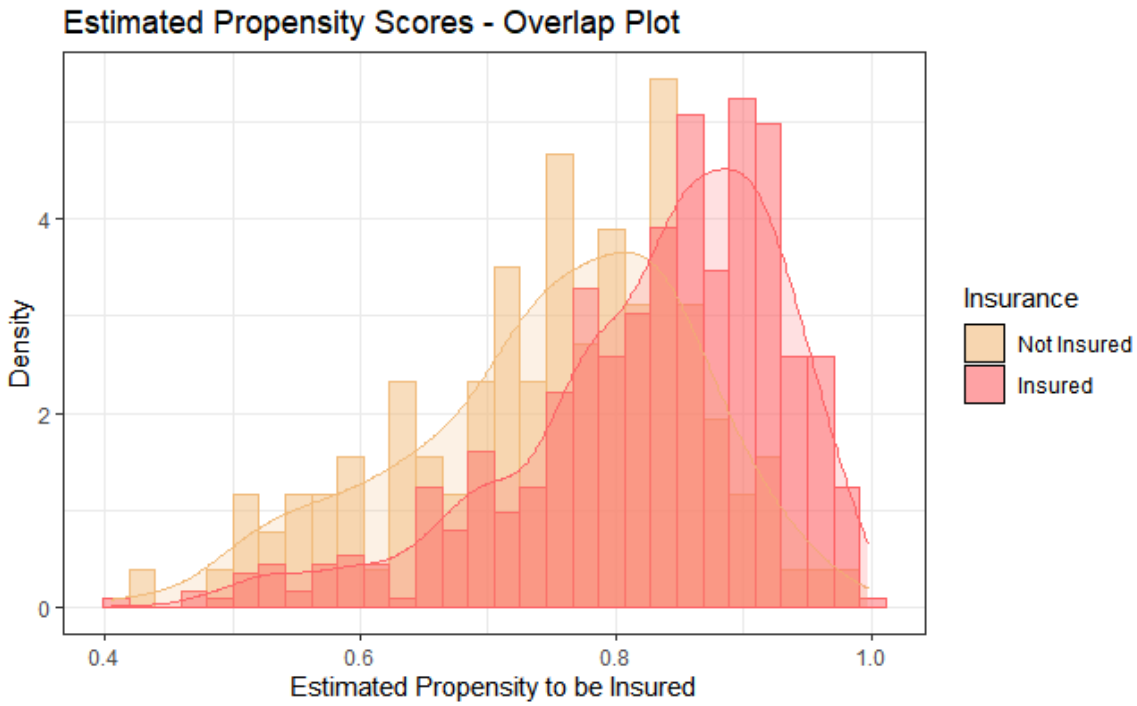
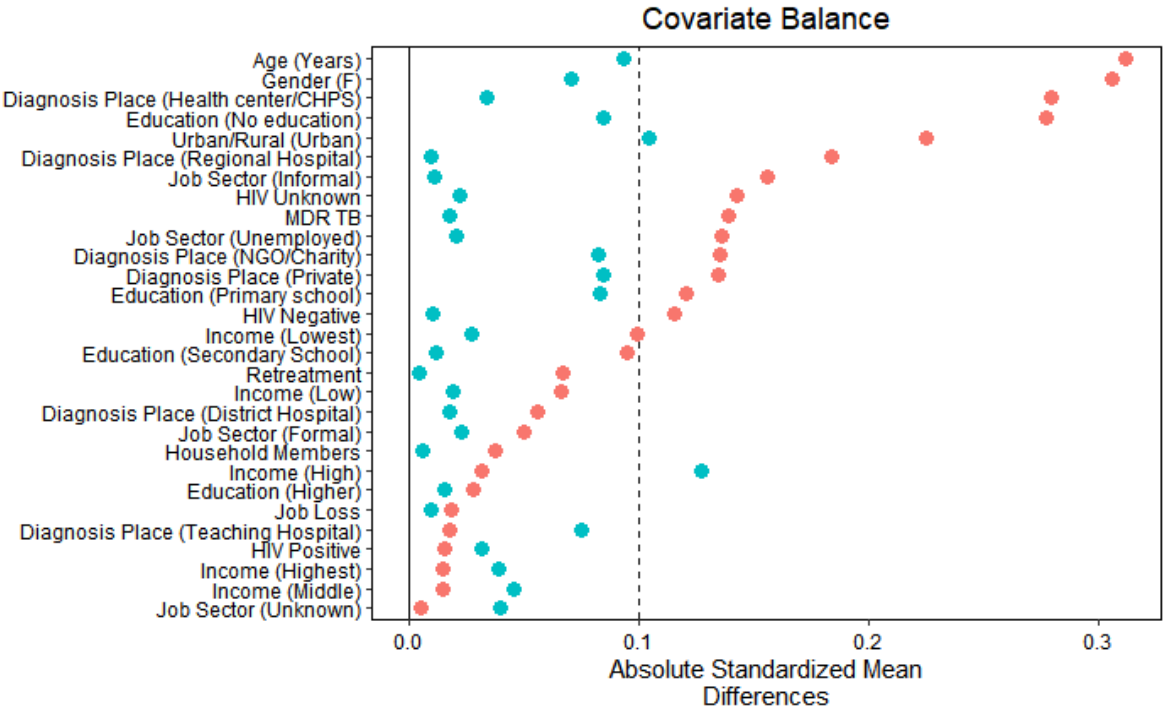


Figure 7: Change in mean difference in the matched and unmatched groups for each variable

A smaller difference indicates improved balance between groups; being below the threshold of 0.1 is conservatively considered to be effectively balanced. Balance has been largely improved by matching though some imbalance remains on the urban/rural variable and on the high income variable.



Analyses were run in STATA 13.0 (StataCorp, College Station, TX) and R v3.4.1 (ipw package) for the Inverse Probability of Treatment Weighting analysis.

5.4.3 Results

Descriptive analysis

Among survey participants, 46.0% were enrolled in the NHIS at the time of TB diagnosis. A further 35.5% enrolled after diagnosis, and the remaining 18.5% were uninsured throughout the duration of their anti-TB treatment.

Table 11: Costs incurred during a TB episode, and potential determinants of cost stratified by exposure status

	Uninsured	Insured	*p-value*
Total (N; % of sample)	128 (19%)	562 (81%)	
Incurred Costs (mean; median (IQR) in USD)			
Total Costs	896; 437 (148-888)	901; 457 (162-1079)	0.66
Medical Costs	133; 83 (83-101)	142; 83 (83-129)	0.03
Non-Medical Costs	454; 151 (31-518)	438; 152 (37-533)	0.74
Income Loss	309; 0 (0-253)	321; 0 (0-202)	0.85
Catastrophic Cost (N experiencing; %)			
Experience of Catastrophic Cost	75 (59%)	367 (65%)	0.15
Experience of Conventional Catastrophic Cost	56 (44%)	282 (50%)	0.19
Potential Drivers of Cost			
Age (median; IQR)	36 (27-45)	42 (30-53)	0.002
Sex (male), N (%)	101 (79%)	364 (65%)	0.002
Education Level, N (%)			
No Education	14 (11%)	122 (22%)	0.05
Primary School	29 (23%)	101 (18%)	
Secondary School/High School	78 (61%)	314 (56%)	
University and Higher	6 (4%)	24 (4%)	
Job Sector, N (%)			
Formal Sector	17 (13%)	86 (15%)	0.36
Informal Sector	75 (59%)	288 (51%)	
Unemployed	31 (24%)	171 (30%)	
Don't Know/No Answer	2 (2%)	15 (3%)	
Job loss (following TB), N (%)	51 (40%)	232 (41%)	0.77
Urban/Rural Place of Residence (urban), N (%)	80 (63%)	411 (73%)	0.03
Household Income Quintile, N (%)			
Low	26 (20%)	135 (24%)	0.90
Low-Middle	30 (24%)	118 (21%)	
Middle	19 (15%)	87 (15%)	
High-Middle	28 (22%)	115 (20%)	
High	25 (20%)	107 (19%)	
MDR-TB (MDR), N (%)	8 (6%)	57 (10%)	0.17
HIV status, N (%)			
Positive	23 (18%)	106 (19%)	0.42
Negative	91 (71%)	371 (66%)	
Unknown	14 (11%)	85 (15%)	
Place of Diagnosis, N (%)			
Teaching Hospital (tertiary)	5 (4%)	20 (4%)	0.01
Regional Hospital (secondary)	12 (9%)	86 (15%)	
District-level Hospital (primary)	79 (62%)	331 (59%)	
Health Center/CHPS Zone (primary)	22 (17%)	44 (8%)	
NGO/Charitable Centre or Hospital/Mission	7 (5%)	50 (9%)	
Private Clinic or Hospital	3 (2%)	28 (5%)	
Household size (median; IQR)	5 (3-11)	4 (6-11)	
Retreatment Status (retreated), N (%)	11 (9%)	60 (11%)	0.47

The characteristics of patients who were insured and of those who were not did not differ significantly overall, although insured patients were more likely to be older, female, and to live in an urban area (Table 11).

There was no difference in total costs between insured and uninsured patients, but overall medical costs were significantly higher for insured patients. Patients who were already insured at the time of diagnosis incurred medical costs before TB diagnosis that were significantly lower

compared to the costs of patients who got insured afterwards (mean: US$ 29.3; median (IQR): US$ 26.7 (26.7-26.7) *vs*. mean: US$ 45.4; median (IQR): US$ 26.7 (26.7-27.7) (*P-value*=0.0002).

Determinants of cost and affordability

After adjusting for other relevant variables, being a woman was associated with higher medical, non-medical, and total cost but not with income loss. Having a high income was associated with an approximate doubling of non-medical cost, as well as an increase in medical costs, income loss, and total costs. Patients who had been at primary and secondary school incurred higher non-medical and total costs just above US$ 200 compared to those without education, as did those living in an urban area compared to those residing in rural areas. Job loss increased income loss by just above US$ 200, and total costs by just above US$ 300. Larger households had increased medical, non-medical, and total costs compared to smaller households. Having MDR-TB nearly doubled medical, non-medical and total costs. Being a patient experiencing retreatment was also associated with increased non-medical and total costs compared to newly diagnosed patients, suggesting about an additional US$ 400 of total costs (Table 12).

Regardless of how catastrophic costs were measured, higher incomes were associated with decreased odds of experiencing catastrophic costs due to TB. Living in an urban environment, losing one's job, and having MDR-TB increased the odds of experiencing catastrophic costs with both definitions. Being unsalaried or unemployed reduced the odds of catastrophic costs when using the standard calculation, while being HIV positive reduced the odds of catastrophic expenditure when using the conservative calculation (Table 13).

Impact of NHIS on cost

There was no evidence to suggest that enrolment in health insurance defrayed medical, non-medical, or total costs, nor mitigated income loss (Table 14). The marginal effect, interpreted as the difference in mean cost if all individuals in the study had been insured compared to if no individuals had been insured, also suggested there was no impact of insurance on medical cost, income loss, or total cost. The analyses suggest that if all TB patients were to be covered with insurance, compared with none, we might expect an average reduction in non-medical cost of about US$ 126 (95% CI: -US$ 33, US$ 285). Although there was a reduction in non-medical costs and these constitute the majority of total costs for TB patients, there is no evidence for the total cost being reduced by insurance coverage.

There was no evidence that the odds of experiencing catastrophic costs would be affected were all TB patients enrolled in health insurance versus not enrolled in health insurance.

Table 12: Results of OLS & gamma GLM models – all types of cost

	Medical Cost				Non-Medical Cost				Income Loss		Total Cost			
Mean Cost (SD)	141 (181)				441 (792)				318 (1004)		900 (1343)			
Median Cost (IQR)	83 (83-124)				152 (36-528)				0 (0-202)		450 (159-1057)			
	Linear		Gamma		Linear		Gamma		Linear		Linear		Gamma	
	Adjusted Coef. (95%CI)	*P-value*	Adjusted Coef. (95%CI)	*P-value*	Adjusted Coef. (95%CI)	*P-value*	Adjusted Coef. (95%CI)	*P-value*	Adjusted Coef. (95%CI)	*P-value*	Adjusted Coef. (95%CI)	*P-value*	Adjusted Coef. (95%CI)	*P-value*
Gender: Female (vs Male)	32.36 (1.04,63.68)	0.043	1.21 (1.01, 1.45)	0.032	93.37 (-38.65,225.38)	0.165	1.31 (0.99, 1.43)	0.05415	-75.32 (-235.14,84.49)	0.355	50.4 (-161.66,262.47)	0.641	1.19 (0.95, 1.48)	0.099
Age (per year)	0.57 (-0.31,1.45)	0.204	1 (1, 1.01)	0.174	0.47 (-3.23,4.16)	0.805	1 (0.99, 1.78)	0.44273	-1.95 (-6.43,2.53)	0.393	-0.92 (-6.86,5.03)	0.762	1 (0.99, 1.01)	0.9901
Education: (vs No Education)														
Primary School	-26.91 (-72.16,18.34)	0.243	0.83 (0.65, 1.07)	0.149	219.04 (28.34,409.73)	0.024	2.42 (1.6, 3.66)	< 0.001	-16.95 (-247.8,213.9)	0.885	175.18 (-131.15,481.51)	0.262	1.55 (1.15, 2.09)	0.0038
Secondary School/High School	6.87 (-30.74,44.49)	0.72	1.03 (0.83, 1.26)	0.809	227.39 (68.87,385.92)	0.005	2.43 (1.72, 3.38)	< 0.001	-67.04 (-258.95,124.87)	0.493	167.23 (-87.43,421.88)	0.198	1.56 (1.21, 1.98)	0.0004
University and Higher	13.74 (-64.71,92.18)	0.731	1.13 (0.73, 1.79)	0.592	196.52 (-134.08,527.11)	0.244	1.88 (0.99, 3.87)	0.07293	-182.54 (-582.76,217.67)	0.371	27.71 (-503.36,558.78)	0.918	1.14 (0.7, 1.93)	0.6258
Urban: Urban (vs Rural)	1.16 (-32.09,34.4)	0.946	1.03 (0.85, 1.24)	0.754	175.74 (35.64,315.85)	0.014	1.92 (1.4, 2.59)	< 0.001	45.04 (-124.57,214.65)	0.602	221.94 (-3.13,447)	0.053	1.41 (1.12, 1.75)	0.0022
Household Wealth: (vs Lowest Income)														
Low Income	7.75 (-34,49.5)	0.716	1.07 (0.85, 1.35)	0.565	79.81 (-96.15,255.77)	0.373	1.45 (0.98, 2.14)	0.04981	48.24 (-164.77,261.25)	0.657	135.8 (-146.85,418.46)	0.346	1.36 (1.02, 1.8)	0.0295
Middle Income	14.41 (-31.8,60.61)	0.541	1.16 (0.89, 1.5)	0.272	55.72 (-139.02,250.46)	0.574	1.27 (0.83, 1.97)	0.249	84.79 (-150.96,320.54)	0.48	154.92 (-157.91,467.75)	0.331	1.49 (1.09, 2.06)	0.0095
High Income	35.33 (-7.81,78.48)	0.108	1.28 (1.01, 1.63)	0.045	184.16 (2.33,365.98)	0.047	1.78 (1.19, 2.66)	0.00306	202.71 (-17.41,422.82)	0.071	422.2 (130.12,714.28)	0.005	2.05 (1.53, 2.75)	< 0.001
Highest Income	55.96 (10.7,101.21)	0.015	1.39 (1.08, 1.8)	0.01	216.77 (26.04,407.49)	0.026	2.05 (1.35, 3.14)	< 0.001	1059.27 (828.38,1290.16)	< 0.001	1331.99 (1025.61,1638.37)	< 0.001	4.07 (2.98, 5.57)	< 0.001
Job Loss: Job Loss (vs No Job Loss)	-6.01 (-34.46,22.44)	0.678	0.98 (0.83, 1.15)	0.753	92.74 (-27.15,212.64)	0.129	1.19 (0.92, 1.57)	0.16429	219.54 (74.4,364.67)	0.003	306.27 (113.67,498.86)	0.002	1.28 (1.06, 1.55)	0.0102
Job Type: (vs Informal Sector)														
Formal Sector	31.28 (-10.98,73.55)	0.147	1.17 (0.93, 1.5)	0.186	-30 (-208.12,148.12)	0.741	0.88 (0.61, 1.29)	0.50189	-206.28 (-421.91,9.35)	0.061	-205 (-491.13,81.13)	0.16	0.79 (0.61, 1.05)	0.1006
Unemployed	0.14 (-32.26,32.55)	0.993	1 (0.84, 1.21)	0.97	72.59 (-63.98,209.16)	0.297	1.29 (0.95, 1.78)	0.07798	-153.05 (-318.38,12.27)	0.07	-80.32 (-299.7,139.06)	0.472	1.03 (0.82, 1.29)	0.7793
Don't Know / No Answer	-32.59 (-114.63,49.45)	0.436	0.9 (0.58, 1.47)	0.643	175.85 (-169.91,521.61)	0.318	0.98 (0.49, 2.26)	0.96352	-466.67 (-885.24,-48.1)	0.029	-323.41 (-878.83,232.01)	0.253	0.65 (0.39, 1.18)	0.1168
# Household Members (per member)	1.6 (-0.31,3.5)	0.1	1.01 (1, 1.02)	0.089	10.82 (2.8,18.84)	0.008	1.02 (1, 1.04)	0.0227	-0.46 (-10.17,9.25)	0.925	11.95 (-0.93,24.83)	0.069	1.01 (1, 1.02)	0.0951
Place of Diagnosis: (vs District Level Hospital (Primary))														
Teaching Hospital (Tertiary)	22.99 (-50.52,96.5)	0.539	1.24 (0.84, 1.93)	0.302	-45.88 (-355.67,263.9)	0.771	0.74 (0.4, 1.53)	0.36692	-190.36 (-565.39,184.66)	0.319	-213.26 (-710.89,284.38)	0.4	0.77 (0.49, 1.29)	0.2802
Regional Hospital (Secondary)	13.93 (-27.02,54.87)	0.504	1.14 (0.91, 1.44)	0.273	93.86 (-78.72,266.43)	0.286	1.07 (0.75, 1.58)	0.69867	105.42 (-103.49,314.33)	0.322	213.2 (-64.02,490.42)	0.131	1.2 (0.91, 1.59)	0.1902
Health Centre/CHPS Zone (Primary)	-20.96 (-72.62,30.7)	0.426	0.84 (0.63, 1.13)	0.238	-41.9 (-259.62,175.82)	0.706	0.91 (0.58, 1.49)	0.70029	4.19 (-259.38,267.76)	0.975	-58.67 (-408.42,291.07)	0.742	1 (0.71, 1.43)	0.9941
NGO/Charitable Health Centre or Hospital/Mission	-12.88 (-64.1,38.33)	0.621	0.93 (0.7, 1.25)	0.607	36.37 (-179.48,252.21)	0.741	1.19 (0.74, 1.99)	0.45095	-102.32 (-363.62,158.97)	0.442	-78.84 (-425.57,267.89)	0.655	1.11 (0.79, 1.6)	0.5498
Private Clinic/Hospital	33.53 (-35.54,102.6)	0.341	1.28 (0.89, 1.93)	0.205	-55.87 (-346.96,235.21)	0.706	0.94 (0.53, 1.84)	0.85036	464.33 (111.95,816.72)	0.01	441.99 (-25.61,909.59)	0.064	1.2 (0.77, 1.95)	0.4382
HIV Status (vs HIV Negative)														
HIV Positive	2.11 (-34.66,38.89)	0.91	1.05 (0.85, 1.29)	0.658	-96.01 (-251,58.99)	0.224	0.88 (0.64, 1.24)	0.45294	174.82 (-12.81,362.45)	0.068	80.92 (-168.05,329.9)	0.524	0.98 (0.77, 1.26)	0.8629
Unknown Status	-14.93 (-57.5,27.64)	0.491	0.95 (0.75, 1.21)	0.662	-106.72 (-286.12,72.68)	0.243	0.92 (0.64, 1.36)	0.66473	115.9 (-101.27,333.08)	0.295	-5.74 (-293.93,282.44)	0.969	0.96 (0.73, 1.28)	0.7936
Drug Resistance: MDR (vs No MDR)	58.37 (9.27,107.47)	0.02	1.31 (0.99, 1.76)	0.053	425.9 (218.98,632.83)	< 0.001	2.24 (1.47, 3.56)	< 0.001	52.5 (-198,303)	0.681	536.77 (204.37,869.17)	0.002	1.74 (1.27, 2.45)	< 0.001
TB Retreatment: Retreatment (vs No Retreatment)	21.2 (-24.55,66.95)	0.363	1.11 (0.86, 1.45)	0.419	217.01 (24.19,409.84)	0.027	1.61 (1.06, 2.52)	0.02135	162.2 (-71.23,395.63)	0.173	400.41 (90.66,710.16)	0.011	1.45 (1.07, 1.98)	0.0161
Health Insurance: Insured (vs Not Insured)	-3.4 (-39.75,32.94)	0.854	0.99 (0.8, 1.21)	0.922	-60.52 (-213.7,92.66)	0.438	1.03 (0.73, 1.41)	0.87825	11.04 (-174.4,196.48)	0.907	-52.89 (-298.96,193.19)	0.673	1.04 (0.81, 1.31)	0.7577

Values highlighted in light blue colour indicate determinants that are significantly associated with costs in the Gamma model.
Values highlighted in green indicate determinants that are significantly associated with costs in the Linear model.

Table 13: Results of logistic models – catastrophic costs

	Catastrophic Cost			Catastrophic Cost - Conservative		
Proportion Experiencing Catastrophic Cost		64%			49%	
	Crude OR (95%CI)	**Adjusted OR (95%CI)**	***P-value***	**Crude OR (95%CI)**	**Adjusted OR (95%CI)**	***P-value***
Gender: Female (vs Male)	1.29 (0.92,1.82)	1.11 (0.74,1.64)	0.616	1.55 (1.12,2.14)	1.3 (0.87,1.94)	0.198
Age (per year)	1.005 (0.9954,1.0146)	1 (0.9892,1.011)	0.998	1.0008 (0.9917,1.01)	0.9955 (0.9845,1.0067)	0.431
Education: (vs No Education)						
Primary School	0.79 (0.48,1.33)	1.09 (0.61,1.94)	0.771	0.91 (0.56,1.48)	1.35 (0.76,2.41)	0.311
Secondary School/High School	0.82 (0.53,1.25)	1.19 (0.74,1.92)	0.47	0.84 (0.56,1.24)	1.5 (0.93,2.42)	0.096
University and Higher	0.43 (0.19,0.96)	1.07 (0.43,2.69)	0.88	0.55 (0.24,1.25)	2.1 (0.81,5.47)	0.128
Urban: Urban (vs Rural)	1.25 (0.88,1.77)	1.71 (1.12,2.59)	0.012	1.16 (0.83,1.63)	1.86 (1.21,2.86)	0.005
Household Wealth: (vs Lowest Income)						
Low Income	0.2 (0.11,0.36)	0.18 (0.1,0.34)	< 0.001	0.2 (0.12,0.35)	0.17 (0.1,0.31)	< 0.001
Middle Income	0.18 (0.1,0.34)	0.16 (0.08,0.31)	< 0.001	0.15 (0.09,0.27)	0.11 (0.06,0.2)	< 0.001
High Income	0.14 (0.08,0.26)	0.12 (0.06,0.23)	< 0.001	0.13 (0.07,0.22)	0.09 (0.05,0.16)	< 0.001
Highest Income	0.13 (0.07,0.24)	0.11 (0.06,0.22)	< 0.001	0.05 (0.03,0.09)	0.03 (0.02,0.06)	< 0.001
Job Loss: Job Loss (vs No Job Loss)	1.62 (1.17,2.24)	1.87 (1.3,2.69)	< 0.001	1.31 (0.97,1.79)	1.52 (1.06,2.19)	0.023
Job Sector: (vs Informal)						
Formal	0.7 (0.44,1.1)	0.7 (0.42,1.17)	0.17	1.1 (0.71,1.72)	1.24 (0.73,2.11)	0.424
Unemployed	0.9 (0.63,1.3)	0.89 (0.59,1.34)	0.586	1.24 (0.88,1.76)	1.35 (0.89,2.05)	0.153
Don't Know / No Answer	0.45 (0.19,1.1)	0.4 (0.15,1.06)	0.065	1.02 (0.42,2.47)	1.24 (0.44,3.44)	0.684
# Household Members (per member)	1.0032 (0.9819,1.0249)	1.0063 (0.9826,1.0305)	0.606	1.01 (0.99,1.03)	1.02 (1,1.05)	0.067
Place of Diagnosis: (vs District Level Hospital (Primary))						
Teaching Hospital (Tertiary)	0.72 (0.32,1.63)	0.79 (0.33,1.9)	0.603	0.72 (0.32,1.64)	0.87 (0.34,2.22)	0.773
Regional Hospital (Secondary)	1.35 (0.83,2.17)	1.26 (0.74,2.15)	0.387	1.33 (0.85,2.07)	1.23 (0.73,2.07)	0.439
Health Centre/CHPS Zone (Primary)	1.13 (0.65,1.98)	1.37 (0.71,2.66)	0.349	1.27 (0.75,2.16)	1.67 (0.85,3.26)	0.136
NGO/Charitable Health Centre or Hospital/Missio	0.78 (0.44,1.37)	0.65 (0.34,1.23)	0.185	0.97 (0.56,1.7)	0.93 (0.47,1.82)	0.827
Private Clinic/Hospital	0.98 (0.45,2.11)	1.29 (0.56,2.96)	0.546	0.83 (0.39,1.75)	1.55 (0.66,3.66)	0.319
HIV Status (vs HIV Negative)						
HIV Positive	0.99 (0.65,1.49)	0.84 (0.53,1.34)	0.469	0.82 (0.55,1.21)	0.65 (0.41,1.05)	0.08
Unknown Status	0.67 (0.43,1.05)	0.7 (0.42,1.17)	0.172	0.64 (0.41,1.01)	0.69 (0.4,1.19)	0.18
Drug Resistance: MDR (vs No MDR)	1.6 (0.9,2.86)	2.09 (1.1,3.97)	0.025	1.97 (1.16,3.37)	3.13 (1.66,5.91)	< 0.001
TB Retreatment: Retreatment (vs No Retreatment)	1.56 (0.9,2.71)	1.32 (0.72,2.41)	0.365	1.54 (0.93,2.53)	1.32 (0.73,2.39)	0.358
Health Insurance: Insured (vs Not Insured)	1.34 (0.9,1.98)	1.27 (0.81,1.98)	0.293	1.31 (0.88,1.93)	1.21 (0.76,1.91)	0.424

Values highlighted in green indicate determinants that are significantly associated with catastrophic costs or catastrophic health expenditure ("conservative").

Table 14: Results of propensity score weighting

Cost in USD	Observed Mean Cost Uninsured	Observed Mean Cost Insured	Observed Mean Cost Difference	Predicted Mean Cost (All Uninsured)	Predicted Mean Cost (All Insured)	Average Treatment Effect (Risk Difference)	95% CI
Medical Cost	133.6	143.4	9.8	147.45	140.84	-6.61	(-43.64, 30.43)
Non-Medical Cost	460.1	436.8	-23.3	561	434.97	-126.03	(-285.04, 32.98)
Income Loss	314.39	321.63	7.24	288.7	318.62	29.92	(-165.48, 225.33)
Total Cost	908.5	902.19	-6.31	997	894.28	-102.72	(-368.15, 162.71)

	Observed Proportion Experiencing CCs Uninsured	Observed Proportion Experiencing CCs Insured	Observed Catastrophic Cost OR	Predicted Mean Proportion (All Uninsured)	Predicted Mean Proportion (All Insured)	Average Treatment Effect (Odds Ratio)	95% CI
Conventional Catastrophic Cost	59%	66%	1.34	60%	65%	1.19	(0.78, 1.80)
Conservative Catastrophic Cost	44%	50%	1.31	47%	50%	1.12	(0.75, 1.67)

5.4.4 Discussion

Our study advances the literature on financial protection for TB patients by investigating determinants of costs and affordability for TB-affected households, and by looking at the potential impact of expanding enrolment of TB patients in the NHIS.

Drivers for experiencing catastrophic costs are consistent with those found in other studies (25, 26), and our findings suggest that are the poorest patients, from larger households, who have lost their job due to their disease, who are most at risk of confronting financial catastrophe.

Indirect costs for individuals who are unemployed may have been underestimated, which may have resulted in these patients being less likely to incur catastrophic costs, as observed in other studies (27).

Patients undergoing treatment for MDR-TB are also more likely to incur catastrophic costs due to the longer duration of treatment. In Ghana, all MDR-TB patients are supposed to benefit from an "enablers' package" which provides them with cash, transport vouchers and/or nutritional support, according to their needs. Evidence on the effectiveness and acceptability of this intervention is limited (28). Less than a quarter of the MDR-TB patients in our study reported that they received vouchers or goods in kind from the health facility, and this should be further investigated.

In Ghana, the impact of NHIS on household's out-of-pocket payments for health care has been studied quite extensively since its inception (15). This literature does not relate specifically to TB-affected households, and, to our knowledge, our study is the first assessment of the effect of a state-supported health insurance scheme on financial protection of TB patients. Our analyses indicate that the NHIS in its current form is not effective in reducing TB patient cost, and will therefore not protect TB affected households from incurring catastrophic costs due to TB. The marginal association between NHIS and non-medical costs observed in the IPTW analysis suggests a potential impact of non-medical costs but the causal mechanism behind this drop is unclear, as expected impacts should be on mitigating medical costs. One possible explanation could be that individuals who are not insured tend to travel further to a public provider, while individuals who are insured benefit from a greater choice of providers, including private providers, and therefore may not need to travel as far, thus incurring less transport costs (29).

The lack of evidence suggesting that enrolment in the NHIS defrayed medical costs, possibly

explains findings from the survey that medical expenditures are still substantial and constitute 18.2% of the total costs incurred by patients, despite the majority (81%) of patients being covered by NHIS. Such medical expenditures include payments for TB diagnostic procedures not covered by the TB programme or NHIS, such as chest radiography (30), and for co-morbidities (e.g. liver function test), and ancillary drugs (17). There is anecdotal evidence that drug stock-outs at public health facilities sometimes have forced patients to buy medications from private providers. In addition, insured patients can still be asked to pay unofficial fees or make cash payments at NHIS accredited health facilities, for example for unapproved prescribed medicines (15, 18, 31).

Health insurance is one of the key strategies to mitigate the financial hardship faced by TB-affected households, and particularly medical expenditure (7, 32). Findings from the national TB patient cost survey have stimulated policy action to eliminate financial catastrophe for TB and MDR-TB patients in Ghana, and led to the decision of the Ghana National Health Service and National Health Insurance Authority to enrol all TB patients in the NHIS free of charge, under the category of indigent people (33). However, were all TB patients enrolled in the NHIS (in its current form), our analyses suggest no evidence for any impact of insurance on medical cost, income loss, or total cost.

The new policy, which explicitly targets TB, should be rigorously evaluated. The exemption of TB patients from paying the NHIS premium recognises the financial burden caused by TB, and is an important step to ensure all TB patients are covered by the NHIS, but further research is needed to assess to what extent the premium was actually a barrier to enrolment for TB patients. It is plausible that if the premium is not subsidised, it remains unaffordable for households who may not be living below the official poverty line, though are still facing financial hardship (34, 35). Further, even for individuals who are officially classified as indigent, official exemptions were found to be largely non-functional, preventing access to the poor (36, 37).

Future studies should investigate the reasons why the NHIS in its current form is not effective in defraying costs for TB patients in order to inform options and future reforms of the scheme. For example, we could argue that NHIS may have a greater effect on costs if coverage among the general population was higher, as it could encourage a more direct patient journey to public health facilities, given that 38.5% of patients in Ghana seek care at private facilities according to the 2013 TB prevalence survey. In our study, although pre-diagnosis costs only accounted for 7.0% of total costs (19), individuals who enrolled in NHIS only after diagnosis had higher pre-diagnosis costs compared to those who were already enrolled. Were they enrolled in NHIS

because they are indigent or because of expanded coverage, arguably these costs may be lower, and so would be the overall costs incurred by patients. In addition, most TB patients, whose majority belong to the poorest segments of society, could benefit from NHIS prior to being diagnosed with TB, thus reducing diagnostic delays and possibly the severity of the disease.

Mechanisms to refer indigent TB patients identified through NHIS to patient/social support should also be considered. Non-medical costs and income loss accounted for the largest proportion of total costs. Only four (0.6%) of patients in our study were enrolled in the Livelihood Empowerment Against Poverty (LEAP), the national cash transfer programme to extremely poor households. This calls for the establishment and enhancement of social protection measures integrated with TB care, for example by making TB one of the eligibility criteria for LEAP.

Many of these considerations are not specific to TB but apply to many other conditions, and are conducive to ensuring a functional and enhanced health system as countries strive towards UHC. However, as TB is both a critical public health threat and a tracer indicator to monitor progress towards UHC (1), it can act as a powerful driver for improving TB financing and ensuring financial protection for TB patients.

The main limitation of our study lies in the nature of the cross-sectional data from the national TB patient cost survey that we used for our analyses. These data and their limitations have been discussed elsewhere (19). For example, it was not possible to perform further disaggregated analyses comparing costs for individuals who enrolled before TB diagnosis and for those who were already enrolled due to insufficient power. In addition, this survey was designed to assess the level and nature of costs incurred by TB patients, and was not designed to specifically assess the impact of enrolment of NHIS on affordability of TB care. However, we employed a weighting approach to control for confounding, which requires fewer assumptions about the data compared to a traditional parametric methodology (38, 39), and is more robust to estimate treatment effects using observational data (24). Specifying the appropriate model for examining drivers of cost is challenging given the distribution of cost data and the zero-inflation in the income loss variable, though both linear and gamma models provide results that are similarly interpreted.

Finally, the aim of a TB patient cost survey should not only be to measure costs but also to lead to interventions and policy changes that help reduce or mitigate these costs; therefore, it is essential that existing and new initiatives to reduce costs and improve access to care are evaluated. While we acknowledge that our results are context and design specific, our study

serves as an example of how TB patient cost surveys can drive policy change, and how assessing the most relevant and feasible interventions that can improve affordability of care, should be integral to this process. As a growing number of TB patient cost surveys are being planned (2), their potential to inform policy and practice should be fully harnessed, and investigators should take full advantage of this opportunity when designing their study.

5.4.5 Conclusions

Using Ghana as a case study, we showed that even in countries with well-established state-supported health insurance schemes and free TB care policies, TB patients are at risk of incurring high costs when seeking and accessing TB care, including medical costs which are meant to be mostly covered by national health insurance. Recent changes to the NHIS resulting from the findings of the national TB patient cost survey, should be monitored and rigorously evaluated to effectively improve access and provide financial protection to TB patients.

5.4.6 References

1. World Health Organization. Tracking Universal Health Coverage. Washington, DC: World Health Organization; 2017.
2. World Health Organization. Global Tuberculosis Report 2019. Geneva, Switzerland; 2019.
3. Lönnroth K, Raviglione M. The WHO's new End TB Strategy in the post-2015 era of the Sustainable Development Goals. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2016;110(3):148-50.
4. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM. WHO's new End TB Strategy. Lancet. 2015;385.
5. World Health Organization. Tuberculosis patient cost surveys: a handbook. Geneva, Switzerland2017.
6. McIntyre D, Garshong B, Mtei G, Meheus F, Thiede M, Akazili J, et al. Beyond fragmentation and towards universal coverage: insights from Ghana, South Africa and the United Republic of Tanzania. Bulletin of the World Health Organization. 2008;86(11):871-6.
7. Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. The European respiratory journal. 2014;43.
8. Buigut S, Ettarh R, Amendah DD. Catastrophic health expenditure and its determinants in Kenya slum communities. International Journal for Equity in Health. 2015;14(1):46.
9. Xu K, Evans DB, Kawabata K, Zeramdini R, Klavus J, Murray CJ. Household catastrophic health expenditure: a multicountry analysis. Lancet. 2003;362.
10. Habib SS, Perveen S, Khuwaja HM. The role of micro health insurance in providing financial risk protection in developing countries--a systematic review. BMC Public Health. 2016;16:281.
11. Spaan E, Mathijssen J, Tromp N, McBain F, ten Have A, Baltussen R. The impact of health insurance in Africa and Asia: a systematic review. Bulletin of the World Health Organization. 2012;90(9):685-92.
12. Acharya A VS, Taylor F, Masset E, Satija A, Burke M and Ebrahim S. Impact of national health insurance for the poor and the informal sector in low- and middle-income countries.

London: EPPI-Centre, Social Science Research Unit, Institute of Education, University of London; 2012.
13. McIntyre D, Thiede M, Dahlgren G, Whitehead M. What are the economic consequences for households of illness and of paying for health care in low- and middle-income country contexts? Social science & medicine (1982). 2006;62.
14. Wells W, Stallworthy G, Balsara Z. How tuberculosis programs can navigate the world of social health insurance. The International Journal of Tuberculosis and Lung Disease. 2019;23(1):26-37.
15. Kusi A, Hansen KS, Asante FA, Enemark U. Does the National Health Insurance Scheme provide financial protection to households in Ghana? BMC Health Services Research. 2015;15(1):331.
16. National Health Insurance Authority. Annual report. 2013.
17. Nguyen HT, Rajkotia Y, Wang H. The financial protection effect of Ghana National Health Insurance Scheme: evidence from a study in two rural districts. International Journal for Equity in Health. 2011;10(1):4.
18. Kotoh AM, Aryeetey GC, Van der Geest S. Factors that influence enrolment and retention in Ghana'National Health Insurance Scheme. International journal of health policy and management. 2018;7(5):443.
19. Pedrazzoli D, Siroka A, Boccia D, Bonsu F, Nartey K, Houben R, et al. How affordable is TB care? Findings from a nationwide TB patient cost survey in Ghana. Tropical medicine & international health : TM & IH. 2018;23(8):870-8.
20. Dalaba MA, Akweongo P, Aborigo R, Awine T, Azongo DK, Asaana P, et al. Does the national health insurance scheme in Ghana reduce household cost of treating malaria in the Kassena-Nankana districts? Global Health Action. 2014;7(1):23848.
21. Lonnroth K, Glaziou P, Weil D, Floyd K, Uplekar M, Raviglione M. Beyond UHC: monitoring health and social protection coverage in the context of tuberculosis care and prevention. PLoS medicine. 2014;11.
22. World Health Organization. WHO guide to identifying the economic consequences of disease and injury; 2009.
23. Basu A, Manning WG. Issues for the next generation of health care cost analyses. Medical care. 2009:S109-S14.
24. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Statistics in medicine. 2015;34(28):3661-79.
25. Fuady A, Houweling TAJ, Mansyur M, Richardus JH. Catastrophic total costs in tuberculosis-affected households and their determinants since Indonesia's implementation of universal health coverage. Infectious diseases of poverty. 2018;7(1):3.
26. Ministry of Health. The first Kenya tuberculosis patient cost survey 2017. 2018.
27. Muniyandi M, Thomas BE, Karikalan N, Kannan T, Rajendran K, Saravanan B, et al. Association of Tuberculosis With Household Catastrophic Expenditure in South India. JAMA network open. 2020;3(2):e1920973.
28. Nortey Hanson-Nortey N BAF, Suarez P G, Chimzizi R B. Evaluating the effectiveness of patient "enablers' package" in Ghana. 40th Union World Conference on Lung Health; Cancun, Mexico2009.
29. Fiestas Navarrete L, Ghislandi S, Stuckler D, Tediosi F. Inequalities in the benefits of national health insurance on financial protection from out-of-pocket payments and access to health services: cross-sectional evidence from Ghana. Health policy and planning. 2019;34(9):694-705.
30. Pedrazzoli D, Lalli M, Boccia D, Houben R, Kranzer K. Can tuberculosis patients in resource-constrained settings afford chest radiography? The European respiratory journal. 2016.
31. Agyepong IA, Nagai RA. "We charge them; otherwise we cannot run the hospital" front line workers, clients and health financing policy implementation gaps in Ghana. Health Policy. 2011;99(3):226-33.

32. Lönnroth K, Glaziou P, Weil D, Floyd K, Uplekar M, Raviglione M. Beyond UHC: Monitoring Health and Social Protection Coverage in the Context of Tuberculosis Care and Prevention. PLoS medicine. 2014;11(9):e1001693.
33. Pedrazzoli D, Houben R, Viney K, Lönnroth K. Beyond measurement: taking bold multisector actions towards zero catastrophic costs and suffering due to TB. The international journal of tuberculosis and lung disease. 2019;23(11):1236-.
34. van der Wielen N, Falkingham J, Channon AA. Determinants of National Health Insurance enrolment in Ghana across the life course: Are the results consistent between surveys? International Journal for Equity in Health. 2018;17(1):49.
35. Asuming PO. Getting the Poor to Enroll in Health Insurance, and its effects on their health: Evidence from a Field Experiment in Ghana. Job Market Paper–Columbia University. 2013.
36. Nyonator F, Kutzin J. Health for some? The effects of user fees in the Volta Region of Ghana. Health policy and planning. 1999;14(4):329-41.
37. Akazili J, Welaga P, Bawah A, Achana FS, Oduro A, Awoonor-Williams JK, et al. Is Ghana's pro-poor health insurance scheme really for the poor? Evidence from Northern Ghana. BMC Health Serv Res. 2014;14:637.
38. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983:41-55.
39. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behavioral Research. 2011;46(3):399-424.

Chapter 6: Financial burden for tuberculosis patients: beyond treatment outcomes

6.1 Preamble

In line with Objective (4) of this thesis, this chapter aimed to explore the potential impact of catastrophic payments for TB care on TB treatment outcome, and therefore addressed the fourth research gap identified by this PhD. In the paper that makes up this chapter, I present an analysis to illustrate the current methodological limitations of TB patient cost surveys to detect an association between costs incurred by TB patients and treatment outcomes, using data from completed national TB patient cost surveys, including data from the survey in Ghana. Finally, I discuss the relevance and appropriateness of this analyses in the context of TB patient cost surveys and people-centred care. This paper was submitted to Clinical Infectious Diseases at the time of submission of the thesis.

6.2 Cover sheet

The Research Paper Cover Sheet is enclosed on the following pages.

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
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Surname/Family Name	Pedrazzoli		
Thesis Title	The economic burden of tuberculosis and the mitigation effect of social protection: a population-based study in Ghana		
Primary Supervisor	Dr Rein Houben		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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SECTION E

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Date	17/08/2020

6.3 Abstract

The End TB Strategy calls for zero TB-affected families incurring 'catastrophic' costs due to tuberculosis (TB). Progress towards this target is measured through national surveys assessing the costs to patients associated with TB. As part of these surveys, country investigators may also seek to determine the potential impact of costs on TB treatment outcomes routinely collected for surveillance purposes, extracted from the TB register at the health facility.

In the present paper, we argue that the sample size of a TB patient cost survey is determined to optimise precision around the effect estimate of 'prevalence of catastrophic costs'. Thus, TB patient cost surveys are not powered to detect an association between costs incurred by TB patients and treatment outcomes. Limited heterogeneity in income and other socio-economic variables in the survey population poses an additional challenge to assessing this association. The lack of an association using data from TB patient cost surveys may not reflect the reality, but may result in countries drawing the wrong conclusions on the relevance of catastrophic costs for TB care and support.

We then examine potential pathways for the impact of patient costs and treatment outcomes, and argue that TB treatment outcomes as routinely measured and reported by national TB programmes for surveillance purposes, are not a good measure of treatment "success". While patients may be considered to have successfully completed TB treatment, the impact of TB is often far-reaching for many patients, and includes medical conditions, socio-economic consequences, stigma and disabilities.

Therefore, even if a "causal" relationship between TB related costs and treatment outcomes did exist, focusing on such a relationship may be misleading. The TB community should start looking at broader, people-centred outcomes, that take into account the impact of the disease on wider health-related and socio-economic dimensions of the patient (and their household), beyond treatment outcomes. We illustrate our argument using data from completed national TB patient cost surveys, including a previous study conducted in Ghana.

6.4 Manuscript

6.4.1 Introduction

While progress in tuberculosis (TB) control is undeniable, for many countries ending this old disease remains an aspiration rather than an imminent reality (1). The world's deadliest

infectious disease, TB disproportionally affects the most vulnerable and poor people in society. While anti-TB treatment is offered free of charge in many countries, contact with the health care system often still entails costs for the patients (2). These include the costs related to 1) formal and informal payments to health care providers for diagnostic and curative services (direct medical costs (3)), 2) transport costs and costs related to purchasing additional food (direct non-medical costs), and 3) opportunity costs of not being able to work during treatment (indirect costs or income loss) (2).

Aligned with the Sustainable Development Goals (SDGs) and policy efforts towards achieving universal health coverage and ensuring social protection, the World Health Organization's (WHO's) End TB Strategy has among its three targets that no TB patients or their households should face "catastrophic total costs" due to TB, defined as total TB-related costs exceeding 20% of pre-illness annual household income (4). Progress on this target is measured through periodic nationally representative facility-based surveys assessing TB patient costs (in shorthand "TB patient cost surveys"). Survey participants include drug-susceptible or drug-resistant (DR-) TB patients who have been on treatment for at least two weeks at sampled health facilities (5). In line with WHO's recommendations, an increasing number of such surveys have been conducted or are underway globally (1).

The primary focus of national TB patient cost surveys is to evaluate financial protection of TB patients (4). However, as part of a TB patient cost survey, investigators may also seek to determine the clinical importance of costs through assessing their potential impact on TB treatment outcomes. TB treatment outcomes for patients included in the surveys are collected for surveillance at the end of anti-TB treatment from the TB register at the health facility. Most national TB registers categorise TB treatment outcomes as: "cured", "treatment completed", "transferred out", "lost to follow-up", "failure" and "death" (6). In this paper, unfavourable (or adverse) treatment outcome is defined as patients who did not complete treatment because they died, were lost to follow up or had treatment failure. In the present paper, we refer to treatment outcomes as routinely measured and reported by national TB programmes for surveillance purposes.

Although it is plausible that catastrophic costs incurred by TB affected households may have clinical implications, and particularly that they may be independently associated with adverse TB treatment outcomes in TB patients, evidence to support this hypothesis is limited. A study among multi-drug resistant (MDR-) TB patients in Peru found a relationship between costs and unfavourable treatment outcomes (7), and a study in China between costs and treatment

adherence (8). Although the 20% catastrophic cost threshold endorsed by WHO was eventually set through expert opinion voting (5), it was initially informed by the study conducted in Peru, which showed that above this threshold, patients with TB were nearly twice as likely to experience adverse treatment outcome (OR = 1.7 [95% CI = 1.1–2.6], *P-value*=0.01) (4, 7). The WHO handbook on TB patient cost surveys recommends assessing the potential impact of costs on TB treatment outcomes as part of national TB patient cost surveys to help validate or change the threshold endorsed by WHO (4).

Current recommendations for TB patient cost surveys are to estimate the required sample size based on prevalence of catastrophic costs. In the present paper, we argue that the cost surveys may therefore not have sufficient power to detect an association between costs incurred by TB patients and treatment outcomes with appropriate precision. This poses challenges to drawing conclusions on the strength of the evidence supporting an association. We also highlight how the lack of heterogeneity in the survey population poses an additional challenge to assessing this association.

We then examine potential pathways for the effect of patient costs on treatment outcomes, and argue that TB treatment outcomes are not a good measure of treatment "success". Therefore, even if a causal relationship between TB patient costs and outcomes did exist, focusing on such an association may actually be misleading. The TB community should look beyond treatment outcomes, at broader, people-centred outcomes that take into account the detrimental effect of the disease on wider health-related and socio-economic dimensions of the patient (and their household). The End TB strategy's vision of zero suffering and financial hardship due to TB reflects the increasing recognition that traditional microbiologic markers and treatment outcomes, while undoubtedly linked to patients' quality of life, fail to represent the wider impact of the disease, and should be complemented by more holistic and people-centred strategies and related metrics.

We illustrate our argument using data from completed national TB patient cost surveys, including the 2016-2017 study in Ghana, where data on treatment outcomes for the patients enrolled in the survey were collected from TB registers.

6.4.2 Survey sample size

TB patient cost surveys are powered to ensure nationally representative precise estimates of the proportion of patients experiencing catastrophic costs (the primary outcome of these

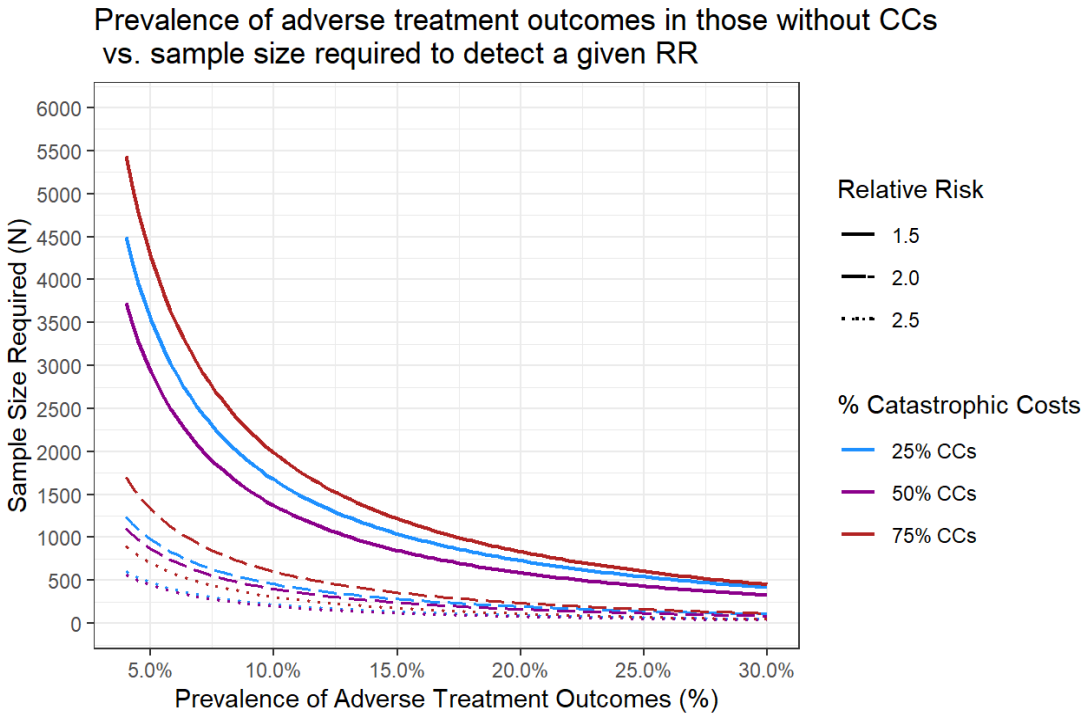
surveys). Sensitivity analysis below shows that the power to find an association between catastrophic costs and TB outcomes (and therefore avoid non-rejection of the null hypothesis of no association), is limited assuming an effect estimate of at least 1.5.

To illustrate this, we calculated the sample size which would be required to detect a difference (risk ratio or relative risk) between individuals experiencing catastrophic costs and those who do not. In our illustration, we employed effect sizes of 1.5, 2 and 2.5. However, there is to our knowledge no risk factor, except MDR-TB (9, 10) and untreated HIV (11), which would increase the risk of adverse outcome by a risk ratio of 2. Thus, risk ratio greater than 1.5 are unrealistic.

We also considered a prevalence of catastrophic costs at 25%, 50% and 75%, proportions commonly reported by completed national TB patient cost surveys, and a prevalence of unfavourable treatment outcomes ranging between 4% (lowest prevalence) and 30% (highest prevalence, excluding data for Angola), based on data from the 30 high-TB burden countries (1). The sample size was calculated using the formula and under the assumptions described in Annex B. Our analysis suggests that studies are likely to be underpowered to investigate an association between catastrophic costs and treatment outcomes, unless prevalence of unfavourable treatment outcome exceeds 15% (Figure 8), prevalence of catastrophic costs is approximately 50% and the effect size is 2.5.

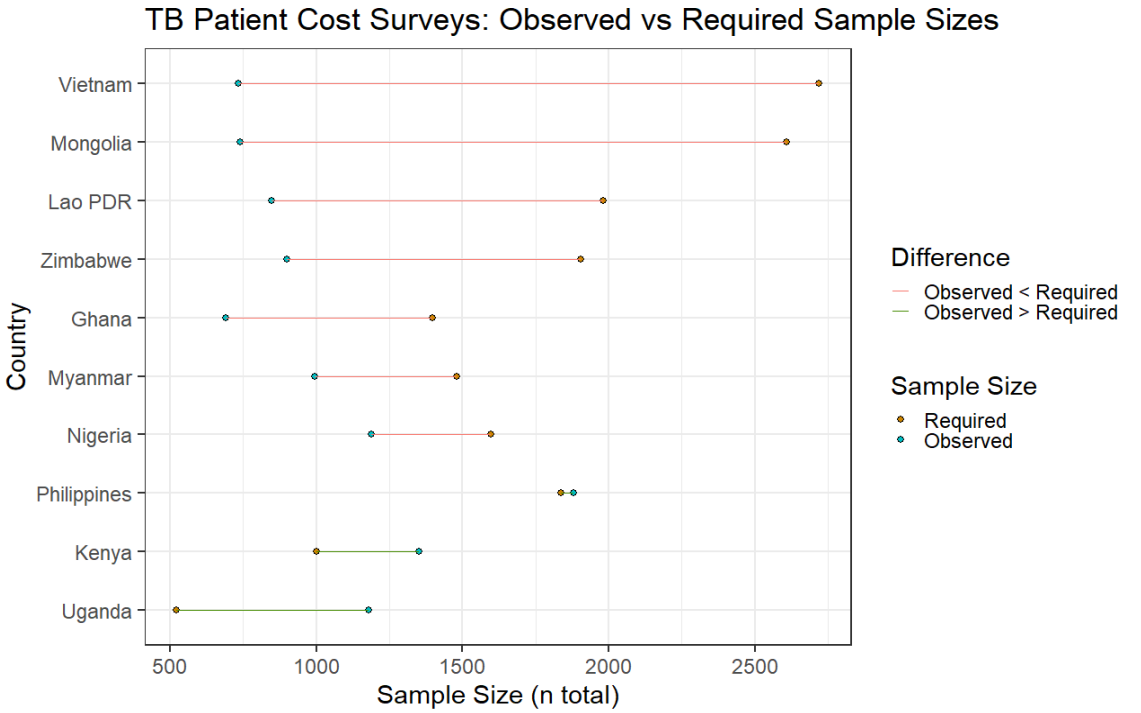
Yet, in most settings, TB-associated mortality in outpatients is <5% and loss to follow-up rarely exceeds 10% (1). The prevalence of catastrophic costs varies greatly between different countries, and is as low as 27% in Kenya and as high as 83% in Timor-Leste (1). Therefore, the sample size of most TB patient cost surveys is too small to detect an association between catastrophic costs and TB outcomes (assuming a relative risk of 1.5). To illustrate this, we calculated the sample size that would be required to detect a risk ratio of 1.5 between individuals facing catastrophic costs and those who do not, based on data from completed national TB patients cost surveys, and using the prevalence of adverse outcomes in these countries. Finally, we compared the estimated sample size to the actual sample size of these surveys (Annex B, Table B1). As shown in Figure 9, surveys were largely underpowered to investigate an association between catastrophic costs and treatment outcomes.

Figure 8: Required sample size (at 0.80 power) by prevalence of unfavourable outcome (range: 4%-30%), catastrophic costs (25%, 50% and 75%), to detect a risk ratio of 1.5, 2.0 and 2.5 between TB patients who experience catastrophic costs and those who do not



CC: catastrophic costs
RR: risk ratio or relative risk

Figure 9: Observed *vs.* required sample size (at 0.80 power) to detect a risk ratio of 1.5 between individuals facing catastrophic costs and those who do not in selected national TB patient cost surveys



In Ghana, where TB treatment outcomes were collected from TB registers for 97% (668/691) of patients enrolled in the survey, of which 8.7% (57/652) had an unfavourable treatment outcome (Annex B, Figure B1), we found no evidence of a difference in adverse treatment outcome between patients experiencing catastrophic costs and those who didn't (7.5% vs 11.0% respectively, *P-value*=0.121). For a study to be powered to investigate this association, a sample size of 1786 patients would have been required to detect a relative risk of 1.5 given the actual proportion of adverse outcomes in those who experienced catastrophic costs and in those who did not (9.9% vs 6.6%, respectively).

Another major limitation is the lack of heterogeneity among TB patients participating in TB patient cost surveys which makes it difficult to assess a potential impact of patient costs on treatment outcomes. Most TB patients belong to the poorest segments of society in the world's poorest settings. For example, the proportion of TB patients included in the TB patient cost survey in Ghana who were living below the poverty line was nearly double compared to the general population (12).

Moreover, among TB patients, heterogeneity in terms of their background characteristics and risk factors is very limited in resource constrained settings (13), and this is unlikely to differentially affect treatment outcomes. For example, in Ghana, there was no evidence of a difference in the monthly household income pre-TB diagnosis of patients who had an adverse treatment outcome (mean: US$ 219; median: US$ 145 [inter-quartile range (IQR): US$ 96-US$ 248]; standard deviation (SD): US$ 224), and of those who had a favourable treatment outcome (mean: US$ 215; median: 145 [IQR: US$ 80-US$ 241]; SD: US$ 305) (*P-value*=0.51).

Besides, the question of what would be a meaningful and relevant effect size has remained unanswered: what effect size would make policy makers adopt an intervention to reduce the burden of catastrophic costs with the aim to improve TB treatment outcomes? This leads on to another (maybe more important) question: does a reduction in catastrophic costs need any justification, such as improved TB treatment outcomes, given that the End TB strategy has among its three targets that no TB-affected families face catastrophic costs?

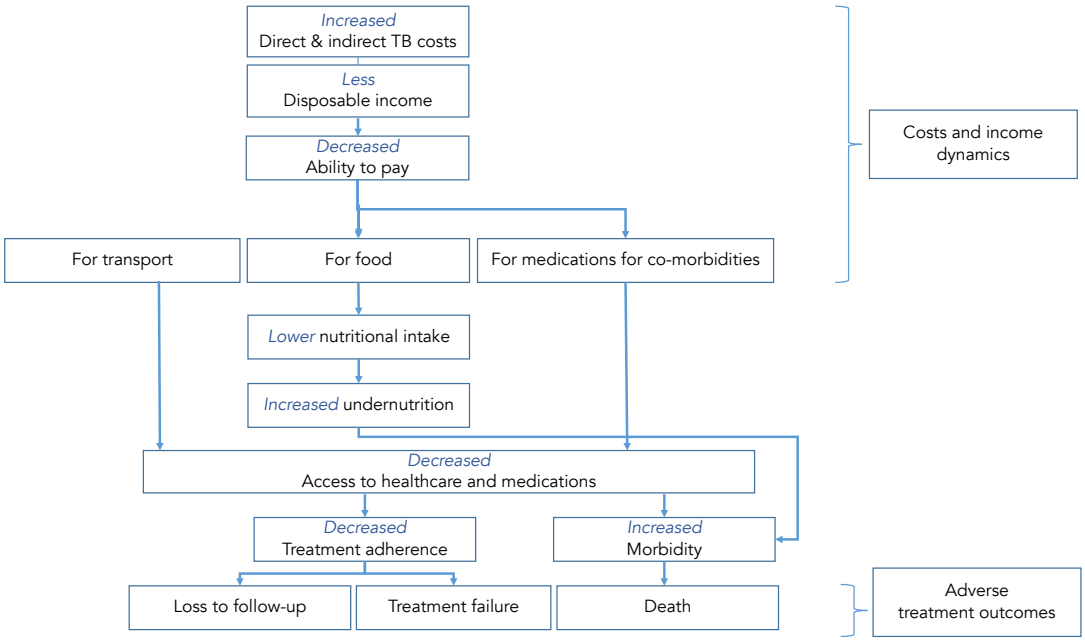
6.4.3 Pathways of impact

To further explore the challenges in drawing conclusions about the strength of the evidence supporting an association between catastrophic costs and adverse treatment outcomes, we attempted to disentangle the hypothetical mechanisms linking patient cost and treatment

outcomes. Higher (or catastrophic) TB related costs ("the exposure") may be associated with TB treatment outcomes ("the outcome") through a true direct/indirect causal relationship, or their association may be confounded. Of note, death, which is arguably the most important TB treatment outcomes, is an extreme event. While catastrophic costs may contribute to death, the process leading to death is usually multifactorial.

Causal relationship: increased TB related costs decrease a household's disposable income and/or assets. In turn, this may decrease the household's ability to pay for food, non-TB related health care costs (such as medications for co-morbidities like diabetes) or transport. While low nutritional intake may result in under-nutrition (low BMI) and nutritional deficiencies, it will only affect treatment outcomes if i) it results in death; ii) it causes loss to follow-up (the patient may be too weak to access health care); or iii) it affects treatment adherence in such a way that it leads to treatment failure (a rare event for drug susceptible TB). Inability to pay for non-TB related health care costs may prevent patients with co-morbidities such as HIV and/or diabetes (which are highly prevalent among TB patients) to access care and medications. This is likely to impact on morbidity, but would only lead to a measurable effect on TB outcomes if resulting in death and loss to follow-up. Unaffordable transport will affect TB outcomes by increasing the risk of loss to follow-up (Figure 10).

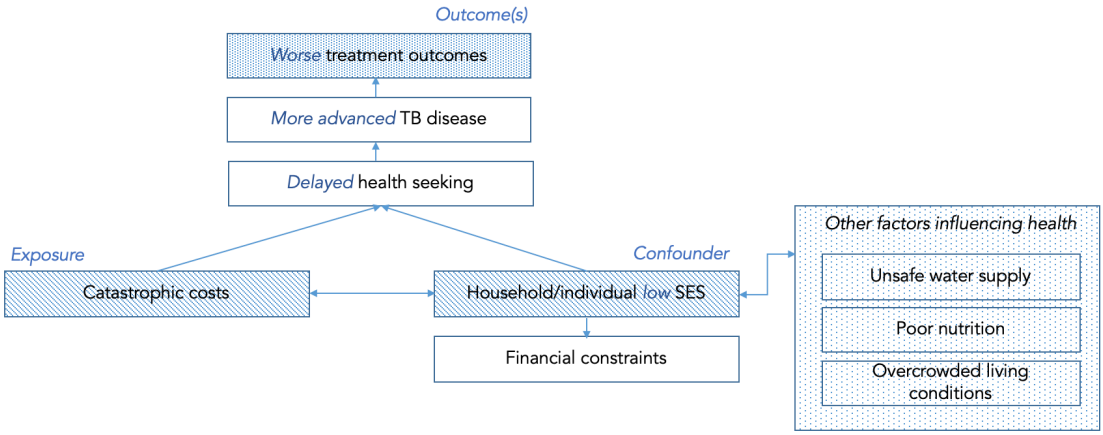
Figure 10: Framework for the potential causal relationship between TB-related costs and treatment outcomes



Confounding: Patient cost surveys have shown that patients living in households with the most constrained income are those most likely to experience catastrophic costs (14). These patients may also be more likely to delay health seeking due to financial constraints and may therefore

present with more advanced TB disease than those living in more affluent households. Other factors influencing health, such as overcrowding, unsafe water supply and poor nutrition are also likely to cluster among the poorest households (15, 16). Thus, any relationship between catastrophic costs and TB outcomes may primarily reflect the socio-economic condition of the patient and their household prior to starting TB treatment, rather than the direct impact of experiencing catastrophic costs (Figure 11).

Figure 11: **Framework for the potential confounding relationship between a household's socio-economic status and TB treatment outcomes.**



6.4.4 Discussion

We showed that the majority of TB patient cost surveys are not powered to detect an association relevant to policy between costs and treatment outcomes, based on current recommendations.

Further, we argued that the relationship between treatment outcomes and costs is not captured by treatment outcomes as routinely measured and reported for surveillance purposes as these metrics are too coarse, and death and loss to follow-up are extreme and rare events, particularly among patients with drug susceptible TB. The TB community should consider to move beyond traditional surveillance outcomes, that tend to overlook the impact of the disease on the livelihood, well-being and quality of life of TB patients and their families. Nonetheless, if countries are determined to investigate the association between costs and treatment outcomes guidance should be provided on how to adequately design such studies.

While patients may be considered to have successfully completed TB treatment, the consequences of the disease are often far reaching for many of them, and include medical conditions (e.g. chronic lung disease), mental health implications, socio-economic consequences, stigma and disabilities (17). Aligned with the End TB Strategy's focus on patient-

centred care and the SDGs, this calls for more meaningful outcomes that would take into account the impact of the disease on morbidity and on the livelihood of patients and their households, including vulnerability, food security, children's schooling and education, and socio-economic position. Then we would possibly be able to detect an effect of costs on outcomes, although the problem of confounding would remain. However, to capture a range of long term sequelae, very large sample sizes would likely be required, and longitudinal study designs rather than the cross-sectional design used for TB patient cost surveys are probably more suited to this purpose (18). TB patient cost surveys have the potential to inform policy and practice, but their current scope and methodology have clear limitations. Future research should expand the evidence base of the impact of financial hardship on more holistic outcomes and inform interventions to mitigate the health and socio-economic consequences of the disease.

6.4.5 Conclusions

National TB surveys are the first step towards documenting the financial hardship faced by TB patients, and ultimately towards achieving the goal of WHO's End TB Strategy, should findings from these surveys result into bold multi-sectoral actions,

Looking at the potential impact of TB-related costs on TB treatment outcomes as add-on and ad-hoc research in these surveys may be tempting, as treatment outcome data are easily available in TB treatment registers. However, there are two major arguments we should bear in mind. First, we should ponder the rationale for performing such analysis given all the limitations inherent to it (including defining what a meaningful effect would be), and the likelihood of obtaining results that are not precise.

Second, to meaningfully address the SDGs and ensure that TB patients are not mere survivors of their disease but they can actually enjoy good quality of life after treatment completion, a more holistic, patient-centred approach is warranted, together with a more comprehensive research agenda. This should naturally look at broader outcomes, that capture the health (e.g. morbidity, health-related quality of life), wellbeing and socio-economic (e.g. educational attainment, employment/return to work) consequences of TB for patients and their households/families, that extend beyond TB treatment completion. Simply achieving a modest reduction in adverse treatment outcomes should not be the goal of interventions addressing the financial hardship experienced by TB patients.

6.4.6 References

1. World Health Organization. Global Tuberculosis Report 2019. Geneva, Switzerland; 2019.
2. Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. The European respiratory journal. 2014;43.
3. Pedrazzoli D, Lalli M, Boccia D, Houben R, Kranzer K. Can tuberculosis patients in resource-constrained settings afford chest radiography? The European respiratory journal. 2016.
4. World Health Organization. Tuberculosis patient cost surveys: a handbook. Geneva, Switzerland2017.
5. Pedrazzoli D, Borghi J, Viney K, Houben R, Lonnroth K. Measuring the economic burden for TB patients in the End TB Strategy and Universal Health Coverage frameworks. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2019;23(1):5-11.
6. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014). Geneva.
7. Wingfield T, Boccia D, Tovar M, Gavino A, Zevallos K, Montoya R, et al. Defining catastrophic costs and comparing their importance for adverse tuberculosis outcome with multi-drug resistance: a prospective cohort study, Peru. PLoS medicine. 2014;11(7):e1001675.
8. Long Q, Smith H, Zhang T, Tang S, Garner P. Patient medical costs for tuberculosis treatment and impact on adherence in China: a systematic review. BMC Public Health. 2011;11(1):393.
9. World Health Organization. Global tuberculosis report 2013: World Health Organization; 2013.
10. Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, et al. Standard Short-Course Chemotherapy for Drug-Resistant TuberculosisTreatment Outcomes in 6 Countries. JAMA. 2000;283(19):2537-45.
11. Kwan CK, Ernst JD. HIV and tuberculosis: a deadly human syndemic. Clinical microbiology reviews. 2011;24(2):351-76.
12. Pedrazzoli D, Siroka A, Boccia D, Bonsu F, Nartey K, Houben R, et al. How affordable is TB care? Findings from a nationwide TB patient cost survey in Ghana. Tropical medicine & international health : TM & IH. 2018;23(8):870-8.
13. Boccia D, Hargreaves J, Ayles H, Fielding K, Simwinga M, Godfrey-Faussett P. Tuberculosis infection in Zambia: the association with relative wealth. The American journal of tropical medicine and hygiene. 2009;80(6):1004-11.
14. Fuady A, Houweling TAJ, Mansyur M, Richardus JH. Catastrophic total costs in tuberculosis-affected households and their determinants since Indonesia's implementation of universal health coverage. Infectious diseases of poverty. 2018;7(1):3.
15. Lienhardt C. From exposure to disease: the role of environmental factors in susceptibility to and development of tuberculosis. Epidemiologic reviews. 2001;23(2):288-301.
16. Addressing poverty in TB control: Options for national TB control programems. Geneva: World Health Organization; 2005.
17. Allwood B, van der Zalm M, Makanda G, Mortimer K. The long shadow post-tuberculosis. The Lancet Infectious diseases. 2019;19(11):1170-1.
18. Rachow A, Ivanova O, Wallis R, Charalambous S, Jani I, Bhatt N, et al. TB sequel: incidence, pathogenesis and risk factors of long-term medical and social sequelae of pulmonary TB - a study protocol. BMC Pulm Med. 2019;19(1):4.

Annex B

Figure B 1: Treatment outcomes collected as part of the TB patient cost survey in Ghana

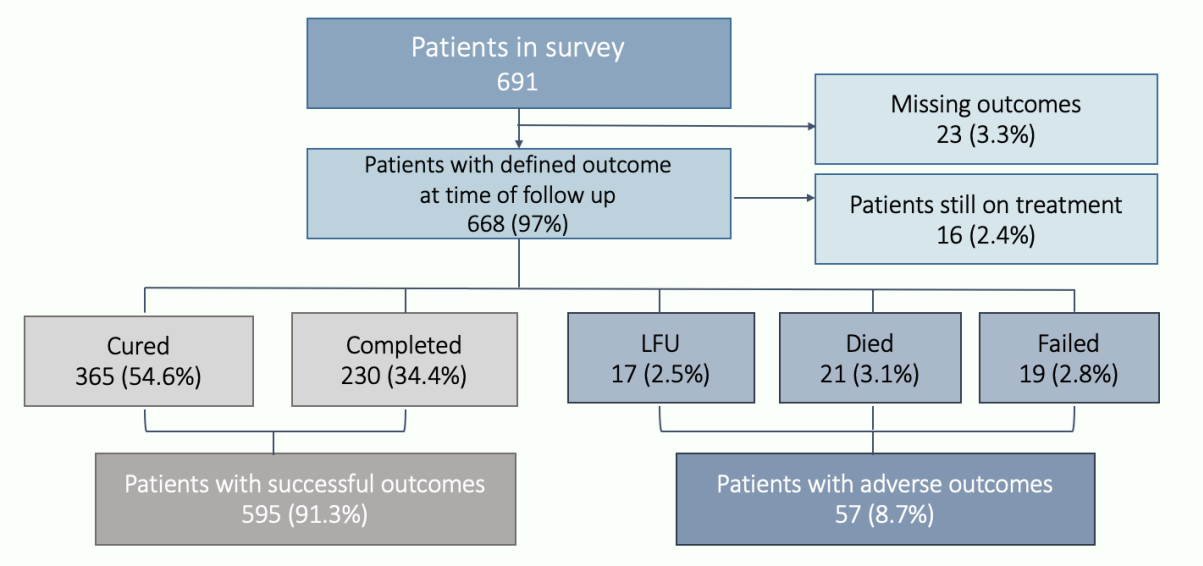


Table B 1: Observed and required sample size, rate of adverse events and catastrophic costs, in selected countries that completed a national TB patient cost survey

Country	Observed sample size (N)	Required sample size (N)	Adverse Event Rate (%)	Catastrophic costs (%)
Ghana	691	1397	15	64
Kenya	1353	1001	17	27
Mongolia	739	2608	9	70
Lao PDR	848	1980	11	63
Myanmar	996	1480	13	60
Nigeria	1190	1599	14	71
Philippines	1880	1836	9	35
Uganda	1181	523	28	53
Vietnam	735	2719	8	63
Zimbabwe	900	1905	17	80

Note on sample size calculations for Figure 8 & 9

Sample sizes displayed in Figure 8 and 9 were calculated based on the following formula:

$$\mathrm{N} = \frac{(r+1)^2 \cdot p_c(1-p_c) \cdot (z_\alpha + z_\beta)^2}{r(RR-1)^2 \cdot P_0^2}$$

Where:

N = total sample size required

r = the sampling ratio of those experiencing catastrophic costs to those not experiencing catastrophic costs (n1/n0; assumed 0.33, 1, and 3 in Figure 8; the observed sampling fraction was used in Figure 9)

za = the acceptable Type 1 error rate (assumed 0.05)

zb = the acceptable power (assumed 0.80)

RR = the relative risk to detect (assumed 1.5)

P0 = the proportion of adverse outcomes in the baseline group (no catastrophic costs; assumed 4% to 30% in Figure 8; the observed proportion experiencing adverse events in each group in Figure 9), and

pc = the approximate pooled proportion of adverse outcomes as given below:

$$p_c = \frac{n_1 RR \cdot P_0 + n2 \cdot P_0}{n_1 + n_2} = \frac{P_0(rRR + 1)}{r + 1}$$

Chapter 7: Conclusion

7.1 Introduction

This thesis set out to contribute to evidence on the financial hardship faced by TB patients and their households, and on the potential of social protection to help mitigate the financial impact of the disease. It addressed four knowledge gaps, each with a corresponding objective of the thesis. These are summarised in Table 15, together with the methods employed, the main findings and the areas for further research.

Focusing on the four knowledge gaps addressed by this thesis and its objectives, this final chapter briefly recalls the state of the evidence before the PhD, and summarises how research completed as part of it advances that area of research. It also discusses the policy implications of the thesis, presents priority next steps for further research, and ends with an overall concluding statement.

Table 15: Synopsis of the research gaps addressed by the thesis, its objectives, methods and main findings, and areas for future research

Research gap	PhD Objective	Method	Main findings	Chapter #
1. Lack of a comprehensive overview of key concepts for TB patient cost surveys, and how they are measured in the End TB Strategy *vs*. the UHC framework.	1. Summarise key measurable concepts for TB patient cost surveys, notably the types of costs that are captured and related affordability measures, and contrast them with the standard methods for measuring these constructs in the UHC framework.	Conceptual review of cost measurement and affordability metrics for the indicator of "catastrophic total costs due to TB" and "catastrophic spending on health"	The types of costs that are captured by TB patient cost surveys as part of monitoring the indicator of "*catastrophic total costs due to TB*" are direct (medical and non-medical) and indirect costs. The TB indicator is restricted to diagnosed TB patients who are on treatment at health services that are part of the NTP network. The indicator of "*catastrophic spending on health*" in the UHC framework is a population-based indicator that measures the share of the population incurring "catastrophic spending" on health, with a threshold defined as exceeding 10% and 25% of a household's total consumption expenditure or income. Health expenditures are defined as direct expenditures on medical care. The denominator of the UHC indicator includes also people who had no contact with the health system and thus had zero expenditures on health. Affordability measures include catastrophe and impoverishment metrics.	Chapter 2
2. Limited evidence on detailed costs, on costs as a proportion of income, and on affordability of TB care.	2. Provide further evidence on the level, and composition of costs incurred by TB-affected households and affordability of care.	a) Survey among TB experts on availability and cost of chest-radiography b) Nationally representative	a) Chest radiography is part of the routine diagnostic algorithm and follow-up in most countries participating in the survey. Patients have to pay for a chest	Chapter 3 & 4

		TB patient cost survey in Ghana	radiography examination in the public health service. The cost for a chest radiography varies between US$ 1.5 and US$ 42 (median US$ 7.8), and it is highest in African countries. b) Catastrophic costs affected 64.1% of TB patients in Ghana. Payments for TB care led to a significant increase in the proportion of households in the study sample that live below the poverty line at the time of survey compared to pre-TB diagnosis (59.8% *vs.* 45.6%).	
3. Limited knowledge on determinants of TB patient costs and on the potential impact of social protection on TB patient costs.	3. Investigate drivers and determinants of costs incurred by TB patients, and the potential impact of social protection on mitigating these costs.	Using data from the Ghana survey: a) Regression models were used to determine drivers of costs and affordability. b) Inverse Probability of Treatment Weighting Analysis was used to investigate the effect of enrolment into NHIS on costs	The poorest patients, those living in an urban setting, patients who lost their job and MDR-TB patients had increased odds of experiencing catastrophic costs. NHIS in its current form is not effective in defraying costs (average reduction in non-medical cost: US$ 126 (95% CI: -$33, US$ 285), and its expansion will not be effective to relieve the financial burden for TB-affected households.	Chapter 5
4. Limited evidence on the potential impact of TB related costs on TB treatment outcomes	4. Explore the potential impact of catastrophic payments for TB care on TB treatment outcomes, and discuss the relevance and appropriateness of this analysis.	Analysis of data from completed national TB patient cost surveys, including the Ghana survey.	Based on current recommendations, TB patient cost surveys are not powered to detect an association between costs incurred by TB patients and treatment outcomes. It is therefore challenging to make conclusions on the strength of the evidence supporting an association. Even if a causal relationship between TB related costs and outcomes did	Chapter 6

	exist, focusing on such a relationship may actually be misleading as the consequences of TB extend well beyond treatment completion ("Post-TB"), and are broader than surveillance outcomes. The TB community should look at broader, people-centred outcomes that take into account the impact of the disease on wider health-related and socioeconomic dimensions of the patient.
Areas for future research	
a) Evaluating the potential impact of social protection on affordability of TB care through dedicated studies. b) Assessing the impact of TB patient costs on treatment outcomes.	

7.2 Main findings

This PhD begets three key messages:

1) Despite the widespread norm of "free TB care" policies, TB care in LMICs is never free as TB patients and their households incur huge and disruptive costs.
2) The disruption caused by costs related to TB diagnosis and care has much wider consequences than just the treatment outcome, that span beyond treatment completion and affect the livelihoods of patients and their households at large.
3) Current TB control measures do not address these costs and the potential role of social protection not only as a poverty-reduction strategy, but also as a tool to improve disease control, should be fully harnessed to make TB care truly affordable and mitigate the consequences of the disease.

The contributions of this thesis to these core messages are recalled in the following sections in relation to each knowledge gap, objective of the PhD and the wider literature.

7.2.1 Measuring the economic burden for TB patients in the End TB Strategy and Universal Health Coverage frameworks

This chapter addressed Research gap #1 and PhD Objective #1.

This chapter provides the conceptual framework of the PhD. It reviews and defines core concepts of relevance to this thesis: costs and their measurement, and affordability. It also discusses the standard methods for measuring these constructs in the UHC framework and contrasts them with how they are measured in TB patient cost surveys (Table 1).

As an increasing number of TB patient cost surveys are being undertaken based on the WHO methodology, this paper also aimed to provide the TB community with a comprehensive description of the concepts and measurements that underlie the End TB Strategy indicator of 'zero catastrophic costs' due to TB. This framework will therefore advance research on affordability of TB care as well as country-level and global monitoring and reporting.

Further, this paper highlights the novel elements of this indicator in relation to approaches used in the UHC monitoring framework. In doing so, this paper shows how the End TB Strategy target is a first important step in broadening the concept and measurement of affordability to account

not only for medical costs but also for the broader economic impact of TB, including non-medical and indirect costs. As a result, these metrics are able to capture the total economic burden of TB on patients and their families, and have the potential to inform the design and implementation of both health care and social protection policies aiming to prevent both direct and indirect costs of care.

7.2.2 How affordable is TB care? Findings from a nationwide TB patient cost survey in Ghana

This chapter addressed Research gap #2 and PhD Objective #2.

This PhD was the first study that adopted and adapted the WHO methodology to undertake a national survey in a sub-Saharan African country. The study provided a detailed assessment of the level and nature of costs incurred by a large, nationally representative sample of TB patients, by drug resistance status. It computed the key measures of catastrophic health spending and impoverishment, described in the conceptual review (Chapter 2), to provide a comprehensive assessment of the affordability of TB care in Ghana.

Strikingly, this PhD found that the median (IQR) costs that TB patients incurred as a result of TB was US$ 455 (159.2–1059.2), which is three times greater than the median household annual income pre-TB diagnosis. As a result, nearly two-thirds of TB patients in Ghana incur catastrophic costs associated with TB care, and MDR-TB patients were pushed significantly further over the threshold for catastrophic payments than DS patients. Nearly half of the patients in the sample were living below the poverty line before TB diagnosis, and an additional 14.2% were pushed into poverty due to the disease.

This study also considered whether patients had to rely on savings, borrowing or selling assets (collectively termed: coping strategies) to pay for TB-related care. It found that over half of TB patients were unable to pay for TB treatment from existing income alone, and had to rely on coping strategies.

Finally, this thesis expanded on the WHO methodology by employing a prediction based approach to estimate missing costs, and by using household consumption expenditure instead of income to compute the catastrophic payment headcount metric. The regression-based approach led to lower levels of costs incurred, leading in turn to lower estimates of catastrophic

costs. Using annual household consumption expenditure instead of income gave fairly consistent results for the proportion of households experiencing catastrophic costs.

While there have been previous assessments of TB patient costs in LMICs (including in Ghana), common findings from four systematic reviews published between 2012 and 2015 of studies looking at TB patient costs were that the majority of studies were outdated, suffered from small sample sizes or focussed on specific sub-populations, and employed heterogeneous methodologies (1, 2). Further, most studies did not report costs as a proportion of income, nor did they measure affordability of TB care (3). This PhD contributed important evidence on TB patient costs and affordability on a nationally representative population sample, using and expanding the WHO methodology.

7.2.3 Does Ghana's National Health Insurance Scheme provide financial protection to tuberculosis patients and their households?

This chapter addressed Research gap #3 and PhD Objective #3.

Given the catastrophic costs incurred by TB patients identified in Chapter 4, this PhD also examined the drivers of these costs, and the effectiveness of social protection strategies in mitigating these costs. This thesis found that the poorest patients, those living in an urban setting, patients who lost their job and MDR-TB patients were more likely to experience catastrophic costs. These findings are consistent with those from other studies (4, 5).

A key contribution of this thesis is its assessment of the impact of social protection, in the form of national health insurance, on costs related to TB care as part of a national TB patient cost survey. Using Ghana as a case study, this PhD showed that even in countries with well-established state-supported health insurance schemes and free TB care policies, TB patients are at risk of incurring high costs when seeking and accessing TB care, and therefore insurance schemes are ineffective in protecting them against these costs. However, while the approach taken in this thesis is innovative, there are methodological limitations that hinder the possibility to evaluate the impact of social protection on affordability of TB care more conclusively. This is further discussed in Section 7.4.

While social protection strategies are formally recognised in the WHO End TB Strategy as a key instrument for preventing TB-affected households from experiencing financial hardship (6), evidence on this potential is growing but remains limited (7, 8). This knowledge gap has

prevented the swift translation of these new policy recommendations into effective interventions. The assessment of the effectiveness of NHIS in defraying TB patient costs undertaken as part of this PhD is the first of its kind, and contributes important evidence to support changes in policy and practice in Ghana and globally.

7.2.4 Financial burden for tuberculosis patients: beyond treatment outcomes

This chapter addressed Research gap #4 and PhD Objective #4.

While the body of literature pointing to a positive impact of social protection on TB treatment outcomes is growing (9-11), evidence on the direct impact of patient costs on treatment outcomes remains scanty (12). In addition to measuring the level and nature of patient costs, the WHO recommends assessing the potential impact of costs on TB treatment outcomes as part of national TB patient cost surveys to help validate the 20% catastrophic costs threshold endorsed by WHO, and also to provide evidence on the clinical implications of catastrophic costs.

Building on findings presented in Chapter 4, this thesis presents an analysis to illustrate the current methodological limitations of TB patient cost surveys to detect an association between costs incurred by TB patients and treatment outcomes. As, based on current recommendations, the study sample of a TB patient cost survey is determined by the prevalence of catastrophic costs, no a priori power calculations are made to evaluate the impact of TB costs on treatment outcomes. Therefore, this thesis shows that most completed TB patient cost surveys are underpowered to detect such an association, and thus it is not possible to evaluate this relationship more conclusively.

Finally, this thesis presents a reflection on the relevance of analysing the potential impact of costs on treatment outcomes, and argues that, even if a causal relationship between TB related costs and treatment outcomes did exist, focusing on such a relationship may actually be misleading as the consequences of TB extend well beyond treatment completion, and are broader than surveillance outcomes. It concludes that the TB community should look at broader, people-centred outcomes that take into account the impact of the disease on wider health-related and socio-economic dimensions of the patient.

7.3 Policy implications

Anchored in the 17 SDGs (13), in recent years TB control has placed its emphasis on the need to design and implement strategies to address the underlying social determinants of the disease, and to protect households from financial hardship due to seeking care (14).

Before this PhD, evidence on the affordability of TB care and on the potential of social protection strategies to provide financial protection was limited. This thesis contributed original findings that have fed into the development of the WHO's methodology to monitor progress towards the target of zero TB affected families facing catastrophic costs. More importantly, the evidence generated in this PhD led to policy change in Ghana.

Based on the survey findings, Ghana's National TB Control Programme (NTP) launched a national roadmap to eliminate TB patient costs in Ghana, which was developed through a multi-sectoral dialogue to identify policy recommendations and related priority actions, in partnership with representatives from the National Health Insurance Authority; the Ministry of Gender, Children and Social Protection; the Ghana Health Service; the Ghana AIDS Commission; the Ministry of Monitoring and Evaluation; representatives of TB patients and civil society; and local and international partners.

Detailed findings on the level and nature of costs incurred by patients allowed the formulation of policy action to address each single cost component. Findings on the extent of the impoverishing effects of the disease, made a strong case for considering TB patients indigent, which had two important policy implications.

First, to reduce direct medical costs, it was proposed that TB patients be included as one of the groups exempt from paying the NHIS premium under the category of indigent people. Second, to defray indirect costs, a key intervention area identified in the action plan was to expand existing social protection interventions to include TB patients, including their enrolment in LEAP, the national cash transfer programme targeting extremely poor and vulnerable households, by making TB one of the criteria for eligibility. In addition, the design of a social support package targeting the specific needs of TB patients, such as nutritional support and transport vouchers, was also agreed to be an important social assistance mechanism to support patients throughout their treatment (15).

At the time of writing this thesis, the exemption of TB patients from paying the NHIS premium had been effective since early 2019 (16), while discussions are still being held with the Ministry of Gender, Children and Social Protection on the expansion of LEAP to TB patients. In addition, the NTP is seeking to provide social support also to drug-sensitive patients as the Enabler's package currently only covers MDR-TB patients through funding from Global Fund to Fight AIDS, Tuberculosis and Malaria.

This thesis therefore sets an example of the potential of TB patient cost surveys to lead to interventions and policy changes that help reduce or mitigate costs incurred by TB patients; it also showed how assessing the most relevant and feasible interventions that can improve affordability of TB care should be integral to this process. This may inform future developments of the WHO's guidance on TB patient cost surveys (17).

While this thesis focused on Ghana, findings from across this PhD lend weight to the formulation of policy recommendations on strategies and interventions to protect TB patients from financial hardship globally.

7.4 Areas for future research

While this thesis provided new insight into each of the research gaps that it set out to fill, it was not able to address all of them completely. This was mainly due to methodological limitations, as discussed below. Priority areas for future research in this field stem from these limitations, and are presented in this section.

The major limitation of this PhD is the cross-sectional study design of the national TB patient cost survey in Ghana, which inevitably focuses on the economic consequences of TB using a measure at one point in time. It therefore fails to capture the long-term economic consequences of the disease for the individual and the household, including the impact on reduced labour supply and productivity, and household resilience, that span beyond the TB episode. This limitation inherent to the study design has implications on the ability of this thesis to evaluate the effectiveness of social protection strategies in mitigating TB patient costs, and to assess the potential impact of costs on treatment outcomes as well as broader socio-economic outcomes.

1. ***Evaluating the potential impact of social protection on affordability of TB care through dedicated studies***

This thesis employed a quasi-experimental design to assess the impact of NHIS on TB patient costs, but it failed to find conclusive evidence as TB patient cost surveys are not designed to assess the potential of social protection to protect TB patients from financial hardship.

Ideally, dedicated studies to evaluate the relationship between social protection and costs would take a longitudinal design, as well as a larger sample size (18, 19). They would repeat the measurement of both financial protection of study participants (level and composition of costs, catastrophic spending and impoverishment), and receipt of social protection over the course of TB treatment and after its completion. Several research studies that have adapted the WHO generic protocol to a longitudinal design, including for long-term follow-up after TB treatment, are now ongoing (19). These studies will also be helpful for the validation and interpretation of cross-sectional TB patient cost survey data.

In addition, recent changes to the NHIS resulting from the findings of the national TB patient cost survey conducted as part of this PhD that led to the exemption of TB patients from paying the NHIS premium (described in Section 7.3), provide further opportunities to generate evidence through rigorous evaluation of this novel intervention, and effectively improve access to care and provide financial protection to TB patients. Future impact evaluations with longitudinal or panel data could therefore use alternative quasi-experimental designs such as Difference in Differences (DiD) with matching.

2. ***Assessing the impact of TB patient costs on treatment outcomes***

Equally, dedicated longitudinal studies with an adequate sample size should be employed to assess the potential impact of TB patient costs on TB treatment outcomes. A first step would be to fully explore the potential pathways linking costs and treatment outcomes. Further, new outcomes and related metrics (beyond surveillance outcomes) should be identified to assess the impact of the financial burden of TB on patients and their households. As mentioned in Chapter 6, such outcomes would include medical conditions (e.g., chronic lung disease), mental health implications, stigma and disabilities, and also socioeconomic consequences, such as loss of livelihoods, vulnerability, food security, coping mechanisms, children's schooling and education.

7.4.1 Methodological developments for TB patient cost surveys

The methods employed in this PhD and its findings may inform future revisions of the WHO guidance on conducting TB patient cost surveys (17). For example, the prediction-based approach to estimate missing costs could be further developed, and provided to investigators as an alternative method to the imputation of the median costs (20).

The computation of all the metrics of affordability based on the concept of catastrophic TB-related expenditure (i.e., catastrophic payment gap in addition to the catastrophic payment headcount on which the TB indicator is based) and the concept of impoverishment due to TB-related spending (i.e., incidence of impoverishment and poverty gap) provided a comprehensive snapshot of the affordability of TB care in Ghana. All these indicators should be routinely computed and monitored as part of the analysis and reporting of TB patient cost surveys.

This PhD also used annual household consumption expenditure instead of income as a robustness check to compute the catastrophic payment headcount metric. While this is best practice in LMICs to estimate a household's ability to pay, this is not often used in TB patient cost surveys due to the length of expenditure modules. The appropriateness of an expenditure module to estimate household income should be further explored.

7.4.5 Concluding remarks

Evidence generated from this thesis provides original insights into affordability of TB care, lending weight to policy recommendations on financial protection for TB patients. This PhD has also shown both the potential and limitations of TB patient cost surveys to assess the impact of social protection strategies on costs, and of TB-related costs on treatment outcomes, thus calling for further methodological developments, and outlining a clear map for future research.

7.4.6 References

1. Ukwaja KN, Modebe O, Igwenyi C, Alobu I. The economic burden of tuberculosis care for patients and households in Africa: a systematic review. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2012;16(6):733-9.
2. Barter DM, Agboola SO, Murray MB, Barnighausen T. Tuberculosis and poverty: the contribution of patient costs in sub-Saharan Africa--a systematic review. BMC Public Health. 2012;12:980.

3. Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. The European respiratory journal. 2014;43.
4. Fuady A, Houweling TAJ, Mansyur M, Richardus JH. Catastrophic total costs in tuberculosis-affected households and their determinants since Indonesia's implementation of universal health coverage. Infectious diseases of poverty. 2018;7(1):3.
5. Ministry of Health. The first Kenya tuberculosis patient cost survey 2017. 2018.
6. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM. WHO's new End TB Strategy. Lancet. 2015;385.
7. Rocha C, Montoya R, Zevallos K, Curatola A, Ynga W, Franco J, et al. The innovative socio-economic interventions against tuberculosis (ISIAT) project: an operational assessment. The International journal of tuberculosis and lung disease. 2011;15(6):S50-S7.
8. Lonnroth K, Glaziou P, Weil D, Floyd K, Uplekar M, Raviglione M. Beyond UHC: monitoring health and social protection coverage in the context of tuberculosis care and prevention. PLoS medicine. 2014;11.
9. Richterman A, Steer-Massaro J, Jarolimova J, Nguyen LBL, Werdenberg J, Ivers LC. Cash interventions to improve clinical outcomes for pulmonary tuberculosis: systematic review and meta-analysis. Bulletin of the World Health Organization. 2018;96(7):471.
10. Andrade KVFd, Nery JS, Souza RAd, Pereira SM. Effects of social protection on tuberculosis treatment outcomes in low or middle-income and in high-burden countries: systematic review and meta-analysis. Cadernos de Saúde Pública. 2018;34.
11. Reis-Santos B, Shete P, Bertolde A, Sales CM, Sanchez MN, Arakaki-Sanchez D, et al. Tuberculosis in Brazil and cash transfer programs: a longitudinal database study of the effect of cash transfer on cure rates. PloS one. 2019;14(2).
12. Wingfield T, Boccia D, Tovar M, Gavino A, Zevallos K, Montoya R, et al. Defining catastrophic costs and comparing their importance for adverse tuberculosis outcome with multi-drug resistance: a prospective cohort study, Peru. PLoS medicine. 2014;11(7):e1001675.
13. Lönnroth K, Raviglione M. The WHO's new End TB Strategy in the post-2015 era of the Sustainable Development Goals. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2016;110(3):148-50.
14. Lönnroth K, Glaziou P, Weil D, Floyd K, Uplekar M, Raviglione M. Beyond UHC: Monitoring Health and Social Protection Coverage in the Context of Tuberculosis Care and Prevention. PLoS medicine. 2014;11(9):e1001693.
15. World Health Organization. Global Tuberculosis Report 2018. Geneva, Switzerland; 2018.
16. Pedrazzoli D, Houben R, Viney K, Lönnroth K. Beyond measurement: taking bold multisector actions towards zero catastrophic costs and suffering due to TB. The international journal of tuberculosis and lung disease. 2019;23(11):1236-.
17. World Health Organization. Tuberculosis patient cost surveys: a handbook. Geneva, Switzerland2017.
18. Wingfield T, Tovar MA, Huff D, Boccia D, Montoya R, Ramos E, et al. The economic effects of supporting tuberculosis-affected households in Peru. European Respiratory Journal. 2016.
19. Rachow A, Ivanova O, Wallis R, Charalambous S, Jani I, Bhatt N, et al. TB sequel: incidence, pathogenesis and risk factors of long-term medical and social sequelae of pulmonary TB - a study protocol. BMC Pulm Med. 2019;19(1):4.
20. Pedrazzoli D, Siroka A, Boccia D, Bonsu F, Nartey K, Houben R, et al. How affordable is TB care? Findings from a nationwide TB patient cost survey in Ghana. Tropical medicine & international health : TM & IH. 2018.

Appendices

Appendix 1: Modelling the social and structural determinants of tuberculosis: opportunities and challenges

Preamble

This paper presents work done as part of the TB Modelling and Analysis Consortium (TB-MAC) expert meeting on modelling the social and structural determinants of TB which was held in October 2015 in New York City, and reflects the renewed interest in measuring the socioeconomic impact of disease on patients and their household. This paper was published in the International Journal of Tuberculosis and Lung Disease in 2017, and it is reproduced as follows with no revisions or adaptation from the published manuscript.

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Cover sheet

The Research Paper Cover Sheet is enclosed on the following pages.

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

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Surname/Family Name	Pedrazzoli		
Thesis Title	The economic burden of tuberculosis and the mitigation effect of social protection: a population-based study in Ghana		
Primary Supervisor	Dr Rein Houben		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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SECTION E

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Date	17/08/2020

Summary

Introduction: Despite the close link between tuberculosis (TB) and poverty, most mathematical models of TB have not addressed underlying social and structural determinants.

Objective: To review studies employing mathematical modelling to evaluate the epidemiological impact of social determinants of TB.

Methods: We systematically searched PubMed and personal libraries to identify eligible papers. We extracted data on modelling techniques employed, research question, type of structural determinants modelled, and setting.

Results: From 232 records identified, we included eight articles published between 2008 and 2015; six employed population-based dynamic TB transmission models and two non-dynamic analytic models. Seven studies focused on proximal TB determinants (four on nutritional status, one on wealth, one on indoor air pollution, and one examined overcrowding, socioeconomic and nutritional status), and one focused on macroeconomic influences.

Conclusions: Few modelling studies have attempted to evaluate structural determinants of TB, resulting in key knowledge gaps. Despite the challenges of modelling such a complex system, models must broaden their scope to remain useful for policy making. Given the inter-sectoral nature of the interrelations between structural determinants and TB outcomes, this work will require multi-disciplinary collaborations. A useful starting point would be to focus on developing relatively simple models that can strengthen our knowledge regarding the potential effect of structural determinants on TB outcomes.

Manuscript

Introduction

Tuberculosis (TB) is widely recognised as a disease of poverty (1-3) with disproportionate disease burden falling on the poorest in society and the most vulnerable communities. The need to design and implement comprehensive strategies to achieve TB elimination through universal health coverage and interventions to address the underlying social determinants of TB is a key element of the World Health Organization's (WHO's) End TB strategy for 2015-2035 (4, 5).

The targets and indicators of this new TB action framework are anchored in the 17 Sustainable Development Goals (SDGs) that were adopted by the United Nations and that mark the global

development agenda that began on 1 January 2016. By placing their emphasis on the interdependence and synergies between socioeconomic development and health (6), these offer unique entry points for addressing the social determinants (SDs) of TB.

In the present paper, we follow the definition of SDs of health of the WHO Commission on Social Determinants of Health (7): "the structural determinants of TB are those conditions that generate or reinforce social stratification (e.g. socio-economic inequalities, population growth, urbanisation), and therefore give rise to unequal distribution of key social determinants of TB epidemiology, such as poor housing, poverty and malnutrition, which in turn influence exposure to risk, vulnerability and ability to recover after developing the disease (8). These definitions are shown in Table 1.

Table 1: Structural and social determinants, and social protection: definitions and examples

Term	Definition	Examples
Structural determinants	Those factors that generate or reinforce socio-economic stratification in the society and that defines the differential distribution of risk factors in a given population (7). Structural determinants are also referred to as upstream or distal factors.	Global socioeconomic inequalities, high level of population mobility, rapid urbanisation, population growth, macroeconomic policies, social protection policies (including welfare, social protection, labour legislation, education), socioeconomic position
Social determinants	All those material, psychological and behavioural circumstances linked to health and generically indicated as 'risk factors' in the conventional epidemiological language (7). Social determinants are also referred to as downstream, proximal factors or intermediary determinants.	Poor housing and environmental conditions, food insecurity and malnutrition, alcohol consumption, smoking, drug consumption, co-morbidities (e.g. HIV/AIDS, diabetes, mental health), imprisonment
Social protection	All public and private initiatives that provide income or consumption transfers to the poor, protect the vulnerable against livelihood risks, and enhance the social status and rights of the marginalised; with the overall objectives of reducing the economic and social vulnerability of poor, vulnerable and marginalised groups (23). At least four types of interventions fall under this definition: social transfers (such as food, cash and inputs); public works programmes (food for work and cash for work); education and vocational training; and financial resources (micro-credit, savings and insurance).	Bolsa Familia, Ghana National Health Insurance, Intervention with Microfinance for AIDS and Gender Equity (IMAGE) in South Africa (24)

Quantitative analytical tools such as mathematical modelling can play an important role in informing the End TB Strategy, evaluating the impact of novel poverty-reduction interventions nested in its vision (including in combination with existing biomedical tools), and exploring the contribution of socioeconomic drivers to the epidemic. However, to do so, TB models will inevitably need to expand their focus beyond diagnosis and treatment to incorporate SDs, but the potential of modelling as well as its main limitations in supporting this research agenda remain unclear.

In the present paper, we report findings from a systematic review of the literature which we carried out with the aim to provide an overview of the current state of knowledge in the field of mathematical modelling of social and structural determinants of TB. We then go on to discuss key methodological challenges and gaps in empirical evidence that existing mathematical models need to overcome to be able to incorporate SDs and remain relevant to policy-making.

Methods

Search strategy and selection criteria

For the purposes of this review "mathematical model" was defined based on that envisaged by Garnett *et al* (9) as mechanistic representations for how disease burden is established. This includes both dynamic transmission and decision (non-dynamic) analytic models.

We searched PubMed for any relevant article on modelling and socio-economic determinants of TB (e.g., nutrition, crowding, poverty). The full search string is included in Table 2. Titles and abstracts were screened for eligibility. Articles were eligible for full-text review if they were written in English (due to limited resources), the target population was human individuals and mathematical modelling assessed the epidemiological impact of the SDs of TB.

Table 2: Full search string for literature review in the PubMed database

Search Term Group		
Modelling	**Tuberculosis**	**Social/structural determinants of TB**

((mathem AND (model OR models)) OR (mathem* modell*) OR (mathem* modelling) OR (modeling OR modelling)) OR "Populations dynamics" OR "System dynamics" OR "Computer simulation" OR microsimulation)) AND*	TB OR tuberculosis OR "Tuberculosis"[Mesh]	*OR "Populations dynamics" OR "System dynamics" OR "Computer simulation" OR microsimulation)) AND ((socioeconomic OR socio-economic OR social OR structural) AND (determinant* OR driver* OR factor* OR protection OR status)) OR poverty OR poor OR deprivation OR ("gross domestic product" OR GDP) OR migration OR wealth OR "financial crisis" OR "economic recession" OR poor OR inequalit* OR under-nutrition OR undernutrition OR nutrition OR malnutrition OR incarceration OR prison OR crowding OR "air pollution"))* [Mesh]

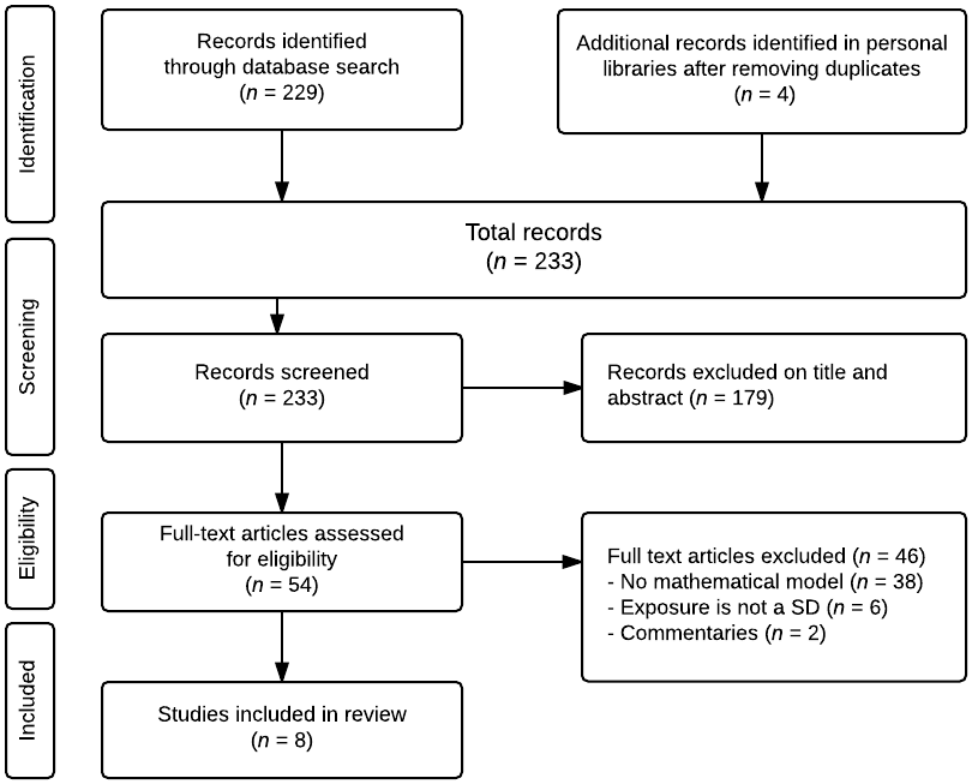
We excluded systematic reviews, epidemiological studies that did not use mathematical modelling techniques and ecological analyses looking at SDs of TB. The search focused on socio-economic factors (i.e., the intervention or exposure involving a socio-economic factor), and excluded studies focusing only on diabetes mellitus (DM), the human immunodeficiency virus (HIV) and behavioural risk factors such as alcohol consumption and smoking unless their association with socio-economic factors were also considered. We applied no restrictions as to the year.

Additional relevant articles were identified in the authors' personal libraries and are included in the review. DP selected the papers with support from RMGJH, DB and KL; data were extracted by DP and RMGJH.

Data abstraction and synthesis

Figure 1 presents details of the selection process. The aim of the study, first author and publication dates, type and feature of the model, the socioeconomic factor, the setting and the main findings were extracted into a pre-designed form. We focused on a qualitative synthesis of the methods employed in the articles we identified.

Figure 1: Systematic review flow chart for selection of papers



Results

A total of 229 unique records were found in the literature search, and four additional articles were added from the authors' personal libraries. Of these, 54 underwent full-text evaluation. After full-text screening, we included eight articles, published between 2008 and 2015, with four articles published in 2015 only. Table 3 gives the main features of the selected studies (12-19).

Table 3: Summary of studies identified in the systematic review

Ref	Aim of the study	Key socioeconomic factors investigated	Mathematical modelling methods/Type and features of the simulation model	Setting	Conclusion(s)
(10) (Reeves, 2015)	To project the potential influence of the economic recession on TB epidemiology in Europe until 2030.	Government expenditure per capita on public health services. GDP and cumulative decline in GDP during the recession period as a measure of the severity of the recession	Dynamic model SLIR (susceptible-latent-infectious-recovered) model. Authors applied the findings from the preceding econometric models to dynamic mathematical models of TB transmission and mortality. The mathematical models simulated longitudinal TB rates in each country – given the data on case detection observed before, during and after the financial crisis – as well as a counterfactual scenario in which case detection was unaffected by either the recession or the related austerity.	Europe	Recession can lead to short-term reductions in the financial support of programmes for TB control. The associated decrease in the detection of TB is projected to result in sustained, long-term rises in TB incidence, prevalence and mortality.
(15) (Andrews, 2015)	To illustrate the role of social mixing in shaping disparities in the distribution of TB, and demonstrate how the concentration of disease risk and transmission among the poor presents challenges and opportunities for TB control	Wealth	Dynamic Deterministic, compartmental model with parallel structure for two wealth groups with varying parameters, contact rates and social mixing.	India	TB control efforts may benefit from preferential targeting toward the poor.
(16) (Lin, 2008)	To predict the effects of risk-factors trends on COPD, lung cancer and TB	Smoking, solid fuel use	Dynamic Dynamic TB transmission model: deterministic compartmental (SLIR)	China	Reducing smoking and solid-fuel use can substantially reduce predictions of COPD and lung cancer burden and would contribute to effective TB control in China (even when DOTS implementation is less effective)

(11) (Oxlade, 2015)	To project future trends in TB related outcomes under different scenarios for reducing under-nutrition in the adult population in the Central Eastern states of India	Under-nutrition	Dynamic Compartmental TB transmission model stratified by body mass index (BMI) parameterised using national and regional data from India (model population is stratified into four exposure levels defined by the mean BMI for each quartile).	India	Intervening on under-nutrition could have a substantial impact on TB incidence and mortality in areas with high prevalence of under nutrition
(14) (Ackley, 2015)	To explore the population-level effects of malnutrition and genetic heterogeneity in TB susceptibility on TB epidemics	Malnutrition, genetic heterogeneity	Dynamic Dynamic TB transmission model: deterministic compartmental susceptible-latent-infectious-recovered model.	First Nations community in Canada	I) Changes in a population's nutritional status can have significant effects on TB dynamics II) Inclusion of heterogeneity in susceptibility to *M.tb* infection or risk of TB disease yields improved fit to data
(17) (Bhunu, 2012	To assess the impact of socioeconomic conditions on TB transmission, taking into account heterogeneous mixing patterns.	Socioeconomic conditions (overcrowding, increased endogenous reactivation, reduced socioeconomic status, reduced treatment uptake and poor nutrition on TB dynamics).	Dynamic Dynamic TB transmission model: deterministic compartmental Susceptible-Exposed-Infectious-Recovered model	Zimbabwe	Poverty enhances TB transmission as overcrowding, poor nutrition, reduced treatment uptake and lower socioeconomic status worsen TB; therefore, TB transmission rates are higher in poor communities than in the rich ones.
(12) (Odone, 2014)	I) To review epidemiological and biological evidence to describe the relationship between TB, diabetes, and nutritional status. II) To review past trends, present burden, and available future global projections for diabetes, overweight and obesity, as well as undernutrition and food insecurity.	Diabetes, overweight and obesity, undernutrition and food insecurity	Non-dynamic Analytical model to estimate the effect of diabetes and undernutrition on TB incidence per person per year in different age groups, WHO regions, and over time in various scenarios.	World	Reduction of undernutrition and better prevention and care for diabetes combined with improved access to prevention of infection, quality diagnosis, and treatment for all people with TB, could produce a large preventive effect on TB and is crucial to reach the post-2015 TB targets.

	III) To estimate how different scenarios of future trends for diabetes and undernutrition could affect TB epidemiology until 2035				
(13) (Dye, 2011)	To explore the consequences for TB epidemiology and control of changes in BMI, diabetes, population age structure and urbanization in India and Korea	BMI, diabetes, population age structure and urbanization	Non-dynamic Analytical model	India, Republic of Korea	The combination of nutritional and demographic changes operating over the decade from 1998 tended to increase TB incidence per capita in high-burden India and reduce it in lower-burden Korea.

Socio-economic factors investigated. The study by Reeves et al. (10) was the only one that looked at the impact of distal determinants (i.e., government expenditure per capita on public health services, gross domestic product (GDP) and cumulative decline in GDP, as a measure of the severity of an economic recession on TB control. The remainder modelled proximal TB determinants: four focused on nutritional status (body mass index [BMI] and undernutrition) (11-14), one on wealth (15), one on smoking and indoor air pollution (16), and one on nutritional status, overcrowding and socio-economic status (17). All studies looked at one factor at a time, with the exception of the study by Dye et al., which also explored the combined effect of nutritional status and demographic changes (including age structure and urbanisation) on TB incidence.

Modelling methods, structure and parameters. Compartmental population-based dynamic TB transmission models were the most common simulation approach employed in the selected articles (6/8, 75%); two studies used non-dynamic analytical models and both investigated the effect of both DM and nutritional status on TB epidemics. Most studies included a conceptual framework to illustrate the mechanics of the models and the hypotheses behind their research questions.

Transmission models employed standard SLIR ("Susceptible-Latent-Infectious-Recovered") models that were adapted to explore the research question set in each study: the model by Oxlade et al., for example, was stratified by levels of undernutrition by wealth quartile. Andrews et al. implemented a parallel structure for two wealth groups to a standard TB model to explore the benefit of assortative mixing to interventions targeting the poor, highlighting the potential importance of including mixing parameters in TB models even if data are currently not available to inform these models.

With regard to model parameters, Ackley et al. explored changes in differences in susceptibility to infection and progression to disease in hypothetical scenarios (14). Different levels of BMI drove changes in reactivation and progression parameters in the model by Oxlade et al. (11). The study by Reeves et al. used an econometric analysis to estimate changes in relevant model parameters controlling case detection (10). Bhunu et al divided the population into "rich" and "poor" communities, and compared the reproduction numbers for these two strata (Appendix Table A) (17).

Data on the different exposures were mainly drawn from the literature (12, 14), national population-based surveys (11, 13, 15, 16), or publicly available databases (10). Very few data

employed in these studies were local or regional. The majority of studies were calibrated to TB data (e.g., incidence trends or point estimates) from WHO estimates.

Key findings of the modelling studies. The studies in our review support the notion that TB control is linked to and would benefit from action on TB social determinants. Reeves et al. found that a decrease in funding to control TB due to an economic recession (distal factor) can lead to a decline in TB case detection, and consequently to higher TB rates (10). Lin et al. showed that interventions on smoking and indoor air pollution (proximal factors) can accelerate TB decline (16). The studies that focused on nutritional status (proximal factor) found that reducing undernutrition would substantially reduce TB incidence. Andrews et al. showed that preferential targeting of the poor can benefit TB control (wealth as proximal factor) (15). From the analysis of reproduction numbers for the poor and rich communities, Bhunu et al. found that overcrowding, poor nutrition, lower socioeconomic status (proximal factors) and reduced TB treatment uptake worsened TB transmission (17). Finally, the study by Dye et al. concluded that a combination of nutritional and demographic changes (proximal factors) operating over the decade from 1998 tended to increase TB incidence per capita in high-burden India and reduce it in lower-burden Korea (13).

Discussion

This review has highlighted the paucity of mathematical modelling studies looking at the effects of socio-economic factors on TB pathogenesis and epidemiology, but has also shown that, although fairly recent, work in this field seems to be growing as the number of articles published has increased from 2011 onwards. This is possibly a reflection of changing policy priorities that are now part of the End TB Strategy.

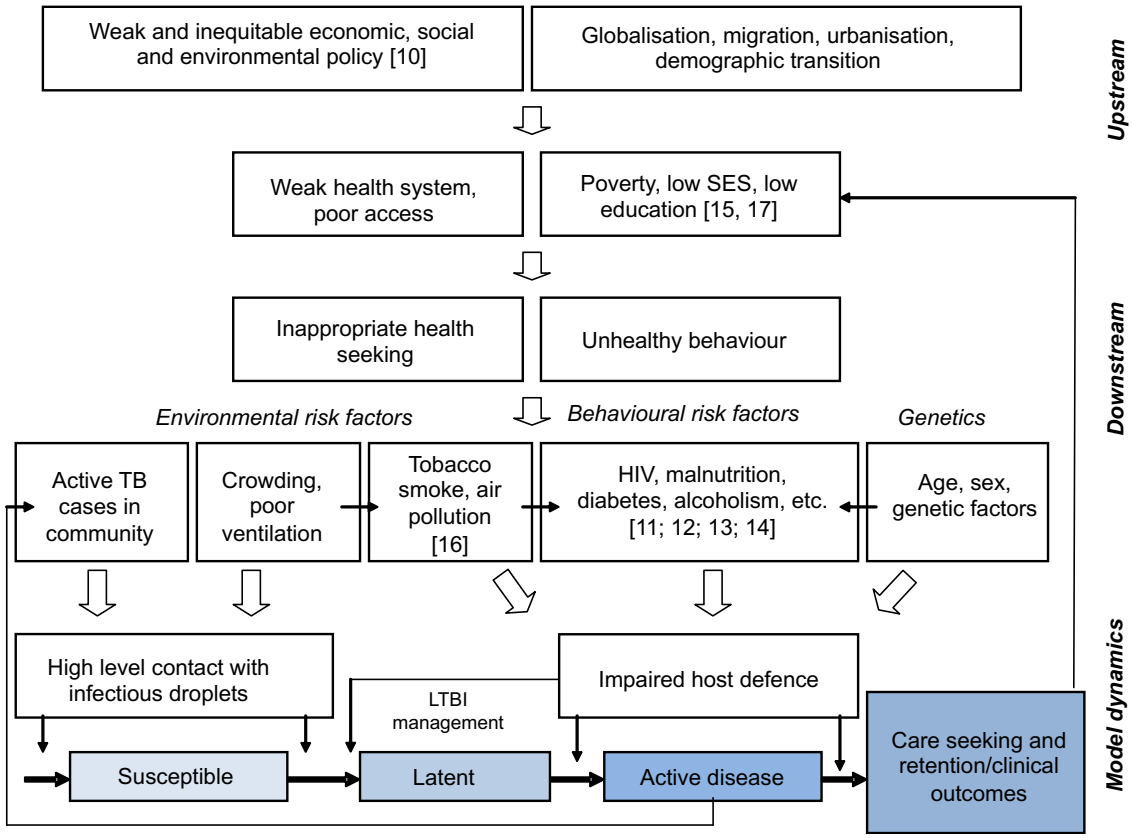
Our findings point to the need, at this stage, to develop relatively simple models that improve and expand the current body of work to incorporate available evidence and strengthen our knowledge of the potential effect of SDs on TB outcomes. For instance, most models focused on one or two factors only, and those that considered two factors did not account for possible interactions between these. It is to be noted that most mathematical modelling studies focussed on assessing the effect of nutritional status and changes in BMI on TB epidemiology. This is not surprising as undernutrition has long been acknowledged as a key socially determined TB risk factor. We found no modelling work looking at the impact of improved socioeconomic macro-indicators on TB outcomes, or of social protection interventions targeting TB patients and their households. With respect to proximal risk factors, only one model assessed the effect of

crowding on TB epidemiology, possibly a reflection of the fact that data on crowding and TB are not rich enough to unpick causality for a model.

Challenges in translating from determinant to model

The narrow focus of past global health and development policies and TB control strategies only partly explains why TB modelling has so far shown some reluctance to include SDs. This has also been due to the real and perceived weaknesses in the empirical evidence needed to populate models and quantify the pathways from socio-economic factors to changes in the natural history of TB in a population. Figure 2 provides a conceptual framework that outlines how distal/structural determinants (such as macro-economic policies), work through a potential array of more proximal determinants (e.g., crowding and nutrition), which in turn affects the dynamics of a standard mechanistic TB model at multiple points (18, 19), such as the intensity of transmission (through crowding) or the rate of progression after recent and/or latent infection (e.g., through nutrition).

Figure 2: Framework for proximate risk factors, upstream determinants and TB mechanics.



Source: Adapted from Lönnroth et al, 2009

This framework provides an example of the complexity when considering SDs in TB models, and it illustrates the complicate cascade of parameters from distal to downstream determinants affecting

development of disease, and care and prevention. Studies identified during the literature review are in square brackets.

While there are some data to inform parts of, for example, the pathway from macro-economic policies (e.g., GDP) to TB incidence (10), our ability to quantify the exact relationship of each step remains limited. However, it should be noted that the same limitations apply to current TB models, ranging from capturing the impact of HIV, or, when models look to evaluate the potential impact of interventions, including current approaches to improving case detection and reducing patient delay, or future hypothetical tools (20, 21).

When translating the effect of changing a socio-economic determinant into a mechanistic model, it does not suffice to have an estimate of the magnitude of the effect (see examples in Table 4). One needs to know, or make assumptions about, the model parameters that should be changed to achieve the estimated impact. As illustrated in Figure 2, changes in disease risk may be due to influences at one or several of the stages on the pathway between exposure and disease that are captured by transmission models. As direct evidence is often still lacking, this means that choices need to be made based on biological plausibility.

Table 4: Known relationships between proximal determinants and risk of developing TB disease

Proximal determinant	Relative risk of TB disease	References
HIV infection	2-20, 1.4 per 100 cells/mm^3 decrement in CD4	Corbett, 2013 (25) Sonnenberg, 2005 (26) Williams, 2005 (27)
Low BMI	1.14 per decrement in BMI	Lönnroth, 2010 (28)
Diabetes	2-4	Jeon, 2008 (29) Stevenson, 2007 (30)
Alcohol use (>40g/day)	2-5	Lönnroth, 2008 (31) Rehm, 2009 (32)
Smoking	1-5	Bates, 2007 (33) Lin, 2007 (34)
Indoor air pollution	1-6	Lin, 2007 (34) Sumpter, 2013 (35)

The range of these potential model parameters includes those directly capturing the intensity of transmission, e.g., social mixing or crowding in households, but also parameters guiding progression to disease after infection, which can be affected, for example, by nutritional status.

It is also plausible that different paths to progression (primary, reactivation, reinfection) are affected at different stages of the pathway. In addition, any interventions that reduce barriers to care and treatment completion will change model parameters capturing the time to diagnosis as well as retention in care (e.g., alcohol and drug abuse).

In addition to effects on incidence, SDs may alter the natural history of disease (e.g., reduced infectiousness and disease duration in people living with HIV) or disease outcomes (e.g., HIV, undernutrition, DM and smoking). Clustering of these risk factors for behavioural or biological reasons, requires an understanding of their interactions, and further increases the level of knowledge required. Finally, separating out composite phenomenological quantities into their mechanistic components may also improve transferability between settings if the data to quantify how these components differ are available.

Conclusions and recommendations

Mathematical modelling is a powerful and flexible tool to inform policy discussions and estimate the potential impact of various interventions relative to one another (9). However, to be useful, models need to be able to reflect the relevant aspects of the epidemic and address the questions faced by policymakers. In the SDGs and End TB Strategy era, this means that mathematical models of TB must translate the impact of socio-economic determinants into their mechanistic components. As a starting point, the TB modelling community should use the existing scientific evidence to construct relatively simple mechanistic models that add to our understanding of the effect of SDs on TB, and help improve specific policy decisions.

As we showed in this article, there exists a scarcity of TB models that include SDs, but also a small but increasing body of work that has explored initial ideas. Some modelling of proximal risk factors and related public health interventions has been done, but, for example, this has never moved upstream. TB models can leverage the existing data, and highlight the value of collecting those that are missing, such as the exact link between changes in nutritional status and changes in progression to disease, or the relationship between transmission intensity and living environments (e.g., urban slums compared with rural settings).

To further our knowledge, projects are urgently needed that advance the field while avoiding the pitfall of developing overly complex models that include population or pathway structures not adequately supported by empirical evidence or fully understood. In addition, the complexity of the pathways involved and the multisectoral nature of new approaches to end TB evidently

require collaborations from different disciplines, including social scientists, epidemiologists, economists, policymakers as well as mathematical modellers (11). While recognising the importance of such projects but at the same time the struggle to identify suitable funding opportunities for such cross-disciplinary collaborative work, the TB Modelling and Analysis Consortium organised a meeting at the end of 2015 to discuss existing experiences and the potential path forward. A range of projects was developed that would both advance the field and be feasible given current data (22). Two of these projects have been funded, preliminary results were produced the end of 2016 and publications are under review: an interdisciplinary project looking at how social protection interventions can accelerate TB elimination (the Social Protection to Enhance the Control of TB Consortium, S-PROTECT), and a project assessing the relative contribution of TB programme (DOTS) expansion and improvements in socio-economic indicators on TB epidemiology in China.

In this article, we highlighted that the literature on mathematical modelling of social determinants of TB remains limited. We argue that to maintain its key role in policy discussions in the era of the SDGs and End TB Strategy, the TB modelling community needs to embrace the technical challenges to adequately represent the interplay between TB and its socio-economic drivers. While some work is underway, more funding, data and capacity are urgently needed to ensure TB modelling remains a useful tool for the ultimate goal of TB elimination.

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References

1. Hoa NB, Tiemersma EW, Sy DN, Nhung NV, Gebhard A, Borgdorff MW, et al. Household expenditure and tuberculosis prevalence in VietNam: prediction by a set of household indicators. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2011;15(1):32-7.
2. Lonnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. Social science & medicine (1982). 2009;68(12):2240-6.
3. RJ D. The White Plague: Tuberculosis, Man, and Society: New Brunswick, NJ: Rutgers University Press; 1987.
4. The End TB Strategy. Geneva, Switzerland: World Health Organization, 2015.
5. Boccia D, Pedrazzoli D, Wingfield T, Jaramillo E, Lönnroth K, Lewis J, et al. Towards cash transfer interventions for tuberculosis prevention, care and control: key operational challenges and research priorities. BMC Infectious Diseases. 2016;16:307.
6. Lönnroth K, Raviglione M. The WHO's new End TB Strategy in the post-2015 era of the Sustainable Development Goals. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2016;110(3):148-50.
7. CSDH. Closing the gap in a generation: health equity through action on the social determinants of health. Final Report of the Commission on Social Determinants of Health. Geneva, Switzerland: World Health Organization, 2008.
8. Rasanathan K, Sivasankara Kurup A, Jaramillo E, Lonnroth K. The social determinants of health: key to global tuberculosis control. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2011;15 Suppl 2:S30-6.
9. Garnett GP, Cousens S, Hallett TB, Steketee R, Walker N. Mathematical models in the evaluation of health programmes. The Lancet.378(9790):515-25.
10. Reeves A, Basu S, McKee M, Sandgren A, Stuckler D, Semenza JC. Tuberculosis control and economic recession: longitudinal study of data from 21 European countries, 1991-2012. Bulletin of the World Health Organization. 2015;93(6):369-79.
11. Oxlade O, Huang CC, Murray M. Estimating the Impact of Reducing Under-Nutrition on the Tuberculosis Epidemic in the Central Eastern States of India: A Dynamic Modeling Study. PloS one. 2015;10(6).
12. Odone A, Houben RM, White RG, Lonnroth K. The effect of diabetes and undernutrition trends on reaching 2035 global tuberculosis targets. The lancet Diabetes & endocrinology. 2014;2(9):754-64.
13. Dye C, Bourdin Trunz B, Lonnroth K, Roglic G, Williams BG. Nutrition, diabetes and tuberculosis in the epidemiological transition. PloS one. 2011;6(6):e21161.
14. Ackley SF, Liu F, Porco TC, Pepperell CS. Modeling historical tuberculosis epidemics among Canadian First Nations: effects of malnutrition and genetic variation. PeerJ. 2015;3:e1237.
15. Andrews JR, Basu S, Dowdy DW, Murray MB. The epidemiological advantage of preferential targeting of tuberculosis control at the poor. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2015;19(4):375-80.
16. Lin H-H, Murray M, Cohen T, Colijn C, Ezzati M. Effects of smoking and solid-fuel use on COPD, lung cancer, and tuberculosis in China: a time-based, multiple risk factor, modelling study. The Lancet. 2008;372(9648):1473-83.
17. Bhunu CP, Mushayabasa S, Smith RJ. Assessing the effects of poverty in tuberculosis transmission dynamics. Applied Mathematical Modelling. 2012;36(9):4173-85.
18. Dowdy DW, Dye C, Cohen T. Data Needs for Evidence-Based Decisions: A TB Modeler's "Wish List". The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2013;17(7):866-77.

19. Houben RMGJ, Lalli M, Sumner T, Hamilton M, Pedrazzoli D, Bonsu F, et al. TIME Impact – a new user-friendly tuberculosis (TB) model to inform TB policy decisions. BMC Medicine. 2016;14(1):1-10.
20. Abu-Raddad LJ, Sabatelli L, Achterberg JT, Sugimoto JD, Longini IM, Jr., Dye C, et al. Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. Proceedings of the National Academy of Sciences of the United States of America. 2009;106(33):13980-5.
21. Dye C, Glaziou P, Floyd K, Raviglione M. Prospects for tuberculosis elimination. Annual review of public health. 2013;34:271-86.
22. TB Modelling and Analysis Consortium. TB MAC 7 Report: Modelling socio-economic determinants and interventions for TB 2015 [Available from: http://tb-mac.org/Content/Meetings/15/26/TB-Mac Meeting 7 Report 2015_12_05 - Final.pdf
23. Devereux S S-WR. Transformative social protection. Brighton: Institute of Development Studies, University of Sussex: Institute of Development Studies, University of Sussex, 2004.
24. Hargreaves J, Hatcher A, Strange V, Phetla G, Busza J, Kim J, et al. Process evaluation of the Intervention with Microfinance for AIDS and Gender Equity (IMAGE) in rural South Africa. Health education research. 2010;25(1):27-40.
25. Corbett EL, Watt CJ, Walker N, et al. The growing burden of tuberculosis: Global trends and interactions with the hiv epidemic. Archives of Internal Medicine. 2003;163(9):1009-21.
26. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. How Soon after Infection with HIV Does the Risk of Tuberculosis Start to Increase? A Retrospective Cohort Study in South African Gold Miners. Journal of Infectious Diseases. 2005;191(2):150-8.
27. Williams BG, Granich R, Chauhan LS, Dharmshaktu NS, Dye C. The impact of HIV/AIDS on the control of tuberculosis in India. Proceedings of the National Academy of Sciences of the United States of America. 2005;102(27):9619-24.
28. Lonnroth K, Williams BG, Cegielski P, Dye C. A consistent log-linear relationship between tuberculosis incidence and body mass index. Int J Epidemiol. 2010;39(1):149-55.
29. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS medicine. 2008;5(7):e152.
30. Stevenson CR, Forouhi NG, Roglic G, Williams BG, Lauer JA, Dye C, et al. Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. BMC Public Health. 2007;7.
31. Lönnroth K, Williams B, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis - a systematic review. BMC Public Health. 2008;8.
32. Rehm J, Samokhvalov AV, Neuman MG, Room R, Parry C, Lönnroth K, et al. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. BMC Public Health. 2009;9(1):450.
33. Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR. Risk of tuberculosis from exposure to tobacco smoke: A systematic review and meta-analysis. Archives of Internal Medicine. 2007;167(4):335-42.
34. Lin H-H, Ezzati M, Murray M. Tobacco Smoke, Indoor Air Pollution and Tuberculosis: A Systematic Review and Meta-Analysis. PLoS medicine. 2007;4(1):e20.
35. Sumpter C, Chandramohan D. Systematic review and meta-analysis of the associations between indoor air pollution and tuberculosis. Tropical medicine & international health : TM & IH. 2013;18(1):101-8.

Appendix

Table A: Summary of model structure and parameters employed in the studies included in the review

Study	Model structure			Parameters employed to capture the effect of socioeconomic factors
	Dynamic	Non-dynamic	Description	
Reeves et al, 2015 (10)	•		SLIR (Susceptible-Latent-Infectious-Recovered) deterministic compartmental model. Authors applied the findings from the preceding econometric models to dynamic mathematical models of TB transmission and mortality. The mathematical models projected TB incidence rates in each country (given the data on case detection observed before, during and after the financial crisis) as well as a counterfactual scenario in which case detection was unaffected by either the recession or the related austerity.	Parameter: diagnostic rate *(the rate (%/year) that TB cases get diagnosed per year).* Quantitative relationship: authors used the cumulative fall in GDP during the recession associated with falling case detection rates (from regression analysis, -0.22%) and applied it to dynamic models as a reduction in diagnosis rate.
Oxlade et al, 2015 (11)	•		SLIR (Susceptible-Latent-Infectious-Recovered) deterministic model. Compartmental TB transmission model stratified by body mass index (BMI) parameterised using national and regional data from India (model population is stratified into four exposure levels defined by the mean BMI for each quartile).	Parameter: rapid progression and reactivation rates by BMI stratum. Quantitative relationship: Relative risks of TB disease by BMI status directly applied to rapid progression and reactivation parameter values in each BMI stratum, i.e. relative risk of two for disease implemented as double the value for rapid progression and reactivation parameter values.
Lin et al, 2008 (16)	•		SLIR deterministic compartmental model. Smoking and indoor air pollution are introduced into the model by stratifying the	Parameter: Transmission and progression to disease.

			model population into the four possible combinations of exposure to these risk factors, proportional to their actual (time-varying) prevalence in each of the nine Chinese province considered.	Quantitative relationship: Relative risks from systematic reviews, applied to specific strata. Effect on prevalence of latent infection applied as change in transmission.
Ackley et al, 2015 (14)	•		SLIR deterministic compartmental model for historical TB epidemics amongst First Nation populations in Canada.	Parameters: rapid progression to disease, reactivation, TB specific mortality, immunity. Quantitative relationship: model sampled from a range of relative risks of 1-3 to find fit to data.
Andrews et al, 2015 (15)	•		SLIR deterministic compartmental model. Parallel model structure for two wealth classes (poorer and wealthier), based on TB epidemic in India.	Parameter: mixing between wealth classes Quantitative relationship: hypothetical scenarios of differential mixing between wealth classes.
Bhunu et al, 2011 (17)	•		SEIR (Susceptible-Exposed-Infectious-Recovered) deterministic compartmental model. The model subdivides the population into 'rich' and 'poor' strata, which is defined according to health status and living conditions. Poverty-stricken individuals are defined as those who live in overcrowded living situations, suffer from poor health, are less likely to receive treatment and who have an increased risk of death from TB.	Parameters: contact rate, transmission upon contact, progression to disease, treatment access, death due to TB. Quantitative relationship: Theoretical scenarios where being poor leads to a higher probability of TB or death, and lower probability of accessing treatment.
Odone et al, 2014 (12)		•	Analytic model where change in TB incidence is directly estimated based on prevalence of diabetes and undernutrition, and relative risk of disease given that risk factor. Authors estimate	Parameter: prevalence of diabetes and/or undernutrition. Quantitative relationship: Relative risk of TB

			the effect of diabetes and undernutrition on TB incidence per person per year in different age groups, WHO regions, and over time in various scenarios.	disease for diabetes and undernutrition.
Dye et al, 2011 (13)		•	Analytic model where change in TB incidence is estimated based on changes in prevalence of diabetes, BMI and urbanization in India and Korea from 1998 to 2008.	Parameter: prevalence of diabetes, undernutrition, and urbanization. Quantitative relationship: Relative risk of TB disease for diabetes and undernutrition.

Appendix 2: Survey protocol

Assessing the financial burden of tuberculosis on tuberculosis-affected households

Study protocol

London School of Hygiene and Tropical Medicine
Ghana National TB Control Programme
Dodowa Health Research Centre

Abbreviations

BMI	Body Mass Index
DCP	Data Coordination Platform
GFATM	The Global Fund to Fight AIDS, Tuberculosis and Malaria
KNCV	Koninklijke Nederlandse Centrale Vereniging tot bestrijding der Tuberculose
MDR-TB	Multi-drug resistant tuberculosis
NTP	National Tuberculosis Control Programme
TIME	TB Impact Model and Estimates
TB	Tuberculosis
UHC	Universal Health Coverage
USAID	United Sates Agency for International Development
WHO	World Health Organization

Executive summary

Even when tuberculosis (TB) care is free, the economic burden of illness due to TB can be devastating, due to the costs of seeking and staying in care for the six months to two years necessary for full treatment for TB or multidrug-resistant TB. Such costs can create access and adherence barriers that can affect health outcomes and increase risk of disease transmission. These costs can also contribute to the economic burden of households. In low- and middle-income countries, TB patients face costs that on average amount to half their annual income.

One of the three targets for the End TB Strategy (2016-2020) is that no TB patient or their household should face catastrophic costs due to TB, and this target should be achieved by 2020. This target is in line with policy efforts to move health systems closer to universal health coverage (UHC) because TB cannot be eliminated without addressing the barriers to uptake and completion of needed treatment.

In 2013, Ghana undertook a national TB prevalence survey which showed a generalised epidemic that is four times higher than previously estimated. Barriers to access, including direct non-medical costs, such as costs for travel and food during health seeking, must be investigated and addressed to ensure effective delivery of TB care interventions, and ultimately contribute to reduction in burden of disease.

This study primarily aims to assess the magnitude and main drivers of patient costs in Ghana to inform the design of policies and interventions to minimise barriers for accessing and adhering to TB care, and mitigate the economic impact of diagnosed TB for patients and their families.

This is a cross-sectional study. All patients attending treatment at the health facilities within the twenty-five selected clusters will be randomly selected and interviewed once through structured questionnaires until the required sample size is reached.

1. Background and rationale

Tuberculosis (TB) patients often incur large costs related to illness, as well as to seeking and receiving health care. Such costs can create access and adherence barriers which can affect health outcomes and increase risk of transmission of disease. These costs can also contribute to the economic burden of households. In low- and middle-income countries, TB patients face costs that on average amount to half their annual income (1). In all settings, TB affects the poorest segments of society. The poverty-aggravating effects of TB are therefore gravest for those that are already most vulnerable.

While out-of-pocket medical expenditures are important, lost income is often the dominant contributor to economic hardship. Direct non-medical costs, such as costs for travel and food during health seeking are also significant given the often long health seeking period and the six months to two years' period of treatment (1).

To overcome access and adherence barriers, as well as to minimise the economic burden for TB patients (and their households) it is therefore essential to address both direct and indirect costs. Interventions are needed to address high medical costs, as well as costs of food and transport, and lost earnings. Therefore, both health financing and delivery models, as well as social protection mechanisms (such as job protection, paid sick leave, social welfare payments, or other transfers in cash or kind) need to be considered (2) (3).

One of the three targets for the End TB Strategy is that no TB patient or their household should face "catastrophic total costs" due to TB, and this target should be achieved by 2020 (4). This target is in line with policy efforts to move health systems closer to universal health coverage (UHC) because TB cannot be eliminated without addressing the barriers to uptake and completion of needed treatment, an important aspect of service coverage. The share of the population incurring "catastrophic expenditures" (expenditures beyond a defined threshold of a household's capacity to pay) is one measure of financial protection that is commonly used as an indicator of progress towards UHC (2) (5). The TB-specific indicator of "catastrophic total costs" is different from the population-based indicator of "catastrophic expenditures" because it incorporates both direct medical payments for treatment, direct non-medical payments (such as transportation, lodging charges) and indirect costs, such as income losses. The TB-specific indicator is also restricted to a particular population: diagnosed TB patients treated in National TB Control Programme (NTP) networks. Furthermore, the objective of the TB-specific measure is to identify and reduce barriers to treatment adherence and not, strictly speaking, to measure financial protection for households.

Reducing direct and indirect costs related to TB care will contribute to improvements in treatment adherence and in financial protection. Thus, the planned work to assess the magnitude of patient costs and identify the main cost drivers can be used to monitor financial barriers to adherence and inform related health and social policy changes to improve TB control. This perspective is essential because, given the nature of the TB treatment protocol, reforms to the health financing system alone are unlikely to be sufficient to enable the diagnosed TB-affected population to overcome fully the barriers to successful completion of treatment. Action on the demand-side is essential, such as e.g. extension of certain social protection mechanisms to ensure treatment success for people in the informal sector and the vulnerable population groups that comprise most of the TB affected population. Reforms to service delivery strategies are likely also needed in many settings to reduce direct and indirect costs associated with care-seeking. Another potential benefit of implementing this type of survey is that it can also inform the development of more in-depth operational research to investigate identified problems and to evaluate proposed solutions.

Countries are recommended to assess the composition and magnitude of these direct and indirect costs through periodic health facility-based surveys. This is complementary to other needed assessments of local and national TB epidemiology, health seeking, and health care and social service coverage and bottlenecks for TB patients. Such assessments are a fundamental part of the End TB Strategy, which stresses the need for national adaptation based on the local epidemiological and health systems situation (4).

1.1. Study setting: Ghana

Ghana represents an ideal setting to implement this survey. It is one of the few countries that piloted the Tool to Estimate Patients' Costs which was developed by WHO and KNCV in 2008 (6). Findings from this study (which was conducted in conjunction with Dodowa Health Research Centre) were instrumental in including pro-poor strategies in the delivery of TB care interventions.

In 2013, Ghana undertook a national TB prevalence survey which showed a generalised epidemic that is four times higher than previously estimated (7). While this survey has allowed more precise prevalence estimates, the catastrophic costs indicator is new and as such it requires urgent assessment to establish baseline data and estimate the contribution of costs to the TB patient and to TB control overall, thereby enabling the Government to address demand-side cost barriers, which may be done through a range of interventions including improving financial access to care, extending patient-centred care delivery models that reduce time needed for care-seeking, and social protection interventions to mitigate loss of earnings due to care-seeking.

For over a year, the LSHTM/TIME team has been providing technical assistance to the Ghanaian NTP during the implementation and re-programming of the Global Fund TB grant under the USAID's Treat TB funding stream. It is expected that findings from this study will inform the application to the next round of funding to GFATM, and the design of policies and interventions to minimise barriers for accessing and adhering to TB care and mitigate the economic impact of diagnosed TB for patients and their families.

Lastly, findings from this study will serve as the basis for further research to examine the determinants of cost barriers amongst the diagnosed TB patient population, and to assess the effectiveness of policies and interventions to mitigate these costs.

2. Study objectives

2.1 Primary objectives

1. To document the magnitude and main drivers of patient costs in Ghana in order to guide policies on cost mitigation and delivery model improvements for the purpose of reducing financial barriers to access and adherence.

2. To determine the percentage of diagnosed TB patients treated in the NTP network (and their households) in the country who incur direct and indirect costs beyond a defined threshold of their annual income.

3. To determine the correlation between facing costs above different thresholds of annual household income and the borrowing or selling assets to finance health care expenditure ("dissaving"), in order to assess if the measure of dissaving is a valid proxy metric of catastrophic total costs.

2.2 Secondary objectives

1. To determine the association between costs incurred by TB patients and TB treatment outcomes amongst patients included in the survey.

   Rationale: In Ghana, despite progress over the last decade, the prevalence of adverse treatment outcomes remains unacceptably high. We hypothesise that TB patients experiencing catastrophic health expenditure have less favourable treatment outcomes than patients who do not. This in turn would increase mortality and morbidity, and exacerbate transmission in the community.

2. To investigate whether TB patients identified through screening of clinic attendees incur lower or higher TB related costs compared to patients who are identified through passive case finding, and experience different treatment outcomes.

   Rationale: Ghana is rolling out an intensified case finding strategy at health centres nationwide. We hypothesise that intensified case finding may reduce patient costs related to TB diagnosis and treatment by shortening the time to diagnosis and the time to treatment initiation. This in turn could improve treatment outcomes.

3. To assess the nutritional status of TB patients (in terms of BMI) and explore its association with levels of TB related costs incurred by the patients.

   Rationale: The NTP estimates that about half of TB patients have poor nutritional status but no data are currently available to support this hypothesis. We would like to assess the proportion of TB patients included in the survey who are malnourished and assess whether this is associated with the level of TB related costs they incur.

4. To help design a standardised approach for periodic measurements of financial barriers to adherence based on baseline experience and to enable reporting on the 2020 End TB Strategy target that no family affected by TB will incur total (direct and indirect) catastrophic costs.

3. Methods

3.1 Study design: Cross sectional survey with retrospective data collection and projections

This study will adopt a cross-sectional design where all consecutive TB patients registered for treatment who are attending a sampled facility for a follow up visit (after a minimum of 2 weeks into the present intensive or continuation treatment phase) should be invited to participate in the survey.

Each patient will be interviewed **once** and will report on expenditures retrospectively. Some patients will be interviewed during the intensive treatment phase and others in the continuation treatment phase, with expenditure and time loss data collected for that particular phase only. Moreover, within these two categories, patients will be interviewed at different time points during their treatment. Data collection for patients in different treatment phases will allow the collection of data that can be used to impute data and inform model projections of future and past costs during the entire illness episode.

The survey instrument has six parts. These are illustrated in Figure 1 and their content described in Table 1.

Table 1: Purpose and content of the five components of the survey instrument

Survey tool component	Content
Part I	Patient information to be obtained from TB treatment card before interview (for all patients)
Part II	Informed consent, inclusion/exclusion criteria, and checklist for which parts of the questionnaire to fill for different patients treated under different TB treatment categories and phases (for all patients)
Part III	Overview of TB treatments before current treatment, up to 2 years before the current treatment started (for re-treatment cases only)
Part IV	Costs before the current TB treatment (for new cases interviewed in the intensive phase only)
Part V	Cost during current TB/MDR-TB treatment (for all patients)
Part VI	Treatment outcomes of patients enrolled in the survey to be obtained through follow up conversation with clinic staff

Information from the TB treatment card (Part I), informed consent (Part II), information about costs related to the current TB treatment (Part V) and about treatment outcomes (Part VI), will be collected for all patients.

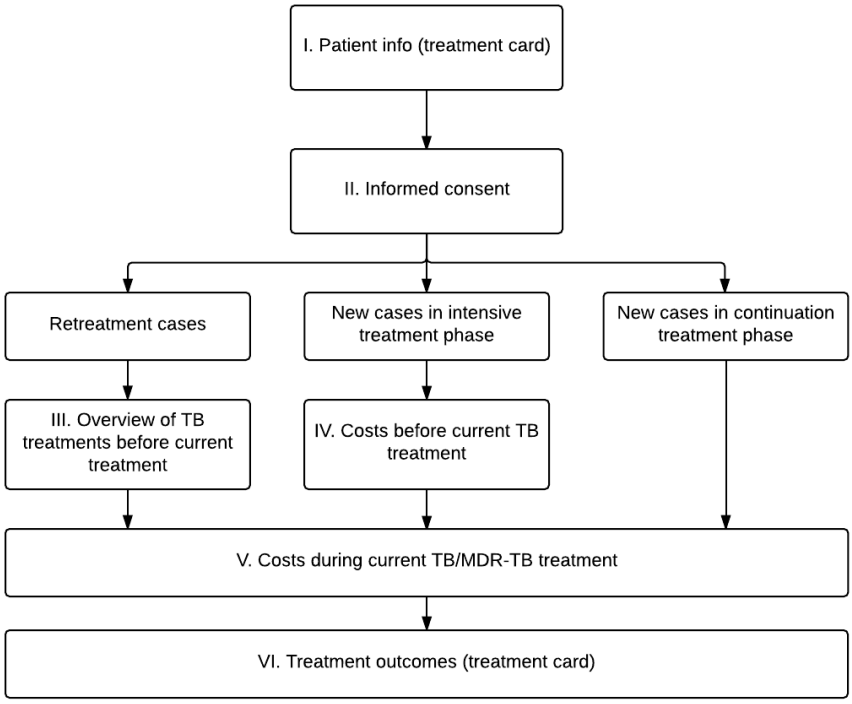
Information about costs related to health seeking and diagnostic procedures before the person was registered as a TB patient within the NTP network (Part IV) will be collected only for new patients (either on 1st line treatment or on MDR treatment) who are interviewed in the intensive phase. For new patients who are interviewed in the continuation phase, information will be collected only about costs related to the continuation phase (with a few exceptions, such as hospitalization cost and coping costs, which should also be collected for the intensive phase for

these patients). This is because of the considerable challenge for patients to remember events and costs incurred many months prior to the time of the interview, which could introduce misclassification and recall bias.

For the same reason, no detailed information should be collected about costs related to health seeking and diagnostic procedures before the person was registered as a TB patient within the NTP network for previously treated cases (either on 1st line treatment or on MDR treatment), regardless of which treatment phase the patient is in at the time of the interview. Instead, all previously treated cases will be asked brief summary questions about the number of previous TB treatments, the start year and duration of previous TB treatments, number of hospitalization episodes and their duration during previous TB treatments (Part III). This will be collected for previous treatment up to 2 years before the start of the present treatment episode.

Information collected in Part IV for new cases interviewed in the intensive phase will be used to impute data and estimate costs for patients interviewed in the continuation phase and for re-treatment cases. Similarly, information about costs in the continuation phase collected from patient interviewed in this phase will be used to estimate these costs for patients interviewed in the intensive phase.

Figure 1: Survey instrument components



3.2 Sampling strategy

3.2.1. Study population

Inclusion criteria: The study population includes all patients (including children) who are on TB or MDR treatment (after a minimum of 2 weeks into continuation or intensive phase) within the NTP network (public facilities and private providers that are part of formal public-private mix initiatives) at selected districts. All consecutive patients attending the facility will be invited to the survey until the required sample size for that geographical area is achieved.

If the patient has not been treated for a minimum of 2 weeks of the current treatment phase the interview should be postponed until this time).

Exclusion criteria: People who are treated in facilities that are unlinked to NTP (i.e. private facilities that are not formal part of a public-private mix initiative) as well as people who have not been put on TB treatment are not included in this study.

3.2.2 Sampling methodology

Government's districts were sampled randomly from a national level list comprising of 216 districts, and their selection was proportional to the total number of TB notifications by district reported to the NTP for 2014. Each district in Ghana has a district hospital. As the number of cases by health facility was not available, all TB patients attending any health facility in the NTP network within the district are eligible. The number of 2014 TB notifications was compared the number of TB notifications reported in 2013 to assess any potential variation in reporting from the previous year.

All TB patients found in the district TB register and attending sampled facilities during the study period are eligible for inclusion in the study.

The initial selection was further modified manually to ensure good representation of all different geographical areas of the country. In addition, clusters with less than 100 TB cases notified in 2014 were excluded due to logistical reasons or grouped together if possible (e.g. Cluster 20).

3.3. Sample size

The calculation of the required sample size for the survey was based on the following assumptions:

1. We hypothesised that the true proportion of households experiencing catastrophic total costs due to TB illness is 40% based on data from a previous TB patient cost survey conducted in Ghana (2).

2. The relative precision around the estimate drawn from the survey (d) was estimated at 5%.

3. The magnitude of the "design effect" (DEFF) was estimated at 2.

Table 2: Sample size scenarios for different levels of precision

Anticipated guess	Absolute precision d=**5.0%**			
	Cluster size			Sample size
	15 clusters	25 clusters	30 clusters	
30%	43	26	22	633
40%	49	29	25	721
50%	50	30	25	750

In total, twenty-five clusters were selected through multi-stage cluster sampling among all Government's districts in Ghana. The size of each cluster was determined to be 29 patients within each sampled district, regardless of catchment population and patient load. This means that the overall sample size is 725 patients (see list of selected clusters in Appendix 2).

4. Planning and conducting the survey

4.1. Data collection

Data will be collected through structured interviews with TB patients at the health facilities. Interviews will be conducted in the participant's mother-tongue. Interviews will be carried out once per patient, after a minimum of two weeks into the treatment phase.

The questionnaire will be translated from English into relevant local languages and back-translated to ensure accuracy of translation.

Prior to the interview, interviewers will be required to complete some questions by checking patient records. These will also include ascertaining whether the patient was recruited through systematic screening at the health facility or passive case finding.

Interviewers will also be required to record anthropometric measures (weight and height) from the patient card, and to measure these also at the time of interview.

Finally, the survey team will conduct follow up conversations with clinic staff to retrieve information on treatment outcomes of patients enrolled in the survey. It is anticipated that most follow-up will happen by phone rather than in person (Figure 1).

4.2 Study sites

Interviews will be conducted by three teams comprising of 4 field officers and one team supervisor. The selected clusters have been divided into three areas of the county (Northern, Central and Southern sector) with each team covering one of these (Appendix 2).

4.3 Information to the participants and ethics

The study population includes all patients (including children) who are on TB or MDR treatment (provided they have undergone 2 weeks or more of anti-tuberculosis treatment) within the NTP

network at selected districts. All consecutive patients attending the facility will be identified by the study team and invited to the survey until the required sample size for that geographical area is achieved. These participants have been chosen as we are interested in the economic burden of TB in Ghana. This is a key indicator in the End TB Strategy and as such has importance for global public health policy.

Patients will be informed in their mother tongue about the purpose of the study. Patients will be told about the confidentiality of the data collected and duration of the interview. It will be their right to withdraw from the study at any time. Interviewers will be trained in processes for getting written informed consent. When seeking to enroll patients into the study they will go through a clearly worded written informed consent form with them, which makes it clear that people are free to consent to participate in the research, or not (see Annex 1, 2 and 3).

To ascertain whether the individual really understands the implications of consent, the survey will allow individuals to ask questions for clarification. After ensuring that the subject has understood the information, the investigator should then obtain the subject's freely given informed consent. If the consent cannot be obtained in writing (e.g. if the patient is illiterate), then the thumb print of participant must be formally documented and witnessed.

Patients will be compensated with a pastry/sandwich and drink for the time, travel or inconvenience allocated during the interview. Section 4.6 provides further details about the place of interview and time required.

This research involves negligible risks however depending on the patient's individual circumstances there may be some risk of psychological harm if answering the questions stirs up painful emotions for some people. The interviewers will be trained to recognise any signs of distress among the participants. If the participants appear to upset by any of the questions we will request that the interviewers pause and offer the participant the chance to continue or defer the interview.

Patient confidentiality will be maintained at all times: every survey participant will be assigned a unique identification number which will be used in all stages of data collection and management. Data will be stored on encrypted servers and datasets will be anonymised for analysis. During the data collection phase we will ensure confidentiality by conducting interviews in private spaces. We will also ensure that only the study team will use the data collection tablets and that these will be stored in locked cupboards overnight when not in use. During the publication of the results all data will be aggregated and de-identified. We are interested in patient costs overall and will report this as aggregated data. Section 4.7 describes in detail data security and storage procedures for this research project.

This study proposal has been submitted for ethical clearance to the Research Ethics Committee of the London School of Hygiene and Tropical Medicine and to the Ghana Health Service Ethics Review Committee.

All the parties involved in this research project have no conflict of interest.

4.4. Training of interviewers

A 5-day training will be conducted prior to starting data collection. The training will be conducted by Dodowa Health Research Centre and LSHTM staff, and will also include NTP staff and international partners involved in the study.

4.4.1 Objectives of the training

For interviewers to:

- be aware of ethical issues in performing such interviews
- to learn interviewing techniques (such as adequate probing)
- to be able to select the appropriate study participants
- to be fully familiar with the questionnaire and the electronic data collection device (Android tablets)
- to able to ascertain weight and height of survey respondents in a consistent way
- to understand the indicators used in the questionnaire
- to enter data appropriately
- to feed back any uncertainties or concerns with the questionnaire or the data collection procedures to the survey coordinator

For team leaders and survey coordinators to:

- Assess the suitability of interviewers to conduct the survey
- Monitor the quality and completeness of data collection

4.4.2 Training methodology

During the training, data collectors will practice the questionnaire on each other and in simulated facilities to ensure that they also understand the questions and responses. Interviewers will also practice entering the data using electronic devices (tablets).

4.4.3 Deliverables of the training

The deliverables of the training are for interviewers to know how to:

1. Introduce themselves and the survey to the participant.
2. Convey to the patient the justification for inclusion criteria for the survey.
3. Convey to the patient the informed consent process.
4. Be able to put participant at ease and ensure comfortable environment in which to ask questions.
5. Be familiar with the questionnaire so that questions are asked conversationally rather than being read stiffly.
6. Be familiar with the electronic version of the questionnaire and the Android tablets employed for data collection.
7. Convey questions in the order in which they are written on the questionnaire, using the same wording (using the local language) as on the questionnaire. It may be that certain questions need further explanation and may need the interviewer to prompt responses from the patient regarding time and types of costs.
8. Understand and able to explain indicator definitions.
9. Avoid influencing the answers to questions by using friendly but neutral body language and not educating the patient.
10. Ensure that all questions are answered. If a participant refuses to answer a question or cannot give an answer, the appropriate field should be completed.
11. Keep control of the interview (off track conversations, silences).
12. Check patient records (included in case of non-participation in the survey).
13. Be sensitized on the different phases (intensive, continuation) and types of TB treatment (hospitalization, different forms of DOT, etc.) and associated costs (sputum conversion test, follow up test, medicine collection etc.), to avoid double counting costs. It also needs to be clear to the interviewers what counts as TB drugs and what are additional drugs that are prescribed/bought.

14. Be informed about the nature of TB, what their participation means for their own health and how they can protect themselves.
15. Be able to ascertain weight and height of survey respondents in a consistent way.
16. Be aware of the difference between passive case finding and systematic screening of attendants at health facilities (intensified case finding), and how to classify patients between categories.

4.5. Piloting of the survey tool

Pilot testing will provide an opportunity to identify any problems with the survey tool and validate assumptions made for sample size calculation, timing of interview, and budget. This will be conducted in one selected study site on a sub sample of respondents.

The survey questionnaire, data entry screens (electronic version of survey questionnaire), transfer of data and feedback loops, will be tested during interviewer training and the pilot to ensure that illogical or missing steps are identified and corrected before starting the patient survey.

4.6. Place of interviews within the facility and time required for the interview

The interview will take place in a separate space/room where the interview can take place undisturbed, while preserving the privacy of the patient. Interviewers will have been made aware during the training of infection control measures (i.e. conducting the interview outside or in a well-ventilated room and wear an N-95 respirator etc.).

The time required to conduct the interview is approximately 60-90 minutes (depending on the number of modules to be used). Prior to the interview, the interviewer will be required to complete some questions by checking patient records, which will take approximately 15 minutes. These will also include ascertaining whether the patient was recruited through systematic screening at the health facility or passive case finding.

Interviewers will also be required to record anthropometric measures (weight and height) from the patient card, or when this information is not already available, to measure weight and height of the respondent.

4.7 Data collection tool and management

The study will employ an electronic survey system that has been set up in the WHO Data Coordination Platform (DCP) for secure management of electronic forms and data in real-time between health and development partners (www.whodcp.org), which is part of the mHero technology suite for effective Ebola response and monitoring (UNMEER).

This application is open access and allows collecting data offline and uploading online to send to the data repository. The DCP will be accessed through ODK (Open Data Kit) Collect, a free Android application. Interviewers will use Android tablets during the interviews and will be required to periodically connect to the internet to upload the completed patient questionnaires.

Every survey participant will be assigned a unique identification number called Personal Identification Number (PIN) which will be used in all stages of data collection and management. Each patient will be followed using the unique identifier and patient registration number in the TB register. This will consist of the following four variables:

	Cluster number	Health facility number	Individual number	TB register number
PIN	##	###	###	######

The Data Management Unit (DMU) will be responsible for performing data management, planning, operation and security of the data and the associated information systems. These will take place at the central and field level and will be supported by survey staff at all levels. The database manager will be based at Dodowa and provide remote support to the survey teams in the field.

Field team leaders will ensure that questionnaires are checked at the end of each day during data collection so that surveyed individuals can still be approached to check any errors or discrepancies. Each survey team will be responsible for transferring all paper-based documents (consent forms) to the DMU where they will be stored in folders in a secured and safe storage room together with all essential survey documents (e.g. signed protocol and amendments, financial reports of the survey, ethical approval).

The electronic data collection form will be set up to perform basic calculations and will have internal data inconsistency checks.

The dataset will be anonymised for analysis and password protected to ensure patient confidentiality.

4.8. Analytical approach

Descriptive, univariate and multivariable analyses will be performed to determine the magnitude and main drivers of patient costs in Ghana **(Objective 1)**. Further disaggregated analysis will be conducted to understand which types of costs are most important in Ghana. This will involve, for example, disaggregating out-of-pocket payments into payments for medicines, tests, consultation fees etc., and disaggregating out-of-pocket non-medical payments into payments for travel, food, etc. Moreover, if patient numbers will allow, associations will be analysed between costs and patient characteristics (socioeconomic position, sex, occupation), place and model of care (ambulatory, self-administered, hospital-based etc.), type of provider (public vs. public-private, NGO), and health seeking before TB diagnosis (health providers utilised, time to diagnosis, etc.). Descriptive analyses of the type of social and economic support that patients receive will also be done. Such analyses will help inform policy decisions aimed to reduce costs and access barriers.

Two approaches will be adopted to determine the percentage of TB patients treated in the NTP network (and their households) in the country who incur catastrophic total costs **(Objective 2)**:

Approach 1: Medical and non-medical out-of-pocket payments and indirect costs exceeding a given fraction of household's income

The first approach will calculate the percentage of TB-affected patients (and their households) that face costs (medical, non-medical expenditures as well as income loss net of transfers and reimbursements) that are above a certain percentage of annual household income. The Task Force convened by WHO suggested to tentatively use 20% as threshold in this analysis, since this level has been associated with poor clinical TB outcomes (8). Other cut-offs will be tested,

depending on association with clinical outcomes, with dissaving strategies or other measures of impoverishment **(Objective 3)**.

Approach 2: Percentage of households experiencing "dissaving"

The second approach will calculate the percentage of households experiencing any level of dissaving (such as taking a loan or selling property or livestock) to face health costs associated with the TB disease. This proxy indicator by definition indicates financial weakening of a household.

The unit of analysis will be the patient but the economic consequences will be considered in the context of the household of the patient. Therefore, the analysis will take into account the number of patients sampled that belong to the same household and make adjustments accordingly.

Costs will be calculated from the patient perspective and costs to the provider and other societal costs (with the exception of caregiver time) will not be considered.

Patients will be interviewed in different phases of the illness episode, and reporting on retrospective expenditures and time loss. As data will be collected for the particular episode phase the patient is in cost will be predominantly estimated for other phases and estimation will be done using costs calculated for similar patients interviewed in the other phases of illness, matched by type of TB and facility. For example, a new drug-susceptible patient interviewed during their continuation phase will not report all costs they incurred during the intensive phase. This patient would be assigned the average cost of the intensive phase among other similar drug-susceptible patients who were interviewed at that facility during the intensive phase.

Cross-tabulations of catastrophic cost experience will be produced by TB treatment outcomes, mode of screening and nutritional status (**Objective 4, 5 and 6**). Univariate and multivariable regression will be performed to determine:

1. Which factors are most significantly associated with an individual TB patient experiencing catastrophic total cost and TB treatment outcomes **(Objective 4)**;

2. Whether TB patients identified through screening of clinic attendees incur lower or higher TB related costs compared to patients who are identified through passive case finding, and experience different treatment outcomes **(Objective 5)**;

3. The association of the nutritional status of an individual TB patient (in terms of BMI) with levels of TB related costs incurred by the patients **(Objective 6)**.

4.9 Dissemination plan

Data collected during the survey will be used to establish a national data repository for patient survey data in Ghana. This will help Ghana conduct periodic measurements of financial barriers to adherence based on baseline experience and to enable reporting on the 2020 End TB Strategy target that no family affected by TB will incur total (direct and indirect) catastrophic costs

Findings from the study will be published in the scientific media and presented at conferences, but also to the community and the participants (through the clinics that take part in the research project), to national policy makers (e.g. Ghana Health Service, Parliament of Ghana, WO Country Office), and international and bilateral donors (e.g. Global Fund, USAID, WHO Headquarters).

References

1. Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low-and middle-income countries: a systematic review. European Respiratory Journal. 2014;43(6):1763-75.
2. Mauch V, Bonsu F, Gyapong M, Awini E, Suarez P, Marcelino B, et al. Free tuberculosis diagnosis and treatment are not enough: patient cost evidence from three continents. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2013;17(3):381-7.
3. Lönnroth K, Glaziou P, Weil D, Floyd K, Uplekar M, Raviglione M. Beyond UHC: Monitoring Health and Social Protection Coverage in the Context of Tuberculosis Care and Prevention. PLoS medicine. 2014;11(9):e1001693.
4. World Health Organization. The End TB Strategy 2015, Geneva. [Available from: http://www.who.int/tb/End_TB_brochure.pdf?ua=1.]
5. Bank WaW. First Global Monitoring Report on Tracking Universal Health Coverage 2015 [Available from: http://www.who.int/healthinfo/universal_health_coverage/report/2015/en/.
6. KNCV Tuberculosis Foundation. Tool to estimate patients' costs. 2008.
7. World Health Organization. Global Tuberculosis Report 2015. Geneva, 2015.
8. Wingfield T, Boccia D, Tovar M, Gavino A, Zevallos K, Montoya R, et al. Defining catastrophic costs and comparing their importance for adverse tuberculosis outcome with multi-drug resistance: a prospective cohort study, Peru. PLoS medicine. 2014;11(7):e1001675.

Annex 1: Consent form

Part I: Information sheet

My name is (*name of interviewer*). I am working for the Dodowa Health Research Centre in collaboration with the London School of Hygiene and Tropical Medicine and the National Tuberculosis Control Programme.

We are interested in the costs that people face when they are treated for TB as well as the costs faced while seeking health care before the diagnosis of TB. We believe that you can help us by telling us about the costs you incurred before being diagnosed with TB and while receiving treatment for TB.

You are being invited to take part in this research project because you are currently receiving treatment for TB in a government health facility. We are planning to interview approximately 725 TB patients across Ghana.

If you accept to take part in this research project, you will be asked to participate in an interview with [*name of interviewer*] or myself. The interview will take approximately 60-90 minutes. In addition, we will take your weight and height measurements. You will only be interviewed once by the study team.

During the interview we will talk about costs you incurred before and during your current TB treatment and TB treatments you might have had in the past: for example, we will ask you to tell us how much you have paid to receive a lab test or for picking up your TB medications. We will also ask you about your occupation and the place you live. You do not have to share any information that you are not comfortable sharing.

The information that you choose to share will be used for research purposes. It will be shared with other researchers for further analysis and published, but all your personal information will be kept separate from the dataset that will be used for analysis in order to ensure full confidentiality. In addition, the dataset will be encrypted and only members of the analysis team will have access to it.

It is important for you to understand that your participation in this study is completely voluntary. We would be really grateful if you would agree to participate in this study, but do feel free to decline. If you decline, there will be no consequence for you and you will receive all the care and treatment you need at the health facility as usual. If you decline to participate you will not lose any benefit that you are entitled to such as receiving care and support that is provided at the clinic.

If you decide to participate, I would like to stress that you will not receive any reimbursements for the costs that you report on in this interview.

If you choose to participate in this study, you may still withdraw from the study at any stage without giving any explanation for your withdrawal. Your answers will be kept confidential. At some point I will ask you about your personal income and the income of your household. We will NOT provide this information to any tax or welfare authorities, even after the study has been completed.

In charge of this study is Dr Margaret Gyapong (margaret.gyapong@ghsmail.org; +233 50 1336170). The outcome of this study will be disseminated in a report and as a scientific article and you may request a copy from the principal investigator.

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions? *[Interviewer to answer patient's questions]*

You can also contact the National TB Control Programme (+233 244 318134) or the Ghana Ethics Board.

Part II: Certificate of consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions I have been asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study.

Print Name of Participant _____

Signature/Thumb print of Participant _____

Date _____
day/month/year

Witness

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness _____

Signature/Thumb print of witness _____

Date _____
day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the purpose, procedures (i.e. interview that will last 60-90 minutes, measuring of height and weight), potential risks and benefits of the study.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent _____

Signature of Researcher /person taking the consent _____

Date _____
day/month/year

v. 3 10/10/2016

Annex 2. Informed assent form

This assent form is for children between the age of 8 and 16 who attend the health facilities selected for this research project and who we are inviting to take part in it. Parents will answer questions on their behalf.

Part I: Information sheet

My name is [*name of interviewer*] and my job is to research the cost that people face when they are treated for TB as well as the costs faced while seeking health care before the diagnosis of TB. There may be some words you don't understand or things that you want me to explain more about because you are interested or concerned. Please ask me to stop at any time and I will take time to explain.

I am going to give you information and invite you to be part of a research study. You can choose whether or not you want to participate. We have discussed this research with your parent(s)/guardian and they know that we are also asking them for your agreement. If you are going to participate in the research, your parent(s)/guardian also have to agree. But if you do not wish to take part in the research, you do not have to, even if your parents have agreed. You don't have to be in this research if you don't want to be. It is up to you. If you decide not to be in the research, it is okay and nothing changes. This is still your clinic, everything stays the same as before. Even if you say "yes" now, you can change your mind later and it is still okay.

You may discuss anything in this form with your parents or friends or anyone else you feel comfortable talking to. You can decide whether to participate or not after you have talked it over. You do not have to decide immediately.

You are being invited to take part in this research project because you are currently receiving treatment for TB in a government health facility. We are planning to interview approximately 725 TB patients across Ghana.

If you accept to take part in this research project, your parents/guardian will be asked to participate in an interview with [name of interviewer] or myself. The interview will take approximately 60-90 minutes. In addition, we will take your weight and height measurements. They will only be interviewed once by the study team. We will not tell other people that you are in this research and we won't share information about you to anyone who does not work in the research study.

During the interview we will talk about costs you and your parents incurred before and during your TB treatment: for example, we will ask you to tell us how much you have paid to receive a lab test or for picking up your TB medications. We will also ask about your parents' occupation and the place you live. You do not have to share any information that you are not comfortable sharing.

Information about you that will be collected from the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key.

When we are finished the research, we will be telling more people, scientists and others, about the research and what we found. We will do this by writing and sharing reports and by going to meetings with people who are interested in the work we do.

In charge of this study is Dr Margaret Gyapong (margaret.gyapong@ghsmail.org; +233 50 1336170). The outcome of this study will be disseminated in a report and as a scientific article and you may request a copy from the principal investigator.

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions? *[Interviewer to answer patient's questions]*

You can also contact the National TB Control Programme (+233 244 318134) or the Ghana Ethics Board.

Part II: Certificate of assent

I have read this information (or had the information read to me). I have had my questions answered and know that I can ask questions later if I have them.

I agree to take part in the research

Only if child assents:

Print name of child: _____

Signature of child: _____

Date: _____
day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the purpose, procedures (i.e. interview that will last 60-90 minutes, measuring of weight and height), potential risks and benefits of the study.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this assent form has been provided to the participant.

Print Name of Researcher/person taking the assent _____

Signature of Researcher /person taking the assent _____

Date _____
day/month/year

Copy provided to the participant _____ (initialed by researcher)

Parent/Guardian has signed an informed consent ___Yes ___No _____(initialed by researcher)

v. 3 10/10/2016

Annex 3. Parental consent form

Part I: Information sheet

My name is (*name of interviewer*). I am working for the Dodowa Health Research Centre in collaboration with the London School of Hygiene and Tropical Medicine and the National Tuberculosis Control Programme.

We are interested in the costs that people face when they are treated for TB as well as the costs faced while seeking health care before the diagnosis of TB. We believe that you can help us by telling us about the costs your family incurred before your child was diagnosed with TB and while receiving treatment for TB.

Your child is being invited to take part in this research project because he/she is currently receiving treatment for TB in a government health facility. We are planning to interview approximately 725 TB patients across Ghana.

If you accept to take part in this research project, you will be asked to participate in an interview with [*name of interviewer*] or myself. The interview will take approximately 60-90 minutes. In addition, we will take your child's weight and height measurements. You will only be interviewed once by the study team.

During the interview we will talk about costs you incurred before and during your child's TB treatment: for example, we will ask you to tell us how much you have paid to receive a lab test or for picking up his/her TB medications. We will also ask you about your occupation and the place you live. You do not have to share any information that you are not comfortable sharing.

The information that you choose to share will be used for research purposes. It will be shared with other researchers for further analysis and published, but all your personal information will be kept separate from the dataset that will be used for analysis in order to ensure full confidentiality. In addition, the dataset will be encrypted and only members of the analysis team will have access to it.

It is important for you to understand that your participation in this study is completely voluntary. We would be really grateful if you would agree to participate in this study, but do feel free to decline. If you decline, there will be no consequence for you and you will receive all the care and treatment you need at the health facility as usual. If you decline to participate you will not lose any benefit that you are entitled to such as receiving care and support that is provided at the clinic.

If you decide to participate, I would like to stress that you will not receive any reimbursements for the costs that you report on in this interview.

If you choose to participate in this study, you may still withdraw from the study at any stage without giving any explanation for your withdrawal. Your answers will be kept confidential. At some point I will ask you about your personal income and the income of your household. We will NOT provide this information to any tax or welfare authorities, even after the study has been completed.

In charge of this study is Dr Margaret Gyapong (margaret.gyapong@ghsmail.org; +233 50 1336170). The outcome of this study will be disseminated in a report and as a scientific article and you may request a copy from the principal investigator.

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions? *[Interviewer to answer respondent's questions]*

You can also contact the National TB Control Programme (+233 244 318134) or the Ghana Ethics Board.

Part II: Certificate of consent

I have been asked to give consent for my daughter/son to participate in this research study. I will complete one interview on his/her behalf. I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions I have asked have been answered to my satisfaction. I consent voluntarily for my child to participate as a participant in this study and to answer questions on his/her behalf.

Print Name of Parent/Guardian _____

Signature/Thumb print of Parent/Guardian _____

Date _____
day/month/year

Witness

I have witnessed the accurate reading of the consent form to parent of the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness _____

Signature/ Thumb print of witness _____

Date _____
day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the purpose, procedures (i.e. interview that will last 60-90 minute, measurements of height and weight), potential risks and benefits of the study.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and

to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent _____

Signature of Researcher /person taking the consent _____

Date _____
day/month/year

v. 3 10/10/2016

Annex 4: Selected survey clusters

District	Population (2014)	High Incident TB	Mining District	High HIV District	2013 Notifications	2014 Notifications	Cluster Number	Number of patients Interviewed	Survey Sector	Survey Team
Obuasi	85,542	Yes	Yes	Yes	229	255	1	29	Central	2
Asante Akim North	84,518	Yes	Yes	Yes	194	155	2	29	Central	2
Kumasi Metro	1,975,627	Yes	No	Yes	1375	1307	3,4,5	29	Central	2
Techiman South	61,849	Yes	No	Yes	194	147	6	29	Central	2
Sunyani Municipal	134,958	Yes	No	No	140	123	7	29	Central	2
Cape Coast	191,961	Yes	No	No	166	156	8	29	South	3
Komenda Edina Egyafo Abrim	154,442	Yes	No	No	158	117	9	29	South	3
Mfantseman	75,269	Yes	No	No	121	102	10	29	South	3
Asikuma Odobeng Brakwa	127,345	Yes	No	Yes	106	126	11	29	South	3
Lower Mannya Krobo	96,982	Yes	No	No	264	230	12	29	South	3
Ashaiman Municipal	88,374	No	No	No	151	154	13	29	South	3
Tema Metropolitan	345,750	Yes	No	Yes	221	193	14	29	South	3
Accra Metro	1,857,558	Yes	No	No	1755	1582	15,16	29	South	3
Tamale	310,736	Yes	No	No	262	283	17	29	North	1
East Mamprusi	135,669	Yes	No	Yes	101	104	18	29	North	1
Bolga Mun	137,979	Yes	Yes	No	246	237	19	29	North	1
Wa	115,597	Yes	No	No	107	103	20	29	North	1
Wa West	87,709	No	No	No	10	18	20	29	North	1
Ketu South	110,285	Yes	No	Yes	401	271	21	29	North	1
Ho Municipal	197,234	Yes	No	No	204	190	22	29	North	1
Keta	162,942	Yes	No	No	162	167	23	29	North	1
Prestea Huni-Valley	172,436	Yes	Yes	No	226	225	24	29	Central	2
Sekondi Takoradi	605,673	Yes	No	No	365	241	25	29	Central	2

Annex 5: Budget

The total budget of this study is USD$ 55,455.

Budget Summary	
Accommodation & Venue Hire	18,120
Catering	1,500
Communication	1,584
Fees	200
Per Diems / Incentives	2,675
Salary Costs	11,200
Transport Costs	15,135
Overheads	5,041
Total	**55,455**

Annex 6: Timeline

Activity	2016								2017		
	M	J	J	A	S	O	N	D	J	F	M
Survey											
Adaptation of the generic protocol and questionnaire											
Ethics Committee Submission											
SOP Writing											
Translation of questionnaire into local languages											
Electronic survey adaptation											
Training for survey team											
Data collection											
Follow-up of treatment outcomes											
Analyses plans											
Data Cleaning / Analysis											
Initial dissemination of results						1		2			

[1] 47th World Union conference on Lung Health (Liverpool, United Kingdom)

[2] Global TB Programme/WHO meeting with countries that are undertaking patient costs surveys

Appendix 3: Survey instrument

	Cluster number	Health facility number	Individual number	TB register number
PIN	[____|____]	[____|____|____]	[____|____|____]	[____|____|____|____|____]

Part I. Patient information to be obtained from TB treatment card before interview			
Question	**Answer categories** *(circle appropriate number or fill answer on the answer line)*	***Action for interviewer*** *Questions in Part 1 are not part of the interview and should be pre-filled before the interview*	***Variable name*** ***(This column does not require translation nor adaptation)***
1. Date of Interview	(day/month/year) [____ | ____ | ____]		*Date_interv*
2. Name of Region	[_____]		*Provin_interv*
3. Name of District	[_____]		*Distr_interv*
4. Place of interview (facility name)	[_____]		*Facilt_interv*
5. Urban/rural	1. Urban [____] 2. Rural [____]		
6. Interviewer Name	[_____]		*Facil_name_interv*
7. Category of treating facility	**1.** Teaching hospital (tertiary level) **2.** Regional hospital (secondary level) **3.** District level hospital (primary level) **4.** Health centre (primary level) **5.** CHPS zone (primary) **6.** NGO/charitable health centre or hospital **7.** Other_____	*The "treating facility" is the place where the patient's treatment card is kept*	*Facility*
8. Name of the patient	[_____]		*Patient*
9. Sex	1. Male [_____] 2. Female [_____]	*Circle appropriate number or fill answer on the answer line*	*Sex*
10. Age of patient	[_____] years		*Age*
11. Weight of patient	[_____] kg [_____] lb	*Please specify if the weight is measured in kilograms or pounds*	
12. Height of patient	[_____] m [_____] in		

13. Date of first bacteriological TB test	(day/month/year) [____ | ____ | ____] [____] not done or unknown		*Date_test*
14. Bacteriological TB test used	1. Smear microscopy: not done, done-positive, done negative 2. Culture: not done, done-positive, done negative 3. Molecular test (e.g. Xpert MTB/RIF): not done, done-positive, done negative		*Bc_ss* *Bc_c* *Bc_xpert*
15. Date of diagnosis	(day/month/year) [____ | ____ | ____]		*Date_diagn*
16. Place of diagnosis	1. Teaching hospital (tertiary level) 2. Regional hospital (secondary level) 3. District level hospital (primary level) 4. Health centre (primary level) 5. CHPS zone (primary) 6. NGO/charitable health centre or hospital Other_____		*Place_diagn*
7. Type of TB	1. Pulmonary, bacteriologically confirmed [____] 2. Pulmonary, clinically diagnosed [____] 3. Extra-pulmonary [____]		*tb-type*
8. Drug susceptibility test done (with result)?	1. Yes [____] 2. No/unknown [____]	*The answer "yes" means the patient has submitted a sample for either a rapid test such as GeneXpert, LPA or for culture/DST, or both. If no, skip to question 18*	*dst*
9. If yes, with what test?	1. Gene Xpert MTB/Rif: [____] yes [____] no [____] unknown 2. LPA: [____] yes [____] no [____] unknown	*Tick the result, several answers are possible.*	*dst_xpert* *dst_lpa* *dst_cu* *dst_oth*

	2. Culture with DST: [____] yes [____] no [____] unknown 4. Other: [____] yes [____] no [____] unknown		
10. If yes, drug susceptible results	1. Rif-resistant [____] 2. MDR-TB [____] 3. Non Rif-resistant/MDR, DR-TB [____] 4. Non Rif-resistant/MDR, DS-TB [____] 5. Unknown [____]	*Provide the answers for each test. Possible options are shown here.*	*dst_rr* *dst_mdr* *dst_nrr_dr* *dst_nrr_ds* *dst_unk*
11. On MDR-TB treatment	1. Yes [____] 2. No [____]		*mdr*
12. Treatment regimen prescribed	1. 2HRZE/4HR 2. Other first line regimen:_____ 3. Second line standardised regimen:_____ 4. Second line individualized regimen: _____		*regimen* *regimen_other* *regimen_sld* *regimen_sld_ind*
13. Total duration of planned treatment from start	[_____] months intensive [_____] months continuation		*Duration_tt_int* *Duration_tt_cont*
14. Treatment registration group	Not MDR 1. 1st line, new [____] 2. 1st line, relapse [____] 3. 1st line, re-treatment after loss to follow-up [____] 4. 1st line, re-treatment after failure [____]	*If "Other" (answer 10), exclude from the study*	*register*

	MDR 5. MDR, new (initial MDR) [____] 6. MDR, relapse [____] 7. MDR, re-treatment after loss to follow-up [____] 8. MDR, re-treatment after failure of first treatment with 1st-line drugs [____] 9. MDR, re-treatment after failure of retreatment regimen with 1st-line drugs [____] 10. Other, specify: [_____]		
15. Start date of current TB treatment	(day/month/year) [____ | ____ | ____]		*Start_dstb*
16. The patient is currently in intensive or continuation treatment phase?	1. Intensive phase, [___] weeks of phase completed 2. Continuation phase, [___] weeks of phase completed	*If patient has completed less than 2 weeks of the current treatment phase, exclude, or postpone interview. Interview takes place after a minimum 2 weeks have been completed.* *Intensive phase for MDR-TB regimens is the initial treatment period which includes an injectable drug (usually 4 to 8 months).*	*Phase*
17. Type of treatment support/supervision; DOT or self-administered treatment?	1. DOT in both the intensive and the continuation phase 2. DOT in intensive phase and self-administered treatment in the continuation phase 3. Self-administered treatment in both the intensive and the continuation phase 4. Other_____ 5. Not known	• *As indicated in the treatment card, or as per the policy in the treating facility if not written on treatment card. The patient will be asked about DOT or self-administered treatment later in the interview.* • *If self-administered treatment in both the intensive and the continuation phase, skip to question 26*	*Drug_admin*

18. If DOT, who is the current DOT provider/supporter?	1. Health facility 2. Community health worker/volunteer 3. Workplace 4. Family member 5. Other_____	*As indicated in the treatment card. The patient will be asked about DOT supported later in the interview.*	*Drug_admin_type*
19. HIV status (as indicated on treatment card)	1. positive [____] 2. negative [____] 3. not tested [____] 4. unknown [____]	*As indicated in the treatment card.*	*Hivstatus*
20. If hospitalised at the time of interview, when is the planned date for discharge?	(day/month/year) [____ | ____ | ____] Not known [____]	*If ambulatory treatment has not yet started, questions in Part V referring to ambulatory care costs cannot be answered. For such a person, the cost of ambulatory treatment will be extrapolated from other patients' data.*	*Discharged*
21. Currency used in interview:	[____] GHC [____] USD	*report type of currency, e.g. GHC, USD*	*Currency*

Part II. Informed consent

See Protocol (Annex 1-3) for informed consent and assent forms.

Question	**Answer categories** *(circle appropriate number or fill answer on the answer line)*		***Action for interviewer***	***Variable name***
Do you have any questions?			*Answer patient's questions*	Add_qu
22. Do you want to participate?	Yes No, because:	1. Language not good enough 2. Time constraint 3. Not comfortable 4. Other, specify: ……	*Yes → Thank you! Go to interview* ***No → End the interview here having filled part I from patient card***	questnquest

Inclusion or exclusion			
Question	**Answer categories** *(circle appropriate number or fill answer on the answer line)*	***Action for interviewer***	***Variable name and data entry boxes***
23. Decision about inclusion or exclusion	1. Included 2. Excluded	*If included, skip to question 32*	*Incl*
24. If excluded, reason for exclusion	1. No informed consent 2. Treatment registration group is "other" (answer 10 in question 14)	*After completing this question, the survey is completed for this patient excluded from the survey.*	*Incl_y*
25. Interviewee identity	1. Patient 2. Guardian 3. Other (please name) _____		*Interviewee*

Checklist for which parts of the questionnaire to fill for different treatment categories						
Answer to question 16	**Answer to question 14**	**Treatment category and treatment phase at time of interview**	**Questionnaire part III** (tick when filled)	**Questionnaire part IV** (tick when filled)	**Questionnaire part V** (tick when filled)	**Super-visor check**
		Not MDR				

1	1	First line, new case, interviewed in the intensive treatment phase	*Do not fill*	*Filled* □	*Filled* □	
1	2	First line, new case, interviewed in the continuation treatment phase	*Do not fill*	*Do not fill*	*Filled* □	
2-4	1 or 2	First line, relapse or retreatment	*Filled* □	*Do not fill*	*Filled* □	
		MDR				
5	1	MDR, new case, interviewed in the intensive treatment phase	*Do not fill*	*Filled* □	*Filled* □	
5	2	MDR, new case, interviewed in the continuation treatment phase	*Do not fill*	*Do not fill*	*Filled* □	
6-9	1 or 2	MDR, relapse or re-treatment	*Filled* ☐	*Do not fill*	*Filled* □	

Part III. Overview of TB treatments before current treatment (for re-treatment cases only) *This part is to be filled if patient is on first line re-treatment and MDR re-treatment cases only! If new case (MDR or non-MDR treatment): skip to section IV*			
26. How many times have you been treated for TB before the current treatment, including completed as well as non-completed treatments?	[____|____] times	*For each treatment, fill details below.*	Pretrt
First treatment			
27. Which year were you treated for ***the first time*** for TB?	[_____]		Pretrt_1
28. Where were you treated?	**1.** Teaching hospital (tertiary level) **2.** Regional hospital (secondary level) **3.** District level hospital (primary level) **4.** Health centre (primary level) **5.** CHPS zone (primary) **6.** NGO/charitable health centre or hospital **7.** Other_____ _____	*Let's say that someone had TB when they were 22 years old, then were cured, then got TB again when they were 40 years old. Here we are*	Pretrt_1_facil

		asking about treatments around the age of 40, not the treatment when s/he was 22 years old.	
29. Was it first line or MDR-TB treatment?	1. First line TB treatment 2. MDR-TB treatment 3. Unknown	Explain to patient that "First line means standard treatment for non-MDR TB in your country"	Pretrt_1_type
30. How many months of treatment did you complete for the first treatment:	[____] months		Pretrt_1_nmths
31. Were you hospitalized during this treatment? If yes, for how long in total?	1. Yes, for [____] days 2. No		Pretrt_1_hosp
Second treatment			
32. Which year were you treated for ***the second time*** for TB?	[_____]		Pretrt_2
33. Where were you treated?	**1.** Teaching hospital (tertiary level) **2.** Regional hospital (secondary level)		Pretrt_2_facil

	3. District level hospital (primary level) **4.** Health centre (primary level) **5.** CHPS zone (primary) **6.** NGO/charitable health centre or hospital **7.** Other_____ _____		
34. Was it first line or MDR-TB treatment?	1. First line TB treatment 2. MDR-TB treatment 3. Unknown	Explain to patient that "First line means standard treatment for non-MDR TB in your country"	Pretrt_2_type
35. How many months of treatment did you complete:	[____] months		Pretrt_2_nmths
36. Were you hospitalized during this treatment? If yes, for how long in total?	1. Yes, for [____] days 2. No		Pretrt_2_hosp
Third treatment			
37. Which year were you treated for ***the third time*** for TB?	[_____]		Pretrt_3
38. Where were you treated?	**1.** Teaching hospital (tertiary level) **2.** Regional hospital (secondary level) **3.** District level hospital (primary level)		Pretrt_3_facil

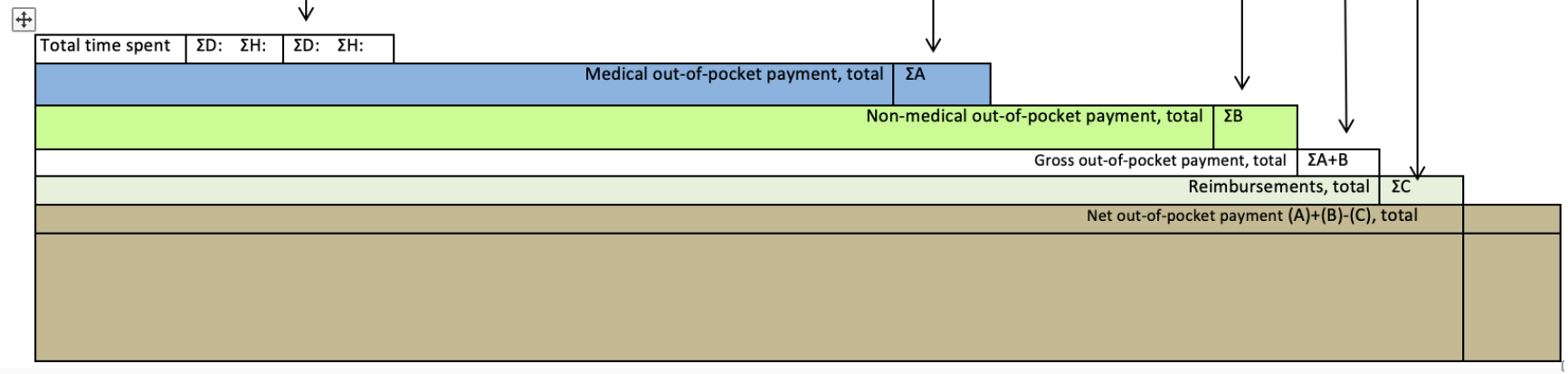
	4. Health centre (primary level) **5.** CHPS zone (primary) **6.** NGO/charitable health centre or hospital **7.** Other_____ _____		
39. Was it first line or MDR-TB treatment?	1. First line TB treatment 2. MDR-TB treatment 3. Unknown	Explain to patient that "First line means standard treatment for non-MDR TB in your country"	Pretrt_3_type
40. How many months of treatment did you complete:	[____] months		Pretrt_3_nmths
41. Were you hospitalized during this treatment? If yes, for how long in total?	1. Yes, for [____] days 2. No		Pretrt_3_hosp

Part IV - Costs before the current TB/MDR-TB treatment (filled for new cases in intensive phase only) • *New cases in intensive phase, non-MDR TB treatment, as well as those on MDR-TB treatment.* • *For retreatment case or new case interviewed in the continuation phase: skip to Part V*			
Out-of-pocket expenditure, reimbursements and time loss before and during TB diagnosis (before start of TB treatment)			
Question	**Answer categories** *(check all that apply or fill answer on the answer line)*	***Instructions and actions for interviewer***	***Variable names/codes***
42. For this episode of TB, when did you first experience symptoms of TB of this TB episode?	Weeks before treatment started: [____|____] Months before treatment started: [____|____]	*First construct a timeline of events, either starting with the first TB symptom, or start with time of TB diagnosis and work backwards. Use the locally adapted calendar with main seasonal events that the patient can relate to and use as a reference point for timing. To help the patient remember when the illness started, you can ask which TB symptom was first experienced, after having probed for cough, weight loss, chest pain, night sweats. If there is a problem defining the difference between TB symptoms and other health problems, ask which symptom led the patient to seek care, then ask when that symptom first occurred or became worse and started to worry the patient.*	*sympt*
43. How long after experiencing symptoms did you seek care?	Weeks before seeking care: [____|____] Months before seeking care: [____|____]	*Here we are trying to assess and quantify care seeking delays*	
44. Did you seek care from any other provider than the current facility?	1. Yes [____] 2. No [____]	*First we ask if they sought care from any other provider before current facility. If yes, then we list (Q 45)*	
45. Before your TB treatment started at this facility, from which of the following types of facilities did you seek care or advice for symptoms of the current illness (including hospitalizations; several facility types can be mentioned)? How many	1st visit, provider type □ Weeks before treatment started:___ 2nd visit, provider type □ Weeks before treatment started:___ 3rd visit, provider type □ Weeks before treatment started:___ 4th visit, provider type □ Weeks before treatment started:___	*Enter in chronological order, using one of these provider categories for each visit, and entering how many weeks before TB treatment start each visit was. Also report on table below.* 1. Government health facility 2. Faith based health facility 3. Private health facility / clinic 4. Pharmacy / Drugstore	*Firstvisit* *Secondvisit* *etc* *Firstvisweeks* *Secvisweek* *Etc*

weeks before starting TB treatment in the current facility did you visit each of these providers?	5th visit, provider type □ Weeks before treatment started:___ 6th visit, provider type □ Weeks before treatment started:___ 7th visit, provider type □ Weeks before treatment started:___ 8th visit, provider type □ Weeks before treatment started:___ 9th visit, provider type □ Weeks before treatment started:___	5. Herbalist / traditional / spiritual practitioners 6. Community Health Worker 7. Other facility:……..	
46. Where you hospitalised during any of these visits?	1. Yes [____] 2. No [____]	*If they were hospitalised, then ask A1 in Q47 applies*	
47. How much money and time did you spend for each of these visits before you were diagnosed with TB, including the visit when you actually received your diagnosis?	• See table below, and ask for each item • Fill one line per visit • For all that don't apply, mark/select NA • If there were payments for an item, but the patient cannot remember the amount, mark NR • Add more rows if more visits were made before diagnosis of TB! Explanation of table headings: Visits: Includes outpatient visits as well as hospitalizations. Should be filled in chronological order, 1st visit=visit 1. Type of provider: fill in provider type according to categories in question 50 where patient sought treatment or advice. Travel time: Hours or days spent to travel to and from facility Time spent for visit: Fill in hours for outpatient visits and days for hospitalizations Day charge: Fees for hospital days. Only for hospitalizations, and <u>only to be filled if not covered by the cost items below (consultation fee, radiography etc.)</u> Consultation fee: Other charges, not covered under day charge, including direct payment to health care staff Radiography and other imaging: out-of-pocket payments for imaging investigation (x-rays, CT-scan, ultrasound), TB-specific and other Lab test fees: out-of-pocket payments for all tests, TB specific and others Other procedures: out-of-pocket payments for biopsy, bronchial lavage etc. but not surgery unrelated to TB Medicine fees: Any medicine (TB or other) prescribed before TB was diagnosed under NTP Other, including nutritional supplements: any other treatments, such as nutritional supplements medically indicated Travel: out-of-pocket payments for travel to the facility (does not include income loss), both ways, for both patient and any household member.		

	Food: out-of-pocket payments for additional food bought in relation to travelling the health care visit, and during visit or hospitalization, for both patient and any household member Other, including accommodation: includes out-of-pocket payments related to renting a room/bed during health care visits, and any other non-medical payments related to health care visit, for both patient and any household member **Health insurance reimbursement**: amount reimbursed to patient through medical insurance (private or social security) so far, does not include expected future reimbursement **Out-of-pocket payments (gross):** Direct payment made to health-care providers by individuals at the time of service use, i.e. excluding prepayment for health services – for example in the form of taxes or specific insurance premiums or contributions. It is calculated as the sum of direct medical (A) and direct non-medical (B) costs. If patient cannot remember the details of costs above, ask for the total out-of-pocket payments of the visit, hospitalization. Out-of-pocket payment (net): medical and non-medical out-of-pocket payments minus reimbursements. These net payments: should be calculated by supervisor after the interview. Not to be calculated during the interview.

				Medical out-of-pocket payments, (Total per visit) (A)								Non-medical out-of-pocket payments, (Total per visit) (B)				Out-of-pocket payments (A+B) (Gross)	(C)	Out-of-pocket payments per stay (A+B-C) (Net)
Visit	Type of provider (see list)	Travel time Days: Hours: Minutes: *(both ways)*	Time spent for visit Days: Hours:	Day charges (for hospitalizations only) A1	Consultation fee A2	Radiography and other imaging A3	Lab tests A4	Other procedure A5	Medicines A6	Other, incl nutritional supplements A7	Medical payments, total ΣA1-7	Travel (both ways) B1	Food during health care visit or hospital stay B2	Other, including accommodation B3	Non-medical out-of-pocket payments (Total) ΣB1-3	Total out-of-pocket payments (ΣA1-7) + (ΣB1-3)	Health insurance reimbursement	
1st		D: H:	D: H:															
2nd		D: H:	D: H:															
3rd		D: H:	D: H:															
4th		D: H:	D: H:															
5th		D: H:	D: H:															
6th		D: H:	D: H:															
7th		D: H:	D: H:															
8th		D: H:	D: H:															
9th		D: H:	D: H:															
10th		D: H:	D: H:															



Part V. Costs during current TB/MDR-TB treatment (to be filled for all patients) *For patients in continuation phase ask for hospitalization and visits in the continuation phase only.*			
Question	**Answer categories** *(check all that apply or fill answer on the answer line)*	***Instructions and actions for interviewer***	***Variable name/code***
48. Are you currently hospitalised?	1. Yes [____] 2. No [____]	*If yes, the cost data collected apply to the first row of the table question 50*	Hosp
49. Have you been previously hospitalised during your current TB treatment phase and because of TB? If yes, how many times?	1. Yes [____] times 2. No [____]	*1. Concerns only hospitalization during the current treatment phase: For patients in continuation phase, ask only for hospitalization in this phase.* *2. Does not include hospitalization before the current TB treatment started:* • *For new cases, hospitalizations prior to TB treatment started should be filled in Part IV.* • *For retreatment cases, hospitalization during previous treatments should be filled in Part III.* *If answer to both question 48 and 49 are "no", then skip to question 55*	Hosp_prev
50. About how much money and time did you spend for each of these hospitalizations?	• See table below, and ask for each item. Fill one line per visit. • For all that don't apply, mark/select NA • If there were payments for an item, but the patient cannot remember the amount, mark NR Explanation of table headings: Type of hospital: fill in provider type according to categories in question 6 Number of days hospitalized: includes outpatient visits as well as hospitalizations. Should be filled in chronological order Day charges: total fees for hospital days for whole hospitalization in total. Only to be filled if not covered by the cost items below) Consultation fee: other charges, not covered under day charge, including direct payment to health care staff Radiography and other imaging: any imaging investigation (x-rays, CT-scan, ultrasound), TB-specific and other Lab test fees: includes all tests, TB specific and others, including cost of transporting samples, if paid by patient Other procedures: includes biopsy, bronchial lavage, etc. but not surgery unrelated to TB Medicine to treat TB: fees for TB medicines only, bought inside or outside hospital Other medicines, including nutritional supplements: any other medicine, including nutritional supplements Out-of-pocket payments (gross): It is the sum of out-of-pocket medical and non-medical. If patient cannot remember the details of payments above, or has a hospital bill for all costs combined, ask for the total out-of-pocket payment for the hospitalization. Out-of-pocket payment (net): sum of medical and non-medical out-of-pocket payments minus reimbursements. These net payments: should be calculated by supervisor after the interview. Not to be calculated during the interview.		

	Travel: out-of-pocket payment for travel to the facility (does not include income loss), for both patient and any household member. Food: out-of-pocket payment for food bought in relation to travelling to and during the hospitalization, patient and household member. Other, including accommodation: payments related to renting a room/bed during health care visits, and any other non-medical expenses for patient and household member. **Health insurance reimbursement:** amount reimbursed to patient so far, does not include expected future reimbursement

				Medical out-of-pocket payments, (Total per stay) (A)								Non-medical out-of-pocket payments, (Total per stay) (B)				Out-of-pocket payments per stay (A+B) (Gross)	(C)	Out-of-pocket payments per stay (A+B-C) (Net)
Hospitalization	Type of hospital (see list)	Number of days hospitalised	Travel time	Day charges (total for stay) A1	Consultation fee (total for stay) A2	Radiography and other imaging (total for stay) A3	Lab tests including cost of transporting samples (total for stay) A4	Other procedures, including surgery, biopsy, etc. A5	Medicines to treat TB (total for stay) A6	Other medicines, including nutritional supplements (total for stay) A7	Medical payment (Total) ΣA1-7	Travel (total for stay) B1	Food (total for stay) B2	Other (payment for linen, soap, other services & administrative) (total for stay) B3	Non-medical out-of-pocket payments (Total) ΣB1-3	Total out-of-pocket payments	Health insurance Reimbursement	
1st																		
2nd																		
3rd																		
4th																		
5th																		
6th																		

Total hospital days (for income loss)	Σ
Medical out-of-pocket payments, total	Σ A
Non-medical out-of-pocket payment, total	ΣB
Gross out-of-pocket payment	Σ(A+B)
Reimbursement, total	ΣC
Net out-of-pocket payment (ΣA)+(ΣB)-(ΣC), total	Σ(A+B-C)

Costs for DOT and food costs during ambulatory care			
Question	**Answer categories** *(check all that apply or fill answer on the answer line)*	***Action for interviewer***	***Variable name***
51. On a daily basis, do you currently take your medicines yourself without supervision or support (self-administered) or do you have a treatment supervisor or supporter (DOT)?	1. Self-administered [____] 2. DOT [____]	• *DOT (Directly observed treatment) visit is for the supervision of daily intake of medicines, i.e., what is done every day. These questions are not referring to less frequent trips to pick up drugs (e.g., weekly), which are explored from question 58 onwards.* • *This question concerns the treatment phase the patient is currently in* • *If patient is interviewed in the intensive phase and on self-administered treatment skip to question 59* • *Responses to be validated against treatment card*	Saf Dot
52. If DOT, how many times a week?	[____] number	*The maximum will be 7 times a week*	Dot_n
53. If you are now in the continuation phase, did you take your medicines in the intensive phase yourself without supervision or support (self-administered) or did you have a treatment supervisor or supporter (DOT)?	1. Self-administered 2. DOT 3. Patient is now in the intensive phase	*If patient is interviewed in the continuation phase and has been on self-administered treatment both now and in the intensive treatment, skip to question 59* *Responses to be validated against treatment card*	Saf_int Dot_int
54. If DOT, who is the DOT provider/supporter?	1. Health facility worker 2. Community health worker/volunteer 3. Workplace 4. Family member 5. Other_____	*Validated against question 17 in the treatment card*	*Drug_admin_type_bis*
55. If DOT, how long did the last DOT visit take, including travel time and waiting time (total turnaround time)?	Travel time [____] minutes Waiting time [____] minutes	*Distinguish between travel and waiting time as travel indicates*	*Travel_dur_dot*

		distance/access, while waiting time is more related to quality of care	
56. Did anyone accompany you?	1. Yes [____] 2. No [____]	*If yes, include also costs for accompanying person*	
57. What was the cost of transport (return) for the last DOT visit, including parking costs, in total for you and any accompanying household member?	[_____]		*C_travel_dot*
58. How much did you spend on food and drinks for the last DOT visit (on the road, while waiting, lunch etc.), in total for you and any accompanying household member?	[_____]		*C_food_dot*
Costs of picking up drugs and food costs during ambulatory care			
59. Do you or a household member pick up TB drugs (for self-administered treatment or to bring to your DOT supervisor/supporter)?	1. Yes [____] 2. No [____]	*This does not concern DOT visits, which should be recorded in questions 51-58, but should be filled if patient or other household member picks up drugs for either bringing to DOT provider or for self-administered treatment.* *If patient is on DOT and patient or household member is **not** picking up drugs to bring to DOT provider then the answer is no.* *If no, skip to question 71*	*4drug*
60. If yes, how often do you or a household member pick up TB drugs in the current treatment phase?	Every week [____] Every 2 weeks [____] Every month [____] Other_____		*4drug_n*
61. Where do you or your household member pick up your TB drugs when you last picked up drugs?	1. Government health facility 2. Faith based health facility 3. Private health facility/ clinic 4. Pharmacy / Drugstore 5. Herbalist / traditional / spiritual practitioners 6. Community Health Worker 7. Other facility:……..	*If the patient has visited different places, tick the most recent one.*	*Drug_srce*
62. Were you able to go and return in one day or did you have to stay overnight when you last picked up drugs?	1. Yes [____] 2. No [____]		
63. If you stayed overnight, did you incur accommodation costs?	1. Yes [____] 2. No [____]		

64. What accommodation cost did you and any accompanying household member have when you last picked up drugs?	[_____]		C_Lodge_4drug
65. How long did the last visit to pick up drugs take, including travel time, waiting time and consultation time (total turnaround time)?	Travel time [____] minutes Waiting time [____] minutes Consultation time [____] minutes		*visit_dur_4drug*
66. Did you incur any transportation cost when you last picked up drugs?	1. Yes [____] 2. No [____]		
67. What was the cost of transport (return) last time you picked up drugs, including parking costs, in total for you and any accompanying household member?	[_____]		C_travel_4drug
68. Did you spend any money on food and drinks) last time you picked up drugs?	1. Yes [____] 2. No [____]		
69. How much did you spend on food and drinks last time you picked up drugs (on the road, while waiting, lunch etc.), in total for you and any accompanying household member?	[_____]		C_food_4drug
70. Was there a fee paid to the DOT provider when you last picked up drugs?	1. Yes [____] If yes, amount: _____ 2. No [____]		*C_4drug*

Costs during outpatient visits for medical follow-up (to see the doctor or nurse, have tests)			
Question	**Answer categories** *(check all that apply or fill answer on the answer line)*	***Action for interviewer***	***Variable name***
71. How many TB-related medical follow-up visits have you had so far during this treatment phase (to see the doctor or nurse, have follow- up tests, etc.)?	[_____] times	*This concerns clinical check-up, follow up, and additional visits due to side effects or other TB related issues. It does not include DOT visits or visits to pick up drugs.* *For patients in the continuation phase, ask only how many visits since the start of the intensive phase.*	fu
72. How long did the last follow-up medical outpatient visit take, including travel time and waiting time (total turnaround time)?	Travel time [____] minutes Waiting time [____] minutes Consultation time [____] minutes		*Travel_dur_fu*

73. Did you incur any transportation cost when you last picked up drugs?	1. Yes [____] 2. No [____]		
74. What was the cost of transport (return) at the last follow-up medical outpatient visit, including parking, in total for you and any accompanying household member?	[_____]	*Cost related to the latest visit. If the interview takes place at the end of such a visit use the costs for the present visit*	C_travel_fu
75. Were you able to go and return in one day or did you have to stay overnight when you last picked up drugs?	1. Yes [____] 2. No [____]		
76. What accommodation cost did you have for the last visit, in total, for you and any accompanying household member?	[_____]	*Cost related to the latest visit. If the interview takes place at the end of such a visit use the costs for the present visit*	C_lodge_fu
77. What fees did you pay during your last follow-up medical outpatient visit for registration/consultation?	Registration/consultation fee [_____]	*Cost related to the latest visit. If the interview takes place at the end of such a visit use the costs for the present visit*	C_visit_Reg
78. What fees did you pay during your last follow-up medical outpatient visit for radiography and other imaging?	[_____]	*See table qu. 54 for explanations*	C_visit_xray
79. What fees did you pay during your last follow-up medical outpatient visit for tests, TB tests and others?	Fees for tests [_____]	*Cost related to the latest visit. If the interview takes place at the end of such a visit use the costs for the present visit*	C_visit_Test
80. What fees did you pay during your last follow-up medical outpatient visit for other procedures?	[_____]	*Cost related to the latest visit. If the interview takes place at the end of such a visit use the costs for the present visit*	C_visit_nTBtest
81. What fees did you pay at your last follow-up medical outpatient visit for TB medicines, including prescriptions for medicines bought outside the facility?	Drug fees [_____]	*Cost related to the latest visit. If the interview takes place at the end of such a visit use the costs for the present visit*	C_visit_Drug
82. What fees did you pay during your last follow-up medical outpatient visit for other medicines, excluding nutritional supplements?	[_____]	*Cost related to the latest visit. If the interview takes place at the end of such a visit use the costs for the present visit. Avoid double counting with question on food supplements in the next section*	C_visit_nTBdrugs
83. What other fees not listed in the previous questions did you pay during your last follow-up medical outpatient visit?	Other fees [_____]	*Cost related to the latest visit. If the interview takes place at the end of such a visit use the costs for the*	C_visit_Other

		present visit and provide local examples	

Costs for nutritional/food supplements			
84. Do you buy any nutritional supplements <u>outside your regular diet</u> because of the TB illness, for example vitamins, meat, energy drinks, or fruits as recommended by health care staff?	1. Yes [____] 2. No [____]	*If no, skip to question 82*	*Food_diet*
85. If yes, how much did you spend on nutritional supplements in the past week approximately?	[_____]		*C_food_diet*
Time loss for guardians • *Not to be filled if the patient is under 15 years – for children, all questions concerning costs, time spent, income, and income loss in sections IV and V concern cost for the guardian* • *Note: out-of-pocket costs of transport, food, accommodation for guardian should be included in questions on Part V (tables)*			
Question	**Answer categories**	***Action for interviewer***	***Variable name***
86. Did somebody in your household accompany you for your last: a) DOT visit b) Visit to pick up drugs (or picked up drugs for you) c) Medical follow up visits d) Hospitalization	1. Yes [____] 2. No [____] 1. Yes [____] 2. No [____] 1. Yes [____] 2. No [____] 1. Yes [____] 2. No [____]	*Several responses possible* *Time loss to be calculated with previous responses by patient*	guard
87. If yes, what would they have been doing during that time if they had not attended?	[_____]	*If several responses in question 86, ask about the latest visit when a household member accompanied.* *Value their time even if they didn't forgo income*	Yloss_guard

Social position			
Question	**Answer categories** *(circle the most appropriate or fill answer on the answer line)*	***Action for interviewer*** *If patient is under 15 years old, these questions concern the guardian*	**Variable name**
88. Where do you live?	[_____]	*Enter name of the place/reference points/landmarks as accurately*	

		as possible (GPS co-ordinate to be added later)	
89. Do you live in a rural or urban area?	**1.** Rural **2.** Urban centre		
90. What is your ethnic background?	1. Dagarti 2. Wala 3. Akan 4. Ga 5. Dagomba 6. Gonja 7. Other (specify)		Ethnic
91. What is your religion?	1. Traditional 2. Christian 3. Muslim 4. Other (specify)		
92. What education level did you complete?	1. Not yet started school 2. Not attended school 3. Primary school 4. Middle/JSS 5. SSS (senior secondary school) 6. A level 7. Training college 8. Tech/prof 9. Tertiary (e.g. university) 10. Koranic 11. Don't know 12. Other 13. Or, total years of schooling: [____]	*Convert to the number of _____years* *If patient is under 15 years, this question is for the guardian.*	Edu Edu_other
93. What education level did the head of the household/primary income earner in the household complete?	1. Not yet started school 2. Not attended school 3. Primary school 4. Middle/JSS 5. SSS (senior secondary school) 6. A level 7. Training college 8. Tech/prof 9. Tertiary (e.g. university) 10. Koranic 11. Don't know 12. Other 13. Or, total years of schooling: [____]	*Convert to the number of _____years* *If patient is under 15 years, this question is for the guardian.*	Edu_main Edu_main_oth

94. What is your main occupation?	1. Legislator, senior official, manager 2. Professional 3. Technician and associate professional 4. Clerk 5. Service worker & shop & market sales workers 6. Skilled agric. & fishery worker 7. Craft and related trade worker 8. Plant and machine operators & assemblers 9. Elementary occupations 10. Armed forces & other security personnel 11. Homemaker 12. In school 13. Other occupations (specify) 14. Don't know 15. Not employed in the 12 months preceding the survey	*If patient is under 15 years, this question is for the guardian.*	Empl_type Empl_oth
95. What was your primary employment, or normal work, or normal other main activity before you contracted TB?	1. Legislator, senior official, manager 2. Professional 3. Technician and associate professional 4. Clerk 5. Service worker & shop & market sales workers 6. Skilled agric. & fishery worker 7. Craft and related trade worker 8. Plant and machine operators & assemblers 9. Elementary occupations 10. Armed forces & other security personnel 11. Homemaker 12. In school 13. Other occupations (specify) 14. Don't know 15. Not employed in the 12 months preceding the survey	*If patient is under 15 years, this question is for the guardian. This refers to the time before TB symptoms developed. Name all options first*	Empl_form_prev Empl_oth_prev Automatic check: Empl_*_oth vs Empl_*
96. Is the house you are staying your own, family house or rent?	1. Own 2. Family house 3. Rent 4. Other (specify)		
97. What is your usual main source of <u>drinking</u> water?	1. Piped or Bottled/Sachet water 2. Dug well (protected/unprotected) 3. Water from spring	*Other includes all sources that are not from a piped source, bottle, or well. This includes natural spring, borehole, rainwater, etc.*	*water_source*

98. Do members of your household usually use a flush toilet?	1. Yes [____] 2. No [____]		*flush_toilet*
99. Do you share this toilet facility with the community or not (i.e. only with your own family)?	1. Yes [____] 2. No [____]		*share_toilte*
100. Does your household have?	Electric 1. Yes 2. No Colour Television 1. Yes 2. No Refrigerator 1. Yes 2. No Motorcycle 1. Yes 2. No Car or truck 1. Yes 2. No Bicycle 1. Yes 2. No Access to the internet in any device 1. Yes 2. No Wrist watch 1. Yes 2. No Bank account 1. Yes 2. No		*electricity* *television* *refrigerator* *motorcycle* *boat* *car* *internet* *bike* *bank_account*
101. What type of fuel does your household mainly use for cooking?	Electricity [____] LPG/natural gas/biogas [____] Kerosene [____] Charcoal [____] Wood planks [____] Straw/Shrubs/Grass [____] Agricultural crop [____] No food cooked in the household [____] Other (specify) [____]		
102. How many rooms are there in the house excluding the bathroom?	[____] (number)		Hous_room
103. How many rooms in your household are used for sleeping?	[_____] (number)		*rooms*
104. How many adult and children regularly sleep in your house? (including patient, if variable, at time of diagnosis)	[____] Adult # [____] Children #		Hous_membr
105. What is the main material of the floor where your household live?	**1.** Natural floor (earth/sand/dung) **2.** Rudimentary floor (wood planks) **3.** Finished floor (parquet/polished wood, vinyl etc.) **4.** Other		

106. Does your household own any livestock, herds, other farm animals, or poultry?	**3.** Yes **4.** No		

Income (reported) before contracting TB *In countries with large informal economies, answers to these questions should be examined critically and compared to the **estimated income** based on asset scores (previous questions)*			
107. Were you the person who earned the highest income in your household before you contracted TB?	1. Yes [____] 2. No [____] 3. Equal contributor [____]	*If patient is under 15 years, this question is for the guardian.*	Empl_main
108. How were you usually paid before you contracted TB?	1. bank transferred salary 2. cash 3. in kind 4. cash and in kind 5. not paid	*If patient is under 15 years, this question is for the guardian.*	Paid_type
109. How many hours a week were you working before you contracted TB?	[_____] hours	*If patient is under 15 years, this question is for the guardian.* *This refers to the time before TB symptoms developed.*	Empl_dur_prev
110. If you were in paid work, how much do you estimate your average net wage or average net revenue from labour related activities (labour income), per month was <u>before you contracted TB</u>?	1. (net wage) 2. (net labour income)	*If patient is under 15 years, this question is for the guardian.* *In setting with an important informal sector you may not want to explicitly refer to taxes to make sure people are giving the right answer.* *May be presented in income brackets if difficult for patient to specify.*	W_pat_pre Inc_pat_pre

111. How many days would you have needed to work to be able to earn the equivalent of GH¢ 7.55 ($1.90)?		*Equivalent of the national poverty line. The actual income will be calculated based on hours worked per week.*		
112. How much do you estimate the average revenue from labour (income), after tax, of <u>your household</u> was per month, <u>before you contracted TB</u>?		*Refers to all persons in the household (May be presented in income brackets if difficult for patient to specify).*		Inc_hous_pre Welfare_hous_pre Gov_hous_pre Other_hous_pre
Household expenditure				
113. In the last month, did the household spend money on the following items?	Education: children school fees, books and other materials, P.T.A and other school contributions	1. Yes [____] 2. No [____]	Amount if Yes [_____]	
	Health care: clinics/HC/hospitals fees, buying drugs from private/market dispensaries, traditional/herbal treatment fees. How much do you think you have incurred for the health care of you and your household members within the past one month on health other than TB?	1. Yes [____] 2. No [____]	Amount if Yes [_____]	*Excludes TB*
	Farming activities: fertilizer, insecticides, purchased of seeds, irrigation, hired labour, renting equipment, animal feeding, etc	1. Yes [____] 2. No [____]	Amount if Yes [_____]	

	Foods: including rice, millet, maize, cassava, yam, plantain, cocoayam, beans groundnuts, salt, pepper, etc.	1. Yes [____] 2. No [____]	Amount if Yes [_____]	
	Clothing and shoes: for both adults and children	1. Yes [____] 2. No [____]	Amount if Yes [_____]	
	Utility services: water, electricity,	1. Yes [____] 2. No [____]	Amount if Yes [_____]	
	Fuel: petrol, gas for cooking, kerosene, charcoal	1. Yes [____] 2. No [____]	Amount if Yes [_____]	
	Household utensils: bowls, pans, buckets, cutlery, pots and other kitchen utensils	1. Yes [____] 2. No [____]	Amount if Yes [_____]	
	Capital goods: motor vehicle, motor, bicycles, radio, buildings and building materials, grinding mills, etc	1. Yes [____] 2. No [____]	Amount if Yes [_____]	
	Rent (only ask if person is renting house)	1. Yes [____] 2. No [____]	Amount if Yes [_____]	
	Direct taxes	1. Yes [____] 2. No [____]	Amount if Yes [_____]	
	Drinks/colanuts/tobacco/funeral celebration, marriages	1. Yes [____] 2. No [____]	Amount if Yes [_____]	
	Paying of debts	1. Yes [____] 2. No [____]	Amount if Yes [_____]	
	Others (specify)	1. Yes [____] 2. No [____]	Amount if Yes [_____]	
	Total expenditure			
Income changes and social consequences				

Question	**Answer categories** *(circle the most appropriate or fill answer on the answer line)*	***Action for interviewer*** *If patient is under 15 years old, these questions concern the guardian*	**Variable name**
114. If you are now in continuation treatment phase, what was your primary employment, or normal work, or normal other main activity in the intensive treatment phase?	1. Legislator, senior official, manager 2. Professional 3. Technician and associate professional 4. Clerk 5. Service worker & shop & market sales workers 6. Skilled agric. & fishery worker 7. Craft and related trade worker 8. Plant and machine operators & assemblers 9. Elementary occupations 10. Armed forces & other security personnel 11. Homemaker 12. In school 13. Other occupations (specify) 14. Not employed **15.** Don't know	*If patient is under 15 years, this question is for the guardian.* *This refers to the time from TB treatment started to end of intensive phase.* *Only for patients in continuation phase*	Empl_intens
115. If you were in paid work, how much do you estimate your average net wage or average net revenue from labour related activities (net labour income), per month is now?	1. [_____] (net wage) 2. [_____] (net labour income)	*If patient is under 15 years, this question is for the guardian.* *Only for patients who were employed*	W_pat_tb Inc_pat_tb
116. How many days would you need to work to be able to earn the equivalent of GH¢ 7.55 (1.90$)?	[_____] (number)	*The equivalent of the national poverty line – benchmark the 1.90$ PPP a day per capita. The actual income will be calculated based on hours worked per week.*	
117. How much do you estimate the average revenue from labour (net labour income), after tax, of your household is per month now?	(net labour income)	*Refers to all persons in the household* *May be presented in income brackets if difficult for patient to specify.*	Inc_hous_tb
118. How many hours per week are you working now?	____hours	*If patient is under 15 years, this question is for the guardian.*	Empl_dur_tb
119. If you are now in the continuation phase, how many	____hours	*If patient is under 15 years, this question is for the guardian.*	Empl_dur_intens

hours per week were you working in the intensive phase?		*This refers to the time from TB treatment started to end of intensive phase.*	
120. Approximately how many working days of income have you lost due to your TB illness overall?	[_____] working days before diagnosis of TB (but due to TB disease) AND [_____] working days after TB diagnosis	*Working days of income: e.g., if a patient was not able to work for 5 half days and lost income for these, the number of days lost is 0.5*5=2.5. Report for total TB episode, incl. all days before and after job loss.*	Lost_tb_pre lost_tb_now lost_tb_tot
Health insurance schemes and welfare payments			
Question	**Answer categories** *(check all that apply or fill answer on the answer line)*	***Action for interviewer***	***Variable name***
121. Do you have any of the following health insurance types?	1. National Health Insurance Scheme (NHIS) 2. Private health insurance 3. Reimbursement scheme medical allowance 4. Family/community fund 5. Other (specify): _____		ins1 ins2 ins3 ins4 ins5
122. How long have you been insured for?	[____|_____] month/year		
123. Did you enrol in the insurance scheme after you were diagnosed with TB?	1. Yes [____] 2. No [____]	*To explore if TB affected their decision to enroll*	
124. How many household members are covered by health insurance?	[_____] persons [_____] don't know/not sure		
125. Do you receive any social welfare payments? If so, which ones?	**1.** Livelihood Empowerment Against Poverty (LEAP) **2.** Labour Intensive Public Works programme (LIPW) **3.** Other (please specify): _____		
126. Does any household member receive any social welfare payments? If so, which ones?	127. ivelihood Empowerment Against Poverty (LEAP) 128. abour Intensive Public Works programme (LIPW) Other (please specify): _____		

129. What is the amount of the transfer?	[_____]		
130. Since when have you/your household been receiving the transfer?	[____|_____] month/year	*This is to find out when the transfer started*	
131. How often do you/or household receive the transfer?	[_____]	*Frequency of transfer*	
132. Did you or your household receive or seek any social welfare payment after you were diagnosed with TB? If yes, what type and amount (after tax) during the last month?	0. No 1. Enablers' package: _____ per month (if cash) 2. Paid sick leave: ____per month 3. Other cash transfer: ____per month	*If patient is under 15 years, this question is for the guardian.* *This question is to find out about cash transfers received by patients after TB was diagnosed.* *More than one category allowed.*	Welfare_type_TB
133. Do you currently receive vouchers or goods in kind (e.g. enablers package) to cope with TB illness? If yes, what is the estimated amount per month?	1. Yes a. Travel voucher: ____per month b. Food support: ____per month c. Other, enablers etc.___per month 2. No	*If patient is under 15 years, this question is for the guardian.* *More than one category allowed.*	*Cop_kind*
134. From whom do you receive the voucher/goods?	1. Government/clinic 2. NGO 3. Employer 4. Private donation 5. Other, specify	*If patient is under 15 years, this question is for the guardian.* *More than one answer allowed*	*Cop_kind_srce*
135. Are these transfers helping you/your household during the illness?	1. Yes 2. No 3. Somewhat helpful		

136. How do you generally spend the money you receive from the transfer/s?	1. Food 2. Transport 3. Education 4. Medicines (other than for TB related drugs) 5. Rent 6. Other, specify		
137. Has this changed since you have had TB?	1. Yes 2. No 3. Has somewhat changed	*This question is to investigate any changes in household expenditure since TB illness*	
138. If you/your household were already receiving transfers prior to TB, has TB made accessing transfers more difficult?	1. Yes 2. No 3. No difference		
139. Besides yourself, does anyone else of your household receive treatment for TB? If Yes: How many?	1. Yes: _____ person(s) 2. No	*If No, go to end question.*	Hous_tb
140. Has the TB illness affected your social or private life in any way?	1. No 2. Food insecurity 3. Divorce or Separated from spouse/partner 4. Loss of Job 5. Interrupted schooling 6. Social exclusion 7. Other	More than one category allowed.	Social Social_oth

Coping			
Question	**Answer categories** *(circle the most appropriate or fill answer on the answer line)*	***Action for interviewer*** *If patient is under 15 years, these questions are for the guardian.*	**Variable name**
141. What if your perception about the costs related to the TB illness?	[____] adequate [____] too high [____] other (specify)	*Perception about affordability of treatment costs*	
142. Did you or your household use any savings (cash or bank deposits) to cover costs due to the TB illness?	1. Yes 2. No		*S*
143. If yes, how much did you use: a) before TB treatment started? b) In the intensive treatment phase? c) In the continuation treatment phase? d) In total	[____] before TB treatment started [____] In the intensive phase [____] In the continuation phase [____] In total	*In case the detail by treatment phase is not available, request the total.*	*S_pre* *S_int* *S_cont* *S_tot*
144. Did you borrow any money to cover costs due to the TB illness?	1. Yes 2. No		*loan*
145. If yes, how much did you borrow: a) before TB treatment started? b) In the intensive treatment phase? c) In the continuation treatment phase?	[____] before TB treatment started [____] In the intensive phase [____] In the continuation phase [____] In total		Rcvd_loan
146. From whom did you borrow?	1. Family 2. Neighbours/friends 3. Private bank 4. Cooperative 5. Employer 6. "Unofficial lender" (Black market) 7. Other, specify	*Multiple responses allowed. Circle all that are mentioned*	*Rcvd_loan_srce*
147. Are you expected to pay the loan(s) back?	1. Yes 2. No	*If no, confirm it is a donation*	*Rcvd_donation*
148. Have you started paying back the loan? If yes, when did you start?	1. Yes, before treatment started 2. Yes, during the Intensive treatment phase		*Loan_back*

	3. Yes, during the continuation phase 4. No		
149. What is the frequency of the repayment on the loan?	[____] Monthly [____] Other (specify)		
150. What is the monthly (*or other frequency*) repayment on the loan, including interest?	1. Amount: _____ per month 2. I have not started repayment or interest payment	*For informal payments, please tease out the average monthly repayment if any.*	*C_loan*
151. Have you sold any of your livestock or other assets (e.g. capital assets) to finance the cost of the TB illness?	1. Yes 2. No		*cop*
152. If yes, what did you sell?	1. Land 2. Livestock 3. Transport/vehicle 4. Household item 5. Farm produce 6. Gold/jewellery 7. Other (specify):	*Multiple responses allowed. Circle all that are mentioned*	*Cop_srce*
153. If yes, when did you sell property?	1. Before TB treatment started 2. In the intensive phase 3. In the continuation phase	*Multiple responses allowed. Circle all that are mentioned*	*Cop_t*
154. How much money did you receive from the sale of all items of your property? a) before TB treatment started? b) In the intensive treatment phase? c) In the continuation treatment phase?	_____before TB treatment started _____In the intensive phase _____In the continuation phase _____In total		*cop_pre* *cop_int* *cop_cont* *cop_tot*
155. The assets that you sold, were they previously supporting the family income (or expenditure)? If yes indicate monthly income previously generated by the assets.	1.. Yes (amount): _____ 2. No		*yield*
156. What is the estimated market value of all the property you sold?	Value:_____		*Cop_value*
157. Did anyone in your household drop out of school/ interrupt schooling/stop work to assist the household as a consequence of your TB illness?	1. Yes, ____persons 2. No		*dropschol*
158. What were their age and sex and for how long did they drop out?	1. Age:__ Sex:__ Duration:__ months	*Fill one line per person who dropped out or interrupted school.*	*Dropschol_age* *Dropschol_t*

	2. Age:__ Sex:__ Duration:__ months 3. Age:__ Sex:__ Duration:__ months		*Dropschol_sex*
159. On a scale of 1 to 5, in which 1 is no impact and 5 is very serious impact, to what extent has the TB illness affected the household financially?	1 = No impact 2 = Little impact 3 = Moderate impact 4 = Serious impact 5 = Very serious impact		*Ecoimpct*

Other members of the household on treatment?			
Question	**Answer categories** *(circle the most appropriate or fill answer on the answer line)*	***Action for interviewer*** *If patient is under 15 years, these questions are for the guardian.*	**Variable name**
160. Are there any members of your household currently on treatment?	1. Yes ([____] number) 2.No	*If no, skip to end of questionnaire.*	*Member2*
161. Category of treating facility for household member(s)	**1.** Teaching hospital (tertiary level) **2.** Regional hospital (secondary level) **3.** District level hospital (primary level) **4.** Health centre (primary level) **5.** CHPS zone (primary) **6.** NGO/charitable health centre or hospital **7.** Other_____	If more than one additional household member please note separately the answers for each household member.	*Facility_member2*

Part VI. Treatment outcomes *To be filled in from treatment cards*			
162. Treatment outcome	1. Cured [____] 2. Treatment completed [____] 3. Treatment failed [____] 4. Died [____] 5. Lost to follow-up [____] 6. Transfer out [____]	*Interviewers to contact clinic staff and ask for treatment outcomes of patients included in the survey*	tx_outcome

Thank you for your cooperation! Is there anything you would like to ask or say?			
Comments by Interviewer:			
Date *(dd/mm/yyyy)*:	[____|____|_____]	**Signature interviewer:**	_____

Questions for clinic staff

Enablers		
1.	Does the clinic provide enabler packages to TB patients?	1. Yes 2. No 3. It used to but not anymore
2.	If so, what do these include?	1. Food 2. Cash 3. Transport vouchers 4. Other [_____]
3.	If patients receive cash, what is the amount?	[_____]
4.	If patients receive food, what type (and quantity) of food do they receive	[_____]; [_____] gr [_____]; [_____] gr
5.	If patients receive vouchers, what is their value?	[_____]
6.	How often patient receive the enabler package?	1. Weekly 2. Monthly 3. Other [_____]
7.	Where patients collect their cash/food/vouchers?	1. Clinic 2. From community workers 3. Other
Intensified case finding (ICF)		
8.	Is the facility in a district that is prioritised for ICF?	
9.	Is the symptoms-based screening tool available in the health facility?	*Need to physically see the form*
10.	Is the symptoms-based screening tool being used?	*Check to see if names appear on the form*
11.	If the health facility is not using the tool or if the tool is not present, then is there another method that the healthcare staff are implementing and logging intensified screening?	
12.	Is there clear assignment to one or more people who are given the role of initial screening (e.g. asking attendants for cough)?	

13.	If so, what is the number of individuals responsible for managing the form?	
14.	Have these individuals received official training on the use of the tool?	
15	What is the number of health care staff trained on using the tool?	*Will need to make adjustments based on population/catchment area, e.g. population covered by BMU?*
16.	How is the tool being implemented, i.e. how to attendants get onto the screening form? (policy is to ask all clinic attendants for cough) 1. All attendants are asked if they have a cough upon entry. If they have a cough, they are marked on the screening form. 2. A healthcare worker goes around the waiting room asking attendants if they have a cough. If they have a cough, they are marked on the screening form. 3. Healthcare workers mark the individual down on the screening form when a cough is heard. 4. When an attendant mentions they have a cough to the healthcare professional, then they are marked down on the screening form. 5. Other: _____	
17.	What is the duration of cough needed for an individual to be marked on the screening form? 1. Cough of any duration 2. Cough of 1 week 3. Cough of 2 weeks 4. Other: _____	

Appendix 4: LSHTM Ethics approval

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Miss Debora Pedrazzoli
LSHTM

13 October 2016

Dear Debora

Study Title: Assessing the financial burden of TB on TB-affected households in Ghana

LSHTM Ethics Ref: 11240

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Investigator CV	CV_Dr_MG	02/06/2016	v1
Investigator CV	Rein_Houben_CVforDP	07/06/2016	v1
Investigator CV	Delia_Boccia_CV	15/06/2016	v1
Investigator CV	Frank_Bonsu_CV	05/07/2016	v1
Information Sheet	Informed consent v1 20160720	20/07/2016	v1
Local Approval	TB_Costing_Approval	03/08/2016	v1
Investigator CV	Debora_Pedrazzoli_CV_July_2016	16/08/2016	v1
Protocol / Proposal	Protocol for the economic evaluation of patient costs Ghana Ethics LSHTM_v2	16/08/2016	v2
Protocol / Proposal	Patient cost survey instrument Ghana 20160613	16/08/2016	v1
Covering Letter	LSHTM Cover Letter_v1	10/10/2016	v1
Protocol / Proposal	Protocol for the economic evaluation of patient costs LSHTM Ethics v3 20161010	10/10/2016	v3

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

Appendix 5: Approval from the Ghana Health Service Ethics Review Committee

GHANA HEALTH SERVICE ETHICS REVIEW COMMITTEE

In case of reply the number and date of this Letter should be quoted.

Research & Development Division
Ghana Health Service
P. O. Box MB 190
Accra
Tel: +233-302-681109
Fax + 233-302-685424
Email: ghserc@gmail.com

My Ref. GHS/RDD/ERC/Admin/App/16/149
Your Ref. No.

Debora Pedrazzoli
London School of Hygiene and Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom

The Ghana Health Service Ethics Review Committee has reviewed and given approval for the implementation of your Study Protocol.

GHS-ERC Number	**GHS-ERC 14/06/16**
Project Title	"Assessing the Financial Burden of TB on TB-affected Households in Ghana"
Approval Date	3rd August, 2016
Expiry Date	2nd August, 2017
GHS-ERC Decision	**Approved**

This approval requires the following from the Principal Investigator

- Submission of yearly progress report of the study to the Ethics Review Committee (ERC)
- Renewal of ethical approval if the study lasts for more than 12 months,
- Reporting of all serious adverse events related to this study to the ERC within three days verbally and seven days in writing.
- Submission of a final report **after completion** of the study
- Informing ERC if study cannot be implemented or is discontinued and reasons why
- Informing the ERC and your sponsor (where applicable) before any publication of the research findings.

Please note that any modification of the study without ERC approval of the amendment is invalid.

The ERC may observe or cause to be observed procedures and records of the study during and after implementation.

Kindly quote the protocol identification number in all future correspondence in relation to this approved protocol

SIGNED…[redacted]……
PROFESSOR MOSES AIKINS
(GHS-ERC VICE-CHAIRPERSON)

Cc: The Director, Research & Development Division, Ghana Health Service, Accra