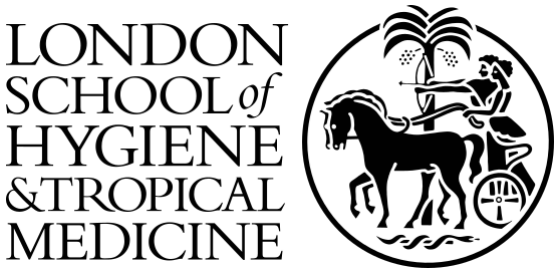

Improving the estimation of patient costs due to TB

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ABSTRACT

With the global scale-up of universal health coverage and a renewed interest in reducing poverty and vulnerability in the context of health, there have been substantial efforts towards including a representation of the economic impact of illness on patients and their households more formally in the evaluation of health care and development of health policy. Programmes increasingly need to track progress against disease-specific global targets, such as the End Tuberculosis (TB) Strategy which identifies a target of "no TB-affected family facing catastrophic cost due to TB" by 2020. There is also an increasing interest in understanding the impact of disease on impoverishment, and the broader dynamics of the interaction between health service delivery, health service expenditures and poverty as part of the economic evaluation of new technologies.

This shift towards including the household perspective in health economics research requires consideration of whether the methods and data currently being used are appropriate. There are inconsistencies in current methodological approaches to estimate disease-specific costs from the patient perspective, and the applicability of methods for different study purposes is unclear. This thesis aims to improve the estimation of disease-specific patient, household, and catastrophic costs collected in the context of facility-level intervention-focused studies for different policy purposes. Focusing specifically on the case of TB in South Africa, this thesis evaluates existing methods for estimating catastrophic costs for TB and highlight methodological issues that researchers need to consider when collecting these costs.

The research presented in this thesis confirms that people in South Africa continue to encounter catastrophic costs due to TB and provides some indications where investment from the South African government can reduce this burden. The thesis also identifies several important limitations in the current implementation of methods to estimate disease-specific catastrophic costs, and makes a strong argument in favour of a reference case on estimating patient, household, and catastrophic costs.

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Finally, I cannot fully express my gratitude for all of the friends and family who have provided me with so much support and encouragement at different stages of this journey. So many of you have been incredible sources of comfort, laughter, inspiration, and distraction when the going got tough. Thanks for keeping me sane and keeping me going.

ABBREVIATIONS AND ACRONYMS

AIC	Akaike information criterion
BCG	Bacillus Calmette–Guérin
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
DIRUM	Database of Instruments for Resource Use Measurement
DOTS	directly observed treatment (short-course)
DS	drug susceptible
FCA	friction cost approach
FDC	fixed-dose combination
GDP	gross domestic product
GHCC	Global Health Cost Consortium
GIS	geographic information system
GLM	generalized linear model
HCA	human capital approach
HIC	high-income country
HIV	human immunodeficiency virus
LMIC	low- and middle-income countries
LSMS	Living Standards Measurement Study
MAR	missing at random
MCA	multiple correspondence analysis
MCAR	missing completely at random
MCDA	multiple criteria decision analysis
MDR	multi-drug resistant
MICE	multivariate imputation by chained analysis
MNAR	missing not at random

NHI	national health insurance
NTP	National TB Programme
OOP	out-of-pocket
PCA	principal components analysis
PHC	primary health care
PMM	predictive mean matching
PPP	purchasing power parity
SDG	Sustainable Development Goals
SES	socio-economic status
TB	tuberculosis
TBCTA	Tuberculosis Coalition for Technical Assistance
USAID	United States Agency for International Development
WHO	World Health Organization
WHS	World Health Survey
WTP	willingness to pay
ZAR	South African Rand

CHAPTER 1. INTRODUCTION

BACKGROUND

The last five years have seen a global scale-up of universal health coverage and a renewed interest in reducing poverty and vulnerability in the context of health. Alongside these developments, consideration of the economic impact of illness on the patient and their household has taken a more prominent role in the evaluation of health care and development of health policy [1–7]. In addition to the monitoring of Universal Health Coverage, there is a growing interest in including poverty-related outcomes such as catastrophic costs as part of disease-specific economic evaluations and global targets used for programme evaluation, such as the End Tuberculosis (TB) Strategy which identifies a goal of "no TB-affected family facing catastrophic cost due to TB" by 2020 [8]. These developments stem from an increasing interest in understanding the impact of specific diseases on impoverishment and the broader dynamics of the interaction between health service delivery, patient and household expenditures, and poverty.

This shift towards broad inclusion of a patient and household perspective in economic and programme evaluation requires consideration of whether the methods and data to measure patient and household costs and impoverishment in the context of specific diseases are adequate. There has been some recent progress in methodological development alongside this increasing interest, most notably with the WHO Task Force to Estimate Catastrophic Costs, and the Global Health Cost Consortium. As part of my position as a Research Fellow at LSHTM, I have been involved with both institutions the past four years. My work with these institutions has highlighted some gaps remaining on these issues, and brought to light the fact that while disease-specific household and patient cost data are critical to help policy-makers and planners understand barriers to access and include the patient perspective in economic and programme evaluation, there remains no consensus on methods for collecting this data. A wide diversity of methods are currently employed for estimation of patient, household and catastrophic costs, and the evidence to support the choice of one practice over another is weak. There is a need for a conversation around estimation of disease-specific patient and household cost, to help researchers and policymakers recognise the impact of varying methodologies and understand the validity of current approaches to address different policy questions.

To measure progress towards the high-level End TB Strategy target, the WHO Global TB Programme developed a handbook for nationally representative cross-sectional surveys to estimate catastrophic costs due to TB which was published in 2017. As part of the WHO Task Force to Estimate Catastrophic Costs, I input into developing these methods, which have been used to carry out surveys in 11 countries in 2015-2018 [9], with a further 13 planned. The handbook specifies a standardised methodology for measurement of catastrophic costs due to TB at the national level. The primary target audience for the handbook includes national TB programmes and partners involved in supporting TB programme planning, implementation, and evaluation, and guidance is specific to the policy purpose of estimating the national prevalence of catastrophic costs due to TB. Methods identified in the handbook are not validated as a gold standard, and it is currently unclear to what extent researchers can adapt the recommended methods for other purposes.

Within the Global Health Cost Consortium, I contributed to writing the Reference Case on Global Health Costing, which aimed to improve the quality of cost estimates through improved consistency and transparency of methods, assumptions, and reporting. In recognition of the work taking place within the WHO Task Force at the time and in order to minimize duplication of effort, the GHCC Reference Case was focused exclusively on methods to estimate provider-side costs. However, at the request of the WHO the GHCC funded research to further develop methods and answer remaining questions after the completion of the Handbook (Chapters 8 and 9 of this thesis; further described below).

This thesis brings together my experience within the WHO Task Force and the GHCC, as well as additional research and experience from other projects and my own independent research.

AIMS AND OBJECTIVES

This thesis aims to assess and improve the measurement of patient, household and catastrophic costs collected in the context of disease-specific economic and programme evaluation, focusing specifically on the case of TB in South Africa.

The thesis has five main objectives:

1. Estimate the prevalence of catastrophic costs among a cohort of people with TB using primary data, collected using conventional methods
2. Identify and critically review the methods used in measuring patient costs for TB

3. Evaluate the impact of methodological variation in catastrophic cost estimation on study findings
4. Estimate nationally representative catastrophic costs due to TB in South Africa using existing data
5. Identify the policy implications and next steps for research in this area

I draw on existing data from research projects conducted within my team at LSHTM to address these objectives. Through case studies and comparative analyses, I evaluate existing methods for estimating catastrophic costs for TB and identify methodological issues researchers need to consider when collecting these costs and applying cost estimates to economic or programme evaluation.

ORGANISATION OF THE THESIS

This PhD is structured in a research paper style and is comprised of five different papers, along with some introductory and linking material. The first three chapters focus on explaining the methods and background of this PhD. This first chapter provides an introduction and justification for the research conducted. In Chapter 2, I present the theoretical background to my thesis; in Chapter 3 I describe the case study used for this PhD: TB in South Africa. Chapter 4 presents the methodological approaches used in the subsequent research papers.

In Chapter 5, I present a study of catastrophic costs for TB, HIV and TB/HIV co-infection in South Africa - the first of its kind for the country (Research Paper #1). Funding for data collection and my time for analysis on this chapter was provided by the President's Emergency Fund for AIDS Relief (PEPFAR). Chapter 6 (Research Paper #2) is a reflection and the development of a framework for the methodological challenges faced by researchers collecting patient costs in pragmatic intervention-based settings such as the one presented in Chapter 5. Data and input for this paper was drawn from four previously published studies; my time for writing this paper was not funded. Chapter 7 reports the results of a bibliometric review of methods for estimating patient costs of disease. This review aims to identify the availability, accessibility, relevance and use of methodological resources to limit the bias introduced into cost estimates due to these methodological compromises. My time for the initial search was funded by the Bill and Melinda Gates Foundation through the Global Health Cost Consortium grant; additional time for the 'second round' search, and patient cost-specific analysis and write-up was not funded. Chapters 8 and 9 (Research

Papers #3 and #4) then assess the applicability of current methods to track and evaluate programmatic progress against the target of "zero catastrophic costs due to TB by 2020". In Research Paper #3 (Chapter 8), I present an analysis to illustrate the potential impact of different methodological approaches on study results. Next, in Research Paper #4 (Chapter 9), I use modelling and regression methods to examine whether the existing data is sufficient to predict catastrophic costs at a national level given the current availability of data and the variability in methods identified in earlier chapters. Funding for data collection for Chapter 8 was funded by the Joint Global Health Trials scheme; data for Chapter 9 was drawn from three previously published studies. My time for analysis on both Chapters 8 and 9 was funded by the Bill and Melinda Gates Foundation through the Global Health Cost Consortium grant.

Finally, in Chapter 10 I summarise the findings of the thesis, its contributions to policy, the limitations inherent in the methods, and areas where further research is necessary.

CHAPTER 2. ESTIMATION OF CATASTROPHIC COSTS

THEORETICAL BACKGROUND

Defining the Household

The main unit for much social science research is the household. Defining the 'household' can be somewhat challenging in many settings where the household is not necessarily synonymous with the nuclear family. Anthropologists and sociologists working in South Africa describe households as dynamic and complex. Restrictive laws during apartheid, and continued differentials in economic opportunities in post-apartheid South Africa, have contributed to a pattern of frequent migration away from the family for work [10] and fluidity of households as children are moved to stay with extended family [11].

Despite this trend being observed across South Africa, demographic and health surveys in South Africa have consistently used the criteria of co-residence and sharing resources to define a household. Statistics South Africa defines a household as "A group of persons who live together and provide themselves jointly with food and/or other essentials for living, or a single person who lives alone" [12]. Similarly, the Demographic and Health Surveys define a household as "a person or group of related or unrelated persons who live together in the same dwelling unit(s), who acknowledge one adult male or female as the head of the household, who share the same housekeeping arrangements and who are considered a single unit" [13]. The definition of a household used by the National Income Dynamics Survey (NIDS) is more fluid and allows for self-definition – potentially including people who are recognised as part of a unit but have migrated for work (or for other reasons) [14].

This simplification is often adopted for convenience, and to enable study populations to be easily grouped by location. However, particularly when looking at household ability to cope with health-related costs, this definition introduces potential bias. By excluding family members not living in the same location, researchers may miss important sources of financial support such as remittances sent home by migrant workers. Equivalently, researchers may miss instances where payments are sent to support children living with extended family members – thereby over-estimating the resources available to pay for health care.

A Model of the Household Economy

According to the Sustainable Livelihoods framework [15], all households are subject to some fluctuations in income and earning capacity over time, and therefore face some level of risk to income or expenditure shocks. Households can limit their exposure to shocks *ex-ante* (for example through joining an insurance scheme or diversifying income or crops), or they can cope with shocks *ex-post* through mobilising wealth stores. Potential stores of wealth for households can include: human capital (skills, good health and ability to work); natural capital (land, water, environmental resources); physical capital (housing, water, transport, electricity); financial capital (savings, credit, pensions); and social capital (networks, associations, institutions) [15–21].

Households can accumulate, exchange, deplete, or otherwise put these assets to work in their day-to-day management of risk and generation of income [22]. For example, a household may invest in human capital through diversifying skills through education, or it may cope with a shock *ex-post* by drawing on underused labour available within the household. The various forms of capital are also linked, and different kinds of capital may be substitutable in some cases – for example investing in a piece of machinery to reduce the need for physical labour or reducing social life (decreasing social capital) to spend more time working.

This idea of a dynamic pattern of investing and divesting household assets is also reflected in the permanent income hypothesis, which poses that income tends to be lumpy and intermittent and is expected to rise and fall over the course of one's life in a pattern of saving and dissaving [23]. In contrast, consumption expenditure tends to be smoothed over time and stays relatively constant according to one's socio-economic status. Consumption expenditure, or the money spent on goods and services eventually consumed by the household, is thought to be a more accurate reflection of household living standards than current income [24]. When faced with income shocks (including crime, natural disasters or illness), households can typically draw on their assets to mitigate income shocks *ex-post* to keep consumption constant [15–18]. Common coping strategies include mobilising savings, deferring expenditure, selling assets, taking loans, income diversification, taking on additional labour, gifts/mutual support, or reducing consumption [25–28]. These coping strategies can help households to avoid any long-term impact on wellbeing.

Affordability in Health Care

However, consumption smoothing or other risk management mechanisms can break down under repeated or long-term shocks such as chronic illness [29–31]. For example, Gertler and Gruber found that while families can typially cope with minor ailments, repeated or chronic illnesses will diminish the household's ability to smooth consumption over time and can push a household into 'chronic' poverty [31].

Substantially large or prolonged income shocks represent a more serious threat to the current and future economic welfare of the household and have prompted policymakers to consider affordability in health care to reduce this burden. Affordability is a normative concept and often involves a judgement based on external values. As such, the precise definition of affordability is problematic not only in the health sector but also those of housing, transport, utilities and education [32–36]. An early theorist defined affordability as "some given standard of [service]…at a price or rent which does not impose, in the eye of some third party (usually government) an unreasonable burden on household incomes" [37]. This concept of identifying a price for services which does not affect a household's ability to pay for other necessary goods requires the development of some thresholds of 'unreasonable' burden.

Across sectors, affordability is most commonly defined in terms of the proportion of income spent on any basic subsistence good [32,34–40]. In the health sector, most studies evaluating poverty and vulnerability in the context of health expenditure focus on the relationship of health-related expenses with total income or expenditures. The most common affordability metrics in the health care sector include catastrophic expenditure (where health spending exceeds a threshold percentage of household income) and impoverishing expenditure (where health spending pushes a household below the poverty line) [41–43]. Measures of absolute poverty have been developed most notably by the World Bank, which currently defines poverty as having an average income below $1.25 per day, at 2005 purchasing power parity (PPP) [44]. A recent update to this approach by Wagstaff and Eozenou [42] extends the definition of impoverishing to include 'immiserizing' expenditure, which is defined where health care expenditure pushes an already poor household further below the poverty line.

Several variations on these metrics have been proposed to clarify or re-define the threshold of 'unacceptable burden' to the household [45–49]. The argument has been made that the term 'catastrophic' should be adjusted to account for people who encounter

zero expenditures because they cannot afford to access care (and therefore cannot be said to be financially protected) [50]. Suggestions have also been made to include measures of dissaving or other coping strategies, to give a better perspective on the long-term economic impact of health spending on household welfare [27,51–53].

Calculating catastrophic expenditure

The term 'catastrophic expenditure' was first coined by Birnbaum in the context of the United States' health care system, in 1978 [54]. 'Catastrophic expenditure' was defined at an arbitrary fixed threshold of $5,000 annual total health expenditure. Further US-based studies further clarified the term [55,56] and popularised its use. The popularity of the term 'catastrophic total health expenditure' grew along with growing concern that user fees were limiting access to health services in low- and middle-income countries (LMICs) in the mid-1990s [57–65]. The metric aims to capture whether out of pocket spending on health care exceeds some percentage of household income beyond which health spending is likely to have a substantial impact on the household's ability to pay for basic subsistence needs [41,43]. This concept is based on capturing a substantial sacrifice of current consumption rather than applying any absolute measure of basic need and reflects society's value of risk avoidance.

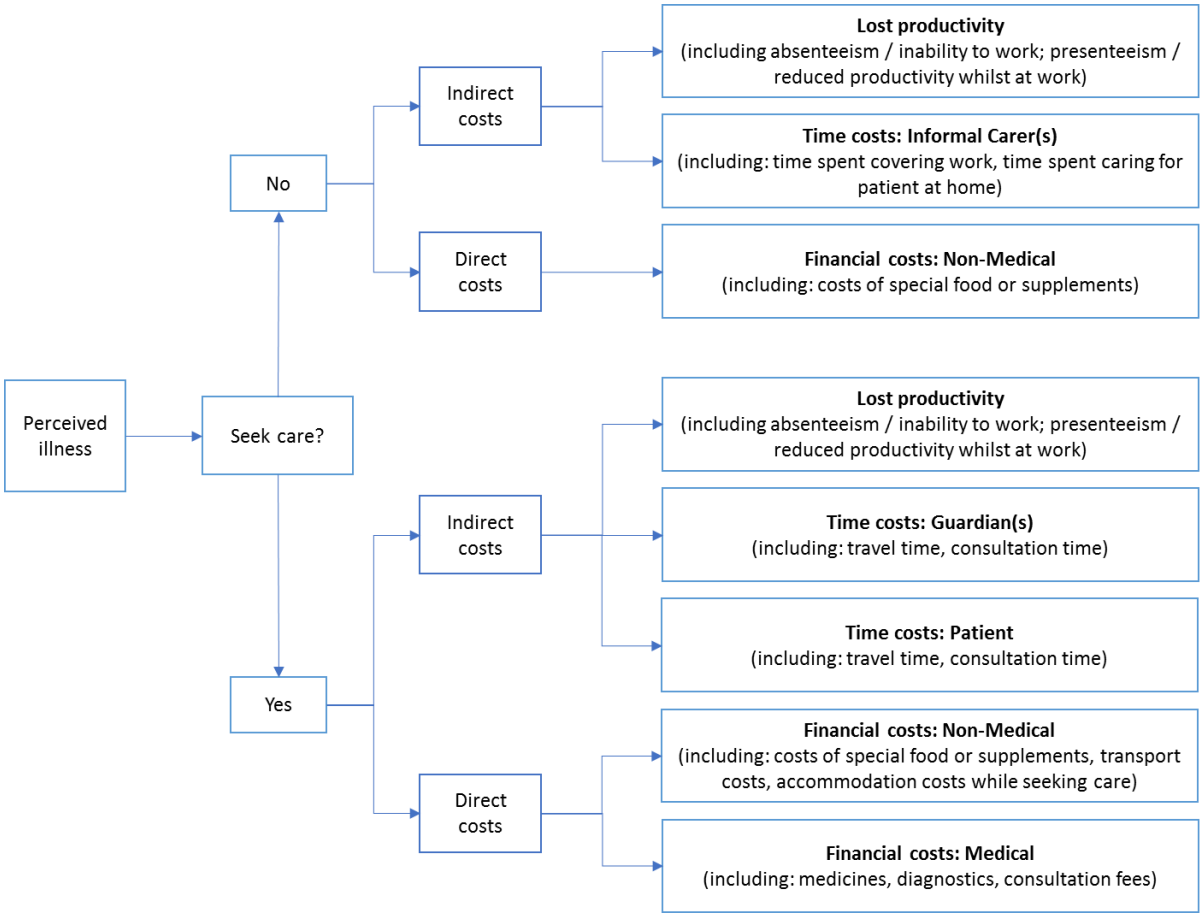
The occurrence of 'catastrophic' expenditures is usually defined as a binary variable, taking the value 1 if total health spending *(T)* is greater than a defined percentage *(x)* of household capacity to pay *(z)*, and 0 otherwise. Catastrophic overshoot can also be calculated as a continuous variable, taking the value $T/z - x$ if $T/z > x$, and zero otherwise. The following section describes each of the elements of the 'catastrophic' expenditures formula in further detail.

Costs associated with illness

First, total health spending *(T)* must be defined. Figure 2-1 depicts a pathway of the potential costs incurred by people with an illness and their households. When a person feels ill, they may or may not choose to seek care. If they seek care, they will likely incur some direct 'out of pocket' costs. Direct costs include any direct expenditures associated with illness, or with accessing care [64,66,67]. Direct costs include, for example, transport costs to attend a health facility, costs of any special foods or supplements taken because of illness, and money paid for medicines, diagnostics, consultation fees, or informal payments made to health workers.

People seeking health care will also encounter some indirect (opportunity) costs [68,69]. Indirect costs refer to the opportunity costs of time incurred by the patient while seeking care, and time with reduced productivity due to illness. It also represents the opportunity cost of time spent by household members who care for the patient. If an individual does not seek care, they will avoid direct and indirect costs of care; however, they are likely to incur higher costs associated with lost productivity due to illness. They will also likely incur some indirect costs of informal care provided for example by a family member [70,71].

Figure 2-1 Patient/household cost pathways



The traditional definition of 'catastrophic total health expenditure' used to inform health financing and risk protection includes only direct medical costs (out-of-pocket expenditure) in the numerator of the equation, not including any non-medical costs, time costs, or income loss due to lost productivity.

Capacity to pay

Calculation of catastrophic expenditures also requires definition of the household's capacity to pay for health care *(z)*. There are several potential indicators of household capacity to pay for health care, including permanent income, current income, and wealth.

Current income is defined as the amount earned by a person or household at any one given time; this tends to be lumpy and can be seasonal or dependent on the local labour market. Current income does not reflect important assets (such as savings) that can be drawn upon to finance health care without affecting economic wellbeing within the household [51,72]. In contrast, permanent income is assumed to be reflected through consumption expenditure and represents the long-term average income expectations of a person and/or household [24,73,74].

The indicator of 'catastrophic expenditures' is intended to capture where spending associated with illness imposes an economic burden that is non-recoverable, beyond typical day-to-day wealth management. Theoretically, permanent income is the best comparator to reach this aim. Measures of permanent income will more appropriately reflect the impact of health costs on the total resources available to the household, thus capturing any potential long-term depletion in financial wellbeing in the household. According to the permanent income hypothesis, permanent income can be captured through consumption expenditure [24], as consumption stays relatively constant according to one's socio-economic status [23].

Catastrophic threshold

In practice, the definition of the denominator of the 'catastrophic expenditures' equation varies in the literature, as does the threshold for defining costs as 'catastrophic' *(z)*. In the late 1990's it was proposed that 3-5% of the annual income spent on healthcare expenditures are affordable, based on observations from health expenditure surveys in LMIC countries that a 'typical household' spends between 2-5% of income on health care [75,76]. More recent studies have used thresholds falling anywhere between 5-20% total household income , or, or 30- 40% of a household's capacity to pay [77,78][79,80]..

In all recent cases, these thresholds for catastrophic spending have been defined arbitrarily with no empirical basis. Recommendations generally encourage researchers to report catastrophic expenditures across a variety of thresholds and allow policymakers to decide the most appropriate threshold for their setting [41,43]. Due to this arbitrary nature of thresholds, an argument could also be made that the definition of 'catastrophic' spending as a binary variable is not useful. For households that already lie very near the poverty line, even a very small proportion of household income may lead to financial catastrophe; alternatively, better-off households may choose to incur very high health-related costs without limiting their spending. Some studies have attempted to address this concern by

using variable thresholds at different income levels or testing the use of dissaving as an alternative indicator of financial hardship [49,81]. While it is always difficult to accurately capture the complexity of financial flows within a household, some flexibility in defining financial 'catastrophe' is often needed to appropriately grasp the pressures that many households face. Qualitative methods may also be useful for researchers looking to represent the economic impact of health-related spending on households.

DISEASE-SPECIFIC MEASURES OF AFFORDABILITY

As described above, the metric of "catastrophic total health expenditures" has been traditionally measured in terms of direct out-of-pocket expenditure as a proportion of total household expenditure, with the aim of informing health financing and risk protection [82]. This metric has been used to understand the impact of direct out-of-pocket payments incurred by the household as a result of insufficient prepayment mechanisms such as tax or insurance [83]. Catastrophic total health expenditures are a key indicator used by the World Health Organization (WHO) and the World Bank to track the performance of health financing systems and universal health coverage. In this context, the population of interest for the metric 'catastrophic total health expenditures' is the whole population of a country.

There is also a growing interest in estimating the impact of specific illnesses on household economic wellbeing. Numerous studies in recent years have estimated the prevalence of disease-specific catastrophic costs for a wide range of conditions, including: surgery [84]; diarrhoea [85]; maternal health [86–88]; HIV [89,90]; neglected tropical diseases [91–93]; chronic non-communicable diseases [94–101]; and TB [87–91]. Some studies have also compared the relative impact of various diseases on medical impoverishment [102,103].

Disease-specific measures of catastrophic costs serve different policy purposes to that of 'catastrophic total health expenditures' and have different data needs. For example, the population of interest for these disease-specific measures is often not the whole population of a country but instead the population affected by these diseases. Some estimates of disease-specific catastrophic costs also include non-medical and indirect costs in addition to direct out-of-pocket expenditures, to understand the broader impact of diseases on the household economy.

Policy applications for disease-specific measures of catastrophic cost

The advent of studies examining disease-specific catastrophic costs serves to address two distinct policy purposes: to inform the allocation of health-related spending, and to inform

targeting of social protection. First, policymakers need to understand how their investments in health interventions may impact the poor so that they can make informed trade-offs.

Methods for economic evaluation are evolving to include considerations such as equity and catastrophic costs more formally. Modelling exercises linked to 'extended' cost-effectiveness analysis can predict the number of catastrophic costs averted by an intervention [104]. 'Distributional' cost-effectiveness analysis allows decision-makers to simultaneously evaluate the cost and equity impact of health-related interventions, allowing them to take decisions which maximise health and minimise unfair variation in health care services [105]. Economic evaluation methods are also being developed to allow researchers to account for demand or supply constraints in a health system, potentially including access barriers due to high patient costs [106], following evidence that high costs of accessing health care can dissuade patients from seeking health care or encourage loss to follow-up resulting in poorer health outcomes [89].

Policymakers are also increasingly using multiple criteria decision analysis (MCDA) to inform resource allocation [107]. MCDA is a method that enables policymakers to simultaneously evaluate the impact of potential interventions on several (sometimes conflicting) concerns. For example, an MCDA approach might allow policymakers to consider a proposed intervention in the context of the cost of implementation, impact on health outcomes, impact on catastrophic costs or social protection, and political impact or consequences.

Disease-specific measures of affordability can also inform programme evaluation more broadly. Programmes are increasingly being asked to demonstrate an impact on poverty and progress towards the Sustainable Development Goals (SDGs). Although disease-specific measures of affordability can underestimate the effect of total health-related spending on a household, for diseases where there is a strong link with poverty (such as TB) this information can be critical in tracking progress. This may be especially important where health-related funding is vertical and where disease-specific programmes interact independently with donors.

Due to the characteristics of certain illnesses and the exceptional vulnerability of populations affected, health-related costs also pose a cross-sectoral concern in that they can be a substantial source of economic hardship and can lead to a downward spiral often referred to as the 'medical poverty trap' [108–110]. There is a strong association between

certain health risks and socio-economic status, and evidence suggests causal links in both directions. For example, poverty is a risk factor for TB and the costs encountered due to TB can push households into poverty [111].

Social protection is a mechanism that governments can use to interrupt this vicious cycle [112]. Implementation of social protection floors is an indicator under SDG Target 1.3, to: "Implement nationally appropriate social protection systems and measures for all, including floors, and by 2030 achieve substantial coverage of the poor and the vulnerable" [113]. Countries seeking to implement adequate social protection floors struggle with limited budgets and often rely on targeting mechanisms to ensure the greatest benefit within a given funding envelope [114,115]. Targeting can be based on the level of poverty, social category (i.e. gender or age), geography, or other criteria such as disability. Better information about the comparative impact of different illnesses on household impoverishment could theoretically help governments make decisions about including those illnesses in social protection targeting mechanisms to achieve an overall aim of reducing poverty or providing support to a particularly vulnerable group.

An important limitation of use of this metric in policymaking is that by including only costs incurred due to TB in the estimate, the metric involves an implicit assumption that the household is able to pool all income in order to finance TB care. This necessarily omits other health-related costs incurred by household members and potentially underestimates the impact of health spending on the economic wellbeing of the household. Disease-specific measures of affordability, therefore, cannot serve as a replacement for the broader metric of 'catastrophic total health expenditures'. Both metrics are necessary to monitor progress and inform decision-making.

Current standardisation of data collection methods

Despite the growing use of disease-specific catastrophic costs to inform policy, systematic reviews on the economic impact of illness on households have consistently found that methods to estimate the household-incurred costs and poverty impact of specific diseases vary widely. First, the design of studies evaluating patient, household, or catastrophic costs is currently inconsistent and often haphazard. A review of statistical methods used for cost data collection in economic evaluations of clinical trials found that only 16% of articles mentioned sample size calculations [116]. Studies included in a review by Kankeu et al. [94] varied widely in terms of sampling methodologies, with many using convenience samples.

Sample sizes amongst papers included in other reviews were also wide-ranging, and methods for choosing samples were unclear [117,118].

Studies also differed widely in terms of which costs were included. Both McIntyre, et al. and Russell, et al. reported that while direct medical costs are usually included, direct non-medical costs and indirect costs were sometimes left out of cost estimates [64,117]. Tanimura et al. and Raban et al. also report wide variation in cost components reported and disaggregation of cost ingredients [118,119].

Methods for estimation of resource use are highly variable across studies. Study timing and recall periods are different across studies in several reviews [64,118,119]. In one review, this was true even where the same metric was being assessed, and across trials funded by the same agency [120].

Methods for the estimation of indirect costs also vary widely. Measurement methods typically include either lost income or some monetisation of lost time. Methods for soliciting estimates of lost income or lost time were found to be inconsistent [94], as were methods for valuation of lost time [64,117]. Some studies chose to include the indirect costs of other household members or guardians, while others did not [94,117].

Finally, the threshold percentage of 'catastrophic' costs and the definition of income for the denominator of the catastrophic costs function were very different across studies [94,118,119]. Threshold percentages varied from 10-60%. Various income definitions used in the denominator of the 'catastrophic cost' equation included: monthly household income, annual household income, non-subsistence household income, 'capacity to pay', or total expenditure. Some alternative definitions were also used, including employment of coping strategies [119], or "high health care expenditure" as compared with other households within the same caste group in India [94].

The reasons behind this wide methodological variation, and the overall impact of this variation on findings and policy decisions, are currently unclear. The potential data quality issues associated with the use of data collected for a different purpose for estimation of prevalence of catastrophic costs have not thus far been formally addressed. Tanimura et al. [119] report a pattern in which indirect costs represented as lost income tended to be lower than indirect costs estimated through the valuation of lost time. Other reviews did not comment on the potential bias that this variation in methodology introduced on review

findings. All of the reviews mentioned above found that synthesis of findings across studies was difficult due to wide variation in the methods adopted to estimate patient costs.

This uncertainty about the impact of methodological variation on findings makes it difficult for policymakers to interpret and compare findings from economic evaluations. It is also difficult for a global body such as the WHO to rank country performance against targets or track country progress through time if results are dependent on data collection methods [121]. In order to be able to compare and interpret findings from multiple studies, there needs to be confidence that data on patient costs and capacity to pay are collected and presented in a way that enables standardisation. For these efforts to be relevant to decision-makers, researchers must take steps to reduce bias in data collection as much as possible [122].

Data requirements for disease-specific measures of affordability

The above-described policy purposes for estimating catastrophic costs require different kinds of data to that of 'catastrophic total health expenditures'. Catastrophic total health expenditure is usually estimated using household expenditure surveys. These are large, household-based surveys with sampling frames typically designed to be nationally representative. These surveys, for example the Living Standards Measurement Survey (LSMS), can cost anywhere from $400,000 to $1.5 million, with each interview lasting roughly an hour [123].

In contrast, due to the often-low prevalence of specific diseases at the household level, disease-specific data will pragmatically need to be captured at health facilities rather than as part of a national household survey. To estimate the impact of specific interventions on economic wellbeing within the household and facilitate economic evaluation, data collection is usually linked to a facility-based trial or study. Sampling requirements for estimating catastrophic costs in the context of economic evaluations are currently unclear; sample sizes are often arbitrary and vary widely from study to study. Studies are often not nationally representative as they usually are focused on answering a specific research question, targeted to a specific intervention or population.

[9]

CHAPTER 3. CASE STUDY: TB IN SOUTH AFRICA

Although many of the lessons in this thesis are applicable to the estimation of disease-specific catastrophic costs in any LMIC setting, TB in South Africa is used as a case study in this PhD. This chapter gives a short background on TB and the policy context surrounding the disease in South Africa.

TUBERCULOSIS

TB is believed to have affected humans for thousands of years. The earliest evidence of human infection is from the Neolithic C period more than 8,000 years ago [124]. The first non-Western reference to the disease appeared in the Vedas [125]; references also appear in writings from ancient China [126]. In Europe, the disease has been referred to under many names, including 'consumption', 'phthisis', and 'white plague' [126].

The disease was the leading cause of death in Europe in the 18th century, accounting for nearly 50% of all deaths in those 15-35 years of age [127]. The epidemic declined in Western Europe in the mid-19th century. Specific causes for this decline are not confirmed; it is widely noted that the decline occurred alongside advancements in social protection, nutrition, and other living standards [126], however other postulations point to increased pasteurization of milk, the introduction of sanatoriums, and natural selection as potential causes of the decline [111]. Despite this decline in western Europe, TB remains the leading cause of death from an infectious agent, affecting around 10 million people and causing around 1.6 million deaths each year [128]. The disease exists in all countries globally, but the burden is highest in 30 countries (including India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, South Africa, and others), which together account for 84% of the world's cases.

TB is caused by the bacillus Mycobacterium tuberculosis, discovered by Dr Robert Koch in 1882 [127]. The bacillus spreads through droplets in the air and commonly infects the lungs, although it can also present in other parts of the body, including but not limited to the lymph nodes, spine, joints, nervous system, and abdomen. Primary infection with the bacillus M. tuberculosis is usually asymptomatic. A relatively small proportion of those infected with M. tuberculosis (about 5-10%) will develop active TB; this can occur any time from 4 weeks to two years following primary infection. Active TB is more likely to develop in people with reduced immune function, including young children, the elderly, and people

with HIV, diabetes, or malnutrition. The infection will remain latent in remaining cases. Latent TB does not cause transmission of the bacterium.

The signs and symptoms of active TB are not consistent and are commonly confused for symptoms of flu or the common cold. Pulmonary TB most commonly presents as a persistent cough, sometimes associated with fever, chills, night sweats, weight loss, and fatigue. Extrapulmonary TB is usually not associated with a cough; signs and symptoms of extrapulmonary TB vary widely depending on which part of the body is infected with TB [129].

TB Diagnosis

Diagnosing active tuberculosis is often difficult as the signs and symptoms are non-specific. Latent TB infection can be identified through a tuberculin skin test. Tests for active TB disease include sputum smear microscopy, sputum culture, or rapid molecular tests (such as the Xpert MTB/RIF assay). Drug-susceptible TB can be diagnosed with sputum smear microscopy; this involves visual examination of sputum samples through a microscope to determine whether the bacteria are present. A chest X-ray is also often examined to confirm smear results. Smear microscopy is relatively cheap and can be conducted relatively quickly; however, it has low sensitivity in people living with HIV and cannot test for drug resistance. Culture-based methods involve placing sputum samples in a culture to promote growth of the bacteria so that it can be more easily observed. Culture can also allow for drug-susceptibility testing, by introducing sputum alongside anti-TB drugs. Culture tests are currently the reference standard for diagnosis and drug-susceptibility testing. However, the culture process can take up to 12 weeks to obtain results and requires more sophisticated equipment than smear microscopy.

Xpert MTB/RIF is a diagnostic system developed by Cepheid Inc., which detects DNA in the M. tuberculosis bacteria. It can process up to four samples at a time and has a running time of 2 hours. The machine has improved sensitivity for those with HIV and can detect rifampicin resistance. This new technology looks like a promising avenue to reduce the long delays often faced by TB patients in receiving a diagnosis and has been found to fall below established cost-effectiveness thresholds in high-burden settings [130]. GeneXpert tests have been approved by the WHO and rolled out globally in the last ten years, despite some concerns about the practical affordability of the tests [131,132].

TB Treatment

Although the bacillus which causes TB was discovered in 1882, effective treatment remained elusive for a very long time. The popularity of sanatorium care for those with TB grew in the early 1900s. A vaccine to prevent TB infection and progression (BCG) was developed in the early 1920s. Unfortunately, it was quickly determined that the BCG vaccine was not as effective as had been originally hoped. The vaccine prevents against infection in around 20% of vaccinated children and protects against progression to active TB in 50% of children vaccinated. It has not been shown to have any protective effects in adults [133]. Nevertheless, BCG vaccination in children is still recommended in high-burden areas by WHO.

Drugs to treat TB were finally discovered in 1945 [126]. The typical treatment regimen for drug-susceptible TB (DS-TB) is a 6-month drug regimen divided into an intensive phase and a continuation phase. During the intensive phase in the first two months of treatment, patients receive a fixed-dose combination (FDC) of four drugs: isoniazid, rifampicin, pyrazinamide, and ethambutol. During the continuation phase in the following four months, isoniazid and rifampicin are used to eliminate remaining bacilli and cure the patient.

Treatment for multi-drug resistant TB (MDR-TB) can be much more difficult, with treatment regimens generally recommended to continue for at least 20 months. Treatment regimens generally involve at least four anti-TB drugs, including an injectable agent in the intensive phase. Drug regimens to treat MDR-TB are designed on a per-patient basis, depending on drug susceptibility and the history of TB treatment [129]. MDR-TB treatment regimens typically involve drugs that are more toxic and can lead to stronger adverse effects. Treatment success for MDR-TB is low, with 55% of cases globally successfully being treated [128].

TB in South Africa

History of TB in South Africa

The high prevalence of TB in South Africa has roots in the social inequality prevalent under the apartheid regime - a system of institutionalised racial segregation that existed in South Africa from 1948 until the early 1990s. During this time, black South Africans were systematically oppressed, disenfranchised, forced into unsanitary and crowded living conditions, and deprived of economic opportunity by the ruling white minority

government. Legislation designed to restrict the black population to rural reserves also caused a substantial increase in the number of black migrant labourers working in South African mines [134]. There was high turnover in mines, and those too ill to be productive were forcibly repatriated to rural reserves.

These conditions caused a rampant spread of TB, which has long been recognised as a 'disease of the poor' [135][125,136,137]. Risk factors for TB include poor nutritional status, crowded living conditions, smoking, harmful alcohol use, indoor air pollution, silicosis, and stress [111,138–143] – all often unavoidable aspects of life in poverty and results of systematic oppression under apartheid. By the late 1920s, more than 90% of adults in some rural reserves were infected with TB [134].

Following democratisation in 1994, the TB epidemic was exacerbated by soaring rates of HIV/AIDS. Following a resurgence of TB in the 1980s and 90s, and in order to counter increasing drug resistance and improve control of TB, the WHO launched a strategy of "directly observed therapy (short-course)" (DOTS) in 1994; this was taken up by the South African National Tuberculosis Control Program in 1996. The DOTS strategy involves direct supervision (usually by health care workers or community volunteers) of patients taking their drugs for the full duration of treatment. Fixed-dose combination drugs for TB were introduced two years later, making it easier for patients to maintain adherence to drugs. Observation and support for patients were shown to improve adherence to treatment, but the decline in TB incidence following DOTS introduction was slower than anticipated [111]. In 2007 a five-year National Strategic Plan for TB was formed, and GeneXpert MTB/Rif was introduced in 2011 as a replacement for sputum smear microscopy.

The long history of social inequality in the country's health care system continues to make it difficult for many poor South Africans to access health care services [134]. Many state hospitals are in crisis, with only 30% of the country's doctors working in the public sector and consistent underfunding and mismanagement plaguing the public health sector [144]. Nationally, governmental expenditure on health care only accounts for about 48% of total health expenditure [145]. Eighty-one per cent of private expenditure on health care is funded through private health insurance; this is mostly only available to those working in the public sector or otherwise formally employed – covering only about 16% of the population [146,147]. In 2011 the South African government published a Green Paper to introduce a national health insurance (NHI) scheme, aiming to provide universal access to health insurance [148]. The government is currently in the second phase of

implementation, focusing on finalising the legislation for NHI and establishing the NHI Fund.

Current status of the epidemic

Today, South Africa still has one of the highest burdens of TB in the world, with an estimated incidence of 454,000 cases and 25,000 deaths in 2015. The country carries 30% of the world's HIV-associated TB cases (roughly 270,000 people) and has the fourth largest prevalence of MDR-TB in the world [149]. More than half (57%) of those infected with TB are also HIV positive.

In 2012, the South African government integrated the National Strategic Plans for HIV/AIDS and TB, creating the National Strategic Plan for HIV, STIs and TB. This and the draft updated Strategic Plan (2017-2022) emphasise the importance of integration of TB, HIV, and STI services. The draft strategic plan for 2012-2022 reaffirms the importance of decentralised care, improved social protection and targeted interventions to address the social and structural drivers of disease, and multi-sectoral cooperation in the national efforts against HIV and TB [150].

The South African National Strategic Plan is aligned with global priorities for TB management, and there is a high degree of political will in South Africa to address the high incidence and impoverishing effects of TB in the country. Recognition that the effectiveness of DOTS was limited led to an increasing number of investigations on the social and structural drivers of TB. Several studies in the last decade have shown that variation in TB trends is more strongly associated with biological, social and economic factors than with National TB Programme (NTP) performance [112,151,152]. This realisation has led to an increase in calls for improved social protection and other interventions to limit socioeconomic factors that may cause a high TB burden in some settings.

There is a strong tradition of social protection in South Africa. In the 2014/15 financial year, South Africa spent R121 billion (USD 10.05 billion) on social protection, including R18.7 billion on sickness and disability grants [153]. Further guidance is needed on targeting and implementation in order for these schemes to be useful for TB patients. For example, the country's Temporary Disability Grant is theoretically available to TB patients, however it is often inconsistently implemented [100,154], there is a lack of evidence on its impact on welfare and health status for beneficiaries, and there is concern that it may provide an incentive for patients not to adhere to treatment [155]. Other social protection schemes available within the country (including the child support grant and old age pension) could

also potentially be targeted to TB patients. However further information is necessary to inform this targeting [156].

Current evidence of catastrophic costs due to TB in South Africa

There is good availability of recent data on patient costs for TB, making the analysis presented in this PhD possible [100,157,166,158–165]. The most recent evidence comes from four papers published in 2015; two presenting patient-incurred costs of drug-susceptible TB, and two presenting costs of drug-resistant TB. Results from these papers are presented in Table 3-1. There is considerable variation in estimates between these existing studies, both for direct and indirect costs. To date, there is no evidence at the national level of patient-incurred costs of TB or how this varies by determinants nationally.

The existing evidence on catastrophic costs due to TB in South Africa is minimal. Verguet et al. report a modelled baseline of 16,848-24,278 households encountering catastrophic costs over 20 years, equivalent to 16-25% of those with TB [104]. Although there are several other studies reporting costs (and several suggesting that costs are likely to be catastrophic), no other studies report a prevalence of catastrophic cost. As part of the effort to gather data on catastrophic costs globally as countries aim to reach the WHO post-2015 target of zero catastrophic costs by 2020, a national TB costing study is planned for South Africa in the next two years. Planning for this national study has just begun, and cost data collection is likely to take place in 2019.

Table 3-1 Recent Evidence on Patient Costs of TB in South Africa

Author	Time frame (Subgroup)	Sample Size	Mean direct cost	Median direct cost	Mean indirect cost	Median indirect cost
Drug-susceptible TB (DS-TB)						
Foster, et al. [100]	Pre-diagnosis	49	$45.82 / episode*	$0.00 / episode*	$39.26 / episode*	$0.00 / episode*
Foster, et al. [100]	Post-diagnosis	175	$66.01 / episode*	$0.00 / episode*	$15.56 / episode*	$0.00 / episode*
Chimbindi et al. [164]	Post-diagnosis	296	$16.74 /month (SD 21.19)	N/R	$7.49 / month (SD 4.82)	N/R
Drug-resistant TB (DR-TB)						
Du Toit, et al. [166]	Pre-diagnosis (LPA)	89	N/R	$6.70 / episode (IQR 1.1 – 28.2)	N/R	$40.00 / episode (IQR 20.4 – 105.9)
Du Toit, et al. [166]	Pre-diagnosis (Xpert)	64	N/R	$4.40 / episode (IQR 0.0 – 22.2)	N/R	$22.1 / episode (IQR 11.0 – 54.5)
Ramma, et al. [165]	Post-diagnosis (inpatients)	82	$26.45 / month*	N/R	$247.13 / month*	N/R
Ramma, et al. [165]	Post-diagnosis (outpatients)	52	$56.98 / month*	N/R	$64.30 / month*	N/R

DS-TB Drug-susceptible TB; DR-TB Drug-resistant TB; SD Standard Deviation; IQR Inter-quartile range; N/R Not reported
*uncertainty not characterized
All costs in 2015 USD

CHAPTER 4. METHODS

METHODS FOR ESTIMATING DISEASE-SPECIFIC CATASTROPHIC COSTS

Collecting cost data is an estimation process involving five steps: defining the problem, identifying costs, measuring resources, valuing resource use, and calculating total and unit costs. Costs are typically estimated using a range of approaches and assumptions, often combining data obtained as part of research studies with data collected as part of routine program implementation. As costing is an estimation process, methods and quality in cost data can vary widely.

Several characteristics are often desired from cost data. For most purposes, cost estimates should be as precise and accurate as possible; meaning they should not be too far off the 'true' value, and there should not be too much uncertainty around the estimates. Estimates should be timely if they are to inform policy decisions. Estimates should also ideally be generalizable to other settings as much as possible; this often requires explicit consideration of any heterogeneity. Finally, methods for estimation should be reliable; ideally if the same costs were collected using the same methods by two different people, results should be consistent.

However, data availability in real-world settings is often variable, and it is not always possible to achieve all of these desirable properties simultaneously. Data collection might be limited for practical reasons (ie. survey budget or timing), or it might be impossible to collect certain types of data. This is true of both high- and low-income settings, although there may be different pressures on data collectors in different settings. For example, in some LMIC settings there might be no generation of routine data, thus requiring this data to be sourced from other places. In contrast, in some high-income settings where routine data is generated in the national health system, researchers might struggle with datasets that are too large or too complex to appropriately analyse within a given set of time. Although pressures may be different, the quality of cost data should not differ between settings; cost estimates should be as high-quality as possible in both high-income and low-income settings.

Often a balance needs to be struck between the above-listed desirable characteristics, within the context of the study, in order to produce an estimate that is fit for purpose given the data available. Transparency in reporting is essential in striking this balance. I use the broad outlines of GHCC principles [122] to describe the process of estimating patient costs

below. Where relevant, I also describe practical limitations that researchers might encounter when collecting data.

Study Design

Study design involves identifying the purpose and perspective of cost estimation, the type of costs estimated, the 'units' in unit costs, the sample and study population, and the time horizon and scope of the costing [122]. Different methodological approaches can be used for different purposes of costing. For example, estimation of household costs as part of an economic evaluation may require sampling for a certain level of confidence around the impact of the intervention on household costs. In contrast, the estimation of catastrophic costs at a national level requires nationally representative sampling.

Disease-specific patient cost data is generally collecting using a 'micro' approach. A 'micro' approach involves first estimating quantities of resources and then assigning prices to reflect the value of those resources. This can be used both for direct costs (where resources include visits to health providers, drugs, diagnostic tests, food, accommodation, and travel), and indirect costs (where resources include time). Given the choice of methods for data collection, valuation, and analysis, as well as variation in underlying assumptions, cost estimates should be communicated clearly and transparently to support interpretation and use. As noted in the GHCC reference case, several properties are desirable in a 'good' cost estimate [122]. These include accuracy, precision, generalizability, transferability, comparability, and reliability.

Before data collection begins, the analyst must design the study to limit bias as much as possible. The population for data collection should be selected in accordance with the study aims, with efforts to avoid bias due to over-inclusion of populations using higher quantities of services or encountering complications [167,168].

Sample size considerations are critical in the planning stages of a study and will depend on the aims, nature, and scope of the study, and the degree of precision (confidence interval and margin of error) deemed appropriate [169]. Household surveys generally follow United Nations guidelines of a 5-10% margin of error at the 95% confidence interval, with further adjustment to account for clustering and non-response [170]. For any study, the sample should be selected to enable statistically significant inferences about the true costs encountered by the population from which the trial sample was drawn [116].

Estimation of Resource Use

Resource use can be estimated through diaries, review of administrative records, or survey questions. There are several potential biases associated with the estimation of resource use. These include: recall error, respondent error, rounding error, cognitive errors, survey fatigue, and 'desirability' errors [171]. These potential errors are also applicable to estimation of income and indirect costs and are summarised below. Survey design can reduce (or increase) the likelihood of these errors.

If adequately filled, the diary method of recording expenditures is regarded as the gold standard [171] as it reduces the potential for recall error. Recall error refers to the inverse relationship between the length of time over which survey respondents are asked to recall something, and the accuracy of the estimates [172]. Recall has often been regarded as the 'second best' option in the measurement of consumption/expenditure. It has also long been recognised that the timing of the recall period can have a significant impact on answers to questions on expenditure [173]. Generally, a shorter recall will result in higher estimates due to telescoping bias. Lu et al. [80], for example, found that in the LSMS and World Health Survey, more detailed questionnaires and shorter recall periods resulted in higher estimates of out-of-pocket payments. However, short recall periods can also be problematic as expenditure on some goods/services is seasonal and can be lumpy, and therefore not accurately represent household wealth or earning capacity if not captured in the right period.

Respondent error is the inability to accurately capture expenditure by household members that occur outside the purview of the survey respondent. This is most problematic where the respondent of a patient cost survey was not the individual making payments, or where individuals are asked to estimate the income or expenditures of the whole household [174,175].

Cognitive error occurs where excessive cognitive demands are placed on a survey respondent, resulting in diminished quality of answers. For example, there is evidence that the cognitive demands associated with using a hypothetical 'usual month' in recall reduces accuracy and increases interview time [171]. Frequent changes of the reference period in a survey (for example, asking for some estimates 'per month' and some estimates 'per week') can also introduce cognitive error.

Survey fatigue occurs where survey length is exceptionally long, and respondents tire of answering detailed questions. Fatigue can also impact data collection through diaries, where respondents stop recording expenditures [176,177].

Finally, 'desirability' error occurs where the respondent gives inaccurate responses due to various social pressures [178]. For example, depending on the attitude and socio-economic position of the enumerator, respondents might feel pressure to inflate their estimations of income or spending. On the other hand, if respondents are not suitably informed of the purpose of a patient costing study or believe that they may receive subsidies to cover the costs of care they may alter their responses to give the impression that they are poorer than they may be in reality.

Valuation of Direct Costs

Direct costs for health care include any direct expenditures associated with illness, or with accessing care. This could include, for example, transport costs to attend a health facility, costs of any special foods or supplements taken as a result of illness, and money paid for medicines, diagnostics, or consultation fees. Estimation of direct costs involves first estimating quantities of resource use (i.e. the number of visits, number and types of drugs, number and types of diagnostics), and second valuing those resources.

To estimate direct costs, researchers often solicit the actual amount that the respondent paid for the given resources. In the context of economic evaluation, this may not always be appropriate if the actual price paid by respondents does not reflect the societal value of the resource, for example if a drug is donated or if care is paid for by a third party. However, in the context of estimating catastrophic costs, where the focus is on the actual financial impact of health-related costs on the household, direct solicitation of the actual money paid for goods and services is appropriate.

The valuation of direct costs is susceptible to the same types of survey error as the estimation of resource use; respondents may not accurately recall the amount they paid for a consultation or transportation to a health facility – especially if this took place a long time ago.

Valuation of Indirect Costs

The measurement and valuation of indirect costs have been the subject of much debate in the literature over the last 20 years. There are several proposed methodologies used for measurement of indirect costs of illness and valuation of patient time (also called

productivity costs), and there is substantial literature devoted to the controversy surrounding choice of methods [69,179–185]. The appropriate methods to estimate indirect costs are different depending on whether the analysis aims to estimate the economic impact of illness on the patient and their household or to estimate the impact of illness on society more broadly.

One of the most common approaches to value time spent seeking care or productivity loss due to illness is the human capital approach (HCA). The HCA is based on Grossman's human capital model, which regards participation in health care as an investment in human capital – increasing productive ability and therefore (theoretically) the income of the individual (measured as the wage rate) [186]. The typical unit of measurement for HCA is the household – as consumption decisions are typically made at the household level. The HCA takes account of indirect costs of illness by measuring the monetary value of lost productivity – for example by measuring income loss due to a lost job or lost days of work, less uptake of paid work, and the opportunity cost of time spent by caretakers providing informal care.

When seeking to include indirect costs in the estimate of total costs incurred at the societal level as part of an economic evaluation, the HCA has been criticized in the 'real-world' applicability of many underlying assumptions, including: full productivity, full employment in the market, competitive labour markets, and wages in direct proportion to productivity [187]. There has also been a good deal of criticism of the HCA's ability to capture the value of non-paid work or labour substitution [75,188]. Firstly, the cost of illness estimates made using the human capital method will be skewed in favour of diseases that affect 'rich white men', due to the tendency for their wages to be higher. Similarly, income/earnings will vary substantially according to cohort, time period, and business cycle [189] and therefore can be extremely unreliable when attempting to compare costs of illness between two cohorts. Finally, the HCA may overestimate the actual production lost, as it does not typically account for coping strategies such as selling capital, substitution of labour, or the ability to make up work after recovering from an illness [190].

The friction cost approach (FCA) was proposed in the mid-1990s as a way to estimate the cost to society from absence from work, disability and mortality without the above-named methodological problems [181]. The FCA is intended as more of a decision-makers approach to evaluation rather than staying strictly in line with welfarist economic theory. The FCA adopts the perspective of employers/society rather than estimating the

affordability or economic impact on the individual. Use of the FCA is therefore not applicable in the estimation of catastrophic costs, as it does not evaluate the economic impact of illness on the household. The basic tenets of the FCA argue that in the long-run from a societal perspective, no production loss will result from a person dropping out of the workforce due to illness – as that person will be replaced by somebody who was previously unemployed. The productivity costs incurred, therefore, are limited to the 'friction period' before the ill person is replaced, and includes any lost productivity through presenteeism, lost productivity before a replacement is hired, and the costs of hiring and training a replacement worker. The FCA has been criticised for its lack of underlying theory and the fact that it does not value leisure time, resulting in a vast underestimation of the value of lost time or productivity [180–182,191]. It is also challenging to operationalise – as there is a lack of reliable data on the length of friction periods. To date, due to these conceptual and practical limitations, the friction cost has not been implemented in measuring indirect costs in a low- or middle-income country.

When including indirect costs in an economic evaluation, there has been some historical debate as to whether loss of productivity is already included as part of the health outcome measures (e.g. QALYs or DALYs). Lost productivity should not be represented in both the numerator and the denominator of an incremental cost-effectiveness ratio (ICER), as this is double-counting. This concern was raised by the first Panel on Cost-Effectiveness in Health and Medicine with the recommendation to exclude costs of productivity loss in the numerator [179]. Upon revision, the Second Panel on Cost-Effectiveness in Health and Medicine agreed that it is unlikely that productivity loss will have been accurately captured in most preference-based measures, and so the costs related to productivity loss should be included in the numerator of an incremental cost-effectiveness ratio [192].

In the context of economic evaluation, recommended practice on inclusion and valuation of indirect costs varies substantially across countries. Table 4-1 summarises and compares the recommended approaches for patient costs from the national economic evaluation guidelines from 33 countries. Of 21 countries that either recommend inclusion of indirect costs in economic evaluations or consider it an optional additional analysis, only 7 make a recommendation as to which approach to take. Of these, five countries recommend HCA and two (Canada and the Netherlands) recommend FCA. A further five countries state that either method is acceptable, while the remainder do not mention methodology in the guidelines at all.

The WHO guide to identifying the economic consequences of disease and injury makes the distinction between ‘marketed’ losses and non-market losses. For marketed losses, recommendations are based on the HCA – however econometric approaches to account for endogeneity between health and wealth and long-term effects of coping strategies are also advocated. For non-market losses, the recommendation is to use an evaluation of willingness to pay (WTP) for health as the valuation method [190].

Table 4-1 Country costing guidelines on patient cost estimation

Guidelines	Recommended Perspective	Include direct costs?	Include indirect costs?	How to value indirect costs?	Indirect costs in numerator or denominator?	Include intangible costs?
Belgium [193]	Costs: health care payer Outcomes: society	No	Optional to present separately	-	-	No
France [194]	"Widest possible perspective"	Yes	Yes	Either HCA or WTP	Denominator	No
Germany [195]	Primary perspective: health care sector Optional perspectives can be social security or societal perspectives	Yes	Optional to present separately	Either HCA or FCA	Due to mortality: Denominator Due to incapacity for work: Numerator	No
Switzerland [196]	Society, third-party payer/ reimbursement agency, health care provider, patient, employer	No	No	-	-	No
Netherlands [197]	Societal perspective; report indirect costs separately	Yes	Present separately	FCA	Numerator	No
Austria [198]	Societal perspective; other perspectives such as payer / social insurance are optional	Yes	Present separately	HCA	Numerator	No
Baltic (Latvia, Lithuania, Estonia) [199]	Mainly health care perspective; societal perspective if relevant	Present separately	Present separately	Not specified	Numerator	No
Ireland [200]	Costs: health and social care system Outcomes: all health benefits accruing to individuals	Reimbursable only	Optional to present separately	Not specified	Numerator	No
Norway [201]	Societal perspective, but with some limitations	Not mentioned	Optional to present separately	Either	Numerator	No
Sweden [202]	Societal perspective	Yes	Yes	HCA	Numerator	No
British Medical Journal [203]	Advocate: societal perspective (however patient perspective only mentioned on effects side)	Not mentioned	Present separately	Either	Not indicated	No

Denmark [202]	Social perspective	Yes	Present separately	Not specified	Not indicated	Present separately
England & Wales [204]	Payer perspective	Reimbursable only	No	-	-	No
Finland [205]	Societal perspective	Yes	Yes	Not specified	Numerator	No
Scotland [206]	Scottish healthcare system, patients and their families	Optional to present separately	Not mentioned	-	-	No
Portugal [207]	Societal perspective; should be broken down into other relevant points of view namely third payer	Yes	Optional to present separately	Not specified	Numerator	No
Croatia [208]	Croatian Institute for Health Insurance (as public payer) Societal perspective may be presented separately	No	No	-	-	No
Italy [209]	Societal perspective; Italian National Health Service	Yes	Yes	HCA	Numerator	Include in denominator
Spain [210]	Societal and payer perspectives to be presented separately	Yes	Yes	Not specified	Numerator	No
Poland [211]	Payer perspective Advised to present social perspective separately	Present separately	Present separately	HCA	Numerator	No
Hungary [212]	The audience to whom the analysis is addressed. If more than one perspective, be reported clearly and separately.	Optional (depending on perspective)	Optional (depending on perspective)	Both to be explored in sensitivity analysis	Numerator	No
Russia [213]	Costs: Health care payer perspective Outcomes: societal perspective	Not mentioned	Not mentioned	-	-	Not mentioned
Canada [214]	Publicly funded health care system. Optional to present wider perspective separately	Present separately	Present separately	FCA	Numerator	No
Malaysia [215]	Provider or funder. Patient and societal perspective are encouraged	Yes	Yes	Either	Numerator	Yes

Taiwan [216]	Mainly societal perspective; may separate into payer and others	Yes	Yes	HCA	Numerator	No
Israel [217]	Sick Funds of the National Health Insurance	No	No	-	-	No
Thailand [218]	Costs: societal perspective Outcomes: depends on the objectives of the study.	Yes	Yes	FCA or WTP	Numerator	Can be included in WTP
New Zealand [219]	The health budget and patient, with respect to PHARMAC's decision criteria.	No	No	-	-	No
Australia [220]	Societal and health care sector perspective	Not mentioned	Not mentioned	-	-	Not mentioned
Egypt [221]	Perspective "should be relevant to the research question and adapted to benefits gained by the health care system"	Not mentioned	Not mentioned	-	-	Not mentioned
South Africa [222]	Third-party payer perspective Optional to use a broader perspective where justified	No	No	-	-	No

In the context of estimating catastrophic cost, the aim of estimating indirect cost is to estimate the actual financial loss to the specific household incurring the cost, rather than to estimate the overall loss at the societal level. The two most common methods to estimate the value of reduced time for catastrophic cost estimates are the HCA and an output approach [9].

Using the HCA, the number of hours spent seeking care or otherwise unable to work due to illness can be estimated, and the value of these hours approximated with an estimate of the earning capacity of the patient for that time (e.g. hourly income):

$$\frac{Direct\ Cost + (Hours \times Hourly\ wage)}{Household\ capacity\ to\ pay} > Threshold\ value\ (\%)$$

Alternatively, when estimating indirect costs for inclusion in catastrophic cost estimates, the total income lost due to illness can be directly solicited using an 'output' approach. First, household income can be estimated before and after the illness episode; any direct income loss due to illness is then captured by taking the difference.

$$\frac{Direct\ Cost + (HH\ IncomePRE - HH\ Income\ POST)}{Household\ capacity\ to\ pay} > Threshold\ value\ (\%)$$

The HCA approach captures all time off work necessitated by symptoms and treatment seeking, but may not include any household mitigation of that loss. The output approach captures only the loss of paid work. Both approaches are is subject to recall error and may be biased where the expected income from a day's work is not easily predictable. The output approach may also not include the value of time that was productive but not income-earning – for example self-production of goods, food, or childcare.

Estimating Capacity to Pay

A fundamental question around the estimation of catastrophic total costs due to TB is the appropriate denominator to represent the resources available to the household. This is discussed briefly in Chapter 2 above, which explains that consumption expenditure (or some other measurement of permanent income) is the most theoretically appropriate metric for the denominator of the 'catastrophic' equation, as it best represents where health-related costs push a household beyond their typical day-to-day management of wealth.

Consumption expenditure tends to be more accurately measured than income [223,224]. This is especially the case where employment is informal or unsalaried. Households with

fewer resources are more likely to remember expenditures than income and may be more willing to disclose what they have spent than what they have earned, counteracting desirability bias [223]. There is also evidence that detailed questions regarding consumption expenditure help to counteract recall and cognitive bias [171].

The above-described sources of bias can impact the estimation of consumption expenditure [174,225–230]. For example, longer recall periods can cause recall bias, where participants may not accurately remember expenditure occurring a long time ago; shorter recall periods are often advised for accurate answers [171,231]. The relationship of the interviewer to the participant may lead to desirability bias, where an individual may under- or over-report their expenditure based on perceived attitudes of the interviewer; this can be minimised through training of enumerators. The burden on the respondent can potentially be minimised by using closed brackets rather than an open-ended format requiring a numerical response [231]. However, the use of brackets can potentially lead to anchoring bias and provides less informative data [232,233]. Unclear framing of questions around expenditure can potentially cause cognitive bias, where the question is difficult to understand or answer. Adding further detail to questions may improve understanding of the question and increase the accuracy of answers, but may also increase non-reporting bias [234]. Finally, there is potential for error in capturing expenditure outside the purview of the survey respondent [171]; in the case of household income, this can often be addressed by interviewing the head of the household where possible.

Researchers have opted to take various approaches to estimate 'capacity to pay', with the majority using self-reported current annual individual income in the denominator of the catastrophic costs equation [235]. Current income is often believed to be quicker and cheaper to measure [228], especially in middle-income and high-income settings where there is more formal employment and fewer consumption items are self-produced. Current income is therefore often the measure of choice for researchers despite the potential for inaccuracy and under-reporting [236].

The WHO guide to estimating catastrophic costs for TB suggests several different approaches to measuring income for catastrophic costs [237], including self-reported household income, estimated household income based on the average net wage rate (from national income data), or estimated household income based on asset scoring. Following on from indications that financial catastrophe is linked with coping strategies [81], the

WHO is also considering a recommendation that household use of coping strategies is in itself an indicator of catastrophe, regardless of total cost or household income.

Reporting study estimates

There is currently no standardised reporting framework applicable to patient, household, or catastrophic costs. Reporting frameworks for economic evaluations, such as the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [238] or the guidelines for authors and peer reviewers of economic submissions to the British Medical Journal [238] currently provide little to no guidance on reporting costing methods. Although a more thorough reporting checklist on cost estimation methods is currently being developed as part of the GTHCC for Estimating the Costs of Global Health Services and Interventions, this is exclusively focused on provider-side costs [238].

Many of the items to include in reporting patient, household, or catastrophic costs are similar to those described in the GHCC Reference Case checklist. For example, researchers should describe the population of interest, setting, location, time horizon, and sampling methods. It is good practice to present patient/household costs by provider type, cost type, and phase of illness in order for researchers and policymakers to identify the pathways driving catastrophic costs. Given the inconsistency and uncertainty around income estimation methods, some studies also choose to present time spent travelling/seeking care in hours, rather than only presenting indirect costs incurred. Uncertainty and heterogeneity in estimates should be appropriately considered where applicable.

Incorporating equity considerations using asset indices

Many studies present the prevalence of catastrophic costs by socioeconomic quintile to facilitate the interpretation of the results of estimating catastrophic costs. Chapters 8 and 9 of this thesis both classify the respective study populations by income quintiles to allow for a comparison of the costs of TB on the household economy by socioeconomic status (SES). Households can be classified based on their household income where this data is available or based on their asset holdings if income data is unavailable or unreliable.

If asset data is used to determine SES, researchers need to aggregate a number of variables to come to a uni-dimensional measure of SES. Vyas and Kumaranayake [239] recommend a principal components analysis (PCA) approach to estimate a wealth index. PCA is a multivariate statistical technique that transforms a set of variables into a set of ‘dimensions’ or principal components. Researchers can then identify the component

explaining the largest possible amount of variation in the data and use this to classify households into a predetermined number of groups (i.e. quintiles).

PCA was designed for use with continuous, normally-distributed variables and therefore its application to the categorical variables in a wealth index is considered by some to be inappropriate [240,241]. MCA is analogous to PCA but is designed for use with discrete data and is more appropriate to categorically coded asset data available in most datasets. In settings where asset ownership and inequality tend to be different in rural and urban areas [242], it is recommended that an MCA is conducted separately for rural and urban households. Both Chapters 8 and 9 of this thesis use an MCA in order to generate an asset index.

EXTRAPOLATING FROM LOCAL DATA TO NATIONAL ESTIMATES

Although it can sometimes be useful to present cost or cost-effectiveness estimates for a single study cohort or another small group of people, much of the usefulness in the practical implementation of health economics research involves using locally-collected data to inform national decision-making. This often necessarily involves extrapolation of study-specific data (drawn on a sample which may or may not be nationally representative) to represent how an intervention or service will play out on a larger scale.

Different studies have taken different approaches to extrapolate data from a sample of patients to the program level, and typically involve some degree of modelling. Model structure can be determined a priori if researchers are sure about the relevant pathways, or informed by empirical data if the relationship between different pathways is uncertain or unknown.

The process of designing a model has been described as “inherently uncertain” [243] because it is almost always impossible to gather complete information on all of the possible consequences of introducing an intervention. Researchers need to determine how best to structure and parameterize the model given the available information. Uncertainty in designing and parameterizing a model can come from several sources, including a lack of appropriate data, insufficient data quality, or differences in methodological choices across different studies.

The first concern for modellers is a lack of data. Where data is lacking, assumptions can in some cases be used to fill gaps if the assumed values are not the primary drivers of the model outcome. Values can come from consultation with experts, previous experience, or

other sources. If assumptions are used, it is critical to evaluate uncertainty around these assumptions through a sensitivity analysis or other formal consideration.

Where data does exist, it is important to consider the quality of the data when applying it to a model. Several elements of data quality are discussed above, including accuracy, precision, timeliness, generalizability, and consistency of methods. The quality of parameterization in a model is dependent on the accuracy (the extent to which the estimate reflects the true value) and precision (the extent of clustering around the central estimate) of the estimator. There is no universal definition of 'acceptable' accuracy or precision of cost data, as much depends on the purpose for which the data is collected and the manner in which it is applied. To suit the purposes of some applications, researchers may need to adjust estimates to account for heterogeneity in demography, epidemiology, or resource prices in different settings [244,245]. When not adequately addressed, the presence of strong bias or imprecision in model parameters can influence the conclusions drawn from a model; models based on biased data can lead to the wrong conclusions, whereas models with a high degree of uncertainty or imprecision may make interpretation of the results for policy purposes difficult.

Finally, if using multiple data sources to parameterize a model it is important to consider any differences in methodological choices across the different studies. Different methodological choices may be fit for different purposes, however if data is not appropriately adjusted before pooling this might lead to biased results. Methods for pooling data from multiple studies are discussed further below.

There are several possible estimators that could be used to parameterize a model, including the mean, an adjusted mean, median, or a regression coefficient (amongst others); each of these has different strengths and weaknesses. A simple mean or median is likely to lead to heavily biased results, especially in a population where there is skewness in cost data and/or where costs vary substantially by subgroup. In the following sections, I describe the strengths, limitations, and steps involved in two popular approaches: meta-analysis of summary statistics, and regression analysis of pooled primary data. I also describe methodological choices taken in the chapters of this PhD where appropriate.

Meta-analysis

Researchers seeking to parameterize a model may choose to use a meta-analysis of summary statistics stratified by subgroup to obtain input values. A meta-analysis obtains a weighted average from the results of individual studies. Weights are derived from study

sample size and uncertainty around each estimate, and sometimes also from the quality of the data. Non-normally distributed data (such as cost data) needs to be log-transformed before a meta-analysis is carried out, as the process for conducting a meta-analysis includes an assumption of normality. Researchers also need to choose between a fixed-effect model or a random-effects model. The fixed-effect model assumes one true effect size that underlies all studies in the analysis, with all variation caused by random sampling. The random-effects model allows for variation in effect sizes between studies, for example because the populations in different studies may have different demographic characteristics or might be receiving different interventions [246].

A meta-analysis has several potential benefits over a simple mean or median value. Meta-analyses can improve the precision of estimates and can identify variability across different studies. Where study quality is readily determined, meta-analyses can limit bias in the pooled estimate using quality weighting. Finally, a meta-analysis is often convenient as summary statistics by subgroup are often reported in papers, and can be input into models without the need to obtain and pool primary data.

There are some limitations associated with meta-analysis. Study quality is sometimes difficult to determine using only the reported summary statistics or a manuscript, making it difficult to adjust for bias where this is unknown. Meta-analysis involves some a priori assumption of the model structure and relevant subgroups and does not allow for interaction between the different explanatory variables, ultimately often making the model less specified or less accurately specified. Finally, where summary statistics have a high degree of imprecision, the results of a meta-analysis will also be imprecise making the results of a model challenging to interpret.

Regression analysis of pooled primary data

If primary data is available, researchers can pool the primary data for regression analysis. There are a number of benefits associated with pooling primary data from multiple studies. With the primary data, researchers can better understand data quality and can recalculate variables if necessary to ensure consistency across the pooled dataset. Pooling data from several studies can increase the sample size, improving statistical power and potentially reducing imprecision across multiple datasets [247]. It can also improve the cultural and economic diversity of patient populations reflected in the data to enable a more appropriate representation of the national population [248]. It can also facilitate better specification of model parameters, by allowing the analyst to include additional

demographic characteristics in the estimation of parameters and understand the interactions between different explanatory variables. Finally, pooled primary data can help describe determinants of unit cost variation more accurately than summary statistics, and can improve understanding of the uncertainty around estimates [249,250].

Pooling data

One strong disadvantage of pooling primary data is that gaining access to primary data has historically been a great challenge for researchers. A survey conducted in 2002 found that 47% of requests for primary data had been declined [251]. Authors might decline requests to share data because of the time required to reformat the data, concerns about how the data will be used, or plans to publish further analysis on the data in the future. This is changing to some degree, with many research funders now requiring that data be made openly accessible. Where data is not already in an online repository, negotiations to access the data might take some time, as often multiple stakeholders must agree to share data. A data-sharing agreement is recommended to facilitate negotiations and address researchers' concerns [251].

Once data sharing arrangements have been agreed, the researcher seeking to pool data must draw up a data coding protocol and resolve differences in data coding across studies. The primary concern in pooling data is to ensure that "variables apparently representing the same phenomenon indeed [do]" [247]. Often this will require recoding or recalculation of variables. Researchers will need to address a number of concerns in maintaining consistency in the data, including: coding of demographic characteristics; currency year and time frame for cost data; discount rate; recall periods; and cost estimation method. There may be some differences in the datasets that are difficult to identify. For example, it is possible that the different studies which represent different patient groups across different settings will exhibit some heterogeneity in the variables of interest which could confound the analysis. There may also be an intervention effect on the variables of interest (e.g. cost) that must be accounted for in the pooled analysis, understanding that there will be variation in interventions themselves and therefore in the intervention effect.

Dealing with missing data

Primary datasets may have data missing; researchers will need to determine the mechanism for missingness; this will help to determine methods to deal with missing data. Reasons for missing data are classified as: missing completely at random (MCAR); missing at random (MAR); and missing not at random (MNAR).

If data is determined to be MCAR (i.e. there is no pattern to missingness of data, and no systematic differences between the missing values and the observed values), a complete case analysis will not lead to bias. The analyst can in this case comfortably conduct analysis without any imputation, taking the assumption that results drawn from the observed data will not be statistically different from results if there were no missing observations.

However, data in the real world are not often truly MCAR. Missing values are often related to observed values; for example, costs are often determined by demographic characteristics such as age, gender, level of education, or income quintile – the frequency of which may vary between observed and non-observed data. In these cases, a complete case analysis will lead to bias, and the researcher must impute the missing observations. There are a number of possible approaches statistical approaches to conducting analysis with missing data; arguably the most widely applicable and practical approach is multiple imputation [252]. The process of multiple imputation uses statistical packages to allow for uncertainty by creating several different plausible imputed datasets based on the observed relationship of various characteristics to the data. The model of interest is then fit to each of the imputed datasets; the variation between the multiple plausible datasets allows for better representation of standard errors around overall associations.

There are several model-based imputation procedures available to researchers. The choice of procedure is dependent on the distribution of the data and characteristics of outcomes. For example, if data is normally distributed and outcomes are binary, a Tobit model may be appropriate; if data is normally distributed and outcomes are semi-continuous, a two-part model (such as the Heckman selection model) may be appropriate. Multiple imputation of non-normally distributed data requires non-parametric techniques for imputation. Predictive mean matching (PMM) is one such non-parametric technique for dealing with non-normally distributed data. PMM imputes missing values using a specified number of 'nearest neighbours', based on the expected values of the missing variables conditional on the observed covariates [253]. This allows for maintenance of the original distribution of data.

As imputation is dependent on regression analysis, where there are missing values in several variables univariate imputation can still result in missing values. A popular solution to this is the use of multivariate imputation by chained equations (MICE); using this approach researchers can identify a series of conditional models which are automatically cycled through by statistical software. Using MICE, different model types can be designated

for each variable as appropriate; for example, a Tobit model may be identified for binary outcomes or PMM model identified for non-normally distributed data as above.

Choosing and fitting the regression model

The process for fitting a regression model begins with the determination of covariates which are likely to influence the outcome. Following the Grossman model of demand for health, people are likely to seek health care as long as the rate of return on investment in health care (in terms of productivity and utility gained from improving health) is greater than the costs of doing so [254]. Health-related costs are therefore likely to be driven by indicators of earning capacity (including wage rate, education, gender, and urbanicity), and anticipated benefits of gaining health (including age and disease/disability).

Researchers will then need to identify the most appropriate functional form for a model. The model specification process often involves testing the efficiency of several functional forms as applied to data. Two functional forms have been recommended as appropriate for non-normally distributed data: a generalized linear model (GLM) with a gamma distribution and log link, and a quantile regression model [255]. In Chapter 9 I choose a quantile regression model to estimate income, and a GLM model to estimate TB-related costs; methods for the analysis are described further in Chapter 9 and in the supplementary materials for Chapter 9.

The goodness of fit for a GLM is generally tested using the Akaike information criterion (AIC). Unlike an R^2 value, the AIC does not provide an absolute estimation of the predictive value of a regression. Instead, the AIC is an estimator of the relative quality of statistical models for a given set of data. Fitting a GLM model involves a process of fitting a series of candidate models; the model with the lowest AIC is then determined to be the highest quality model. Normality of residuals for a GLM model can be tested using the Shapiro-Wilk normality test.

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CHAPTER 5. THE PATIENT COSTS OF CARE FOR THOSE WITH TB AND HIV: A CROSS-SECTIONAL STUDY FROM SOUTH AFRICA

PREAMBLE FOR RESEARCH PAPER #1

This paper presents the results of a patient costing study for people with TB and/or HIV presenting to health facilities in Ekurhuleni North Sub-District, South Africa. At the time this paper was written, there was no comprehensive evidence on the economic impact of illness on people with both TB and HIV, despite the fact that this population group accounts for over 60% of those with TB. The aim of this analysis was to add to the evidence base on the patient costs incurred by people living with TB and/or HIV in order to support policymakers as they assessed potential benefits from the improved implementation of TB/HIV integration.

The study was nested within the MERGE trial, which evaluated the effect of implementing an intervention to optimise/improve TB/HIV integration on morbidity, mortality and retention in care at public primary health care clinics (PHC clinics) . Integration is not binary, but rather encompasses a range of dimensions, including clinical coordination and linkages, physical integration, and/or temporal integration. Theoretically, integration of health services can reduce patient costs associated with time and travel to the health facility through economies of scope, although there is very little practical evidence that this occurs in the real world.

We include an estimate of the number of 'integrated' TB/HIV visits received by patients in this paper (defined for this sub-study as receipt of both TB and HIV services at the same facility, on the same day). However, the practical extent and characteristics of integration at health facilities within the study varied widely. For example, in some study facilities services may have been physically integrated but not temporally integrated, while in other study facilities there may have been clinical coordination but no physical integration. Due to this complexity, it was not possible to estimate economies of scope in this study.

The data for this paper was collected April-October 2013. The methods of this study were in line with the standard for estimating patient costs at the time of cost data collection. The patient questionnaire was adapted from the USAID Tool to Estimate Patient Costs. A descriptive analysis presents the monthly costs of people with TB-only, HIV-only, and

TB/HIV. Catastrophic costs were estimated as occurring when direct and indirect costs exceeded a baseline threshold of 10% of monthly individual participant income; this threshold was varied in sensitivity analysis.

We found high proportions of all patients encountering high catastrophic costs using this definition – ranging from 50-68% of TB/HIV participants, 31-46% of TB-only participants and 33-54% of HIV-only participants depending on the threshold. The results of the paper made a strong case for increased social protection of those living with TB and/or HIV, and improved integration of TB and HIV services. The results of this paper were valuable to policymakers in the context of very little evidence about the relative costs of combined TB/HIV infection.

This was a multi-authored work based on cost data collected during the MERGE trial. All co-authors contributed comments and edited the paper. DM oversaw the collection of the patient cost data. DM and I jointly conducted the analysis and co-wrote the paper.

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Primary Supervisor	Anna Vassall		

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THE PATIENT COSTS OF CARE FOR THOSE WITH TB AND HIV: A CROSS-SECTIONAL STUDY FROM SOUTH AFRICA

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ABSTRACT

Background: This study describes the post-diagnosis care-seeking costs incurred by people living with TB and/or HIV and their households, in order to identify the potential benefits of integrated care.

Methods: We conducted a cross-sectional study with 454 participants with TB or HIV or both in public primary health care clinics (PHC clinics) in Ekurhuleni North Sub-District, South Africa. We collected information on visits to health facilities, direct and indirect costs for participants and for their guardians and caregivers. We define 'integration' as receipt of both TB and HIV services at the same facility, on the same day. Costs were presented and compared across participants with TB/HIV, TB-only and HIV-only. Costs exceeding 10% of the participant`s income were considered catastrophic.

Results: Participants with both TB and HIV faced a greater economic burden (USD $74/month) than those with TB only (USD $68/month) or HIV only (USD $40/month). On average, people with TB/HIV made 18.4 visits to health facilities, more than TB-only participants or HIV-only participants who made 16 and 5.1 visits respectively. However, people with TB/HIV had fewer standalone TB (10.9) and HIV (2.2) visits than those with TB-only (14.5) or HIV-only (4.4). Although people with TB/HIV had access to 'integrated' services, their time loss was substantially higher than for other participants. Overall, 55% of participants encountered catastrophic costs. Access to official social protection schemes was minimal.

Conclusions: People with TB/HIV in South Africa are at high risk of catastrophic costs. To some extent, integration of services reduces the number of standalone TB and HIV of visits to the health facility. It is however unlikely that catastrophic costs can be averted by service

integration alone. Our results point to the need for timely social protection, particularly for HIV-positive people starting TB treatment.

INTRODUCTION

The launch of the Sustainable Development Goals (SDGs) and Universal Health Coverage reflect an increased global focus on the interaction between health outcomes and poverty. Health sector policy-makers are becoming increasingly interested in interventions and service delivery models that may best prevent impoverishment. While there has been much investigation into the impact of service integration on provider costs, much less attention has been focussed on the potential economic and poverty reduction benefits to service users, particularly vulnerable groups (World Bank, 2009; World Health Organization et al., 2009; Atun et al., 2010).

Household and patient-incurred costs associated with health shocks have long been recognized as key contributors to impoverishment (Heltberg and Lund, 2009; Alam and Mahal, 2014; Wagstaff and Lindelow, 2014). In the case of tuberculosis (TB), patient-incurred costs are a major barrier to access to health services in low-income countries (Ensor and Cooper, 2004; Donnell, 2007), and have been associated with negative TB treatment outcomes (Wingfield et al., 2014). Even where TB services are offered free of charge, the high costs of access such as transportation and opportunity cost of time spent accessing care may provide obstacles for vulnerable groups, while worsening or creating poverty in those that proceed to seek care (Xu et al., 2007). When faced with high costs of accessing TB care and a reduced ability to earn income due to illness, some TB patients resort to selling off their assets and taking interest-bearing loans (Lönnroth et al., 2014). This can result in a long term poverty impact for both patients and their households (Xu *et al.*, 2003; Gottret and Schieber, 2006; Etienne *et al.*, 2010; Lönnroth *et al.*, 2014).

For people accessing care for both TB and HIV, health service integration has the potential to reduce this economic burden. Integration may benefit patients by enabling health improvements and cost reductions through less fragmented services, improved continuity of care, and better retention in care (Sweeney et al., 2012). Integration may also facilitate cost reductions through fewer visits to facilities and reduced delays in accessing treatment (Legido-Quigley *et al.*, 2013).

In 2012, TB was the primary cause of death for 25% of all HIV-associated deaths in South Africa, and 61% of all people with TB were HIV-positive (WHO, 2015). The country has

developed guidelines for the integration of TB and HIV services with preference for a "one-stop shop", where services are provided under one roof (National Department of Health South Africa, 2014). TB/HIV integration is expected to "ensure comprehensive management of the patient, reduce morbidity and mortality and improve treatment outcomes" (Chehab *et al.*, 2013; Republic of South Africa Department of Health, 2014). Integration however remains poorly implemented in South Africa (Churchyard GJ *et al.*, 2014). Although services are commonly provided 'under one roof', they may often not be provided by a single provider, nor will patients be correctly referred between providers. As a result the evidence base on the impact of TB/HIV integration on patient-relevant outcomes is small and inconsistent (Kaplan et al., 2014; Jacobson et al., 2015; Ledibane et al., 2015).

To date, TB patient costing studies in South Africa (Chimbindi et al. 2015, Foster et al. 2015) have not comprehensively assessed the economic impact of illness on people with both TB and HIV. The purpose of this paper is to comprehensively describe the post-diagnosis care-seeking behaviour, patient costs incurred and coping strategies adopted by people living with TB and/or HIV and their households, in order to identify the potential benefits of integrated care. To present this, we collected data on the costs incurred by participants in the period immediately following receipt of a TB and/or HIV diagnosis and including the first 3-5 months of care, as this is the period when previous studies have shown patients to incur the highest costs (Foster et al. 2015). We present this evidence in order to support policymakers as they assess the potential benefits from the improved implementation of TB/HIV integration.

METHODS

Study setting

The study was conducted in Ekurhuleni North; a sub-district in Gauteng province, South Africa. Ekurhuleni had approximately 3.2 million inhabitants in 2013 (City of Ekurhuleni, 2013) and a population density of approximately 1609 people per square kilometre (Statistics South Africa, 2011). Ekurhuleni has a high unemployment rates of 28.8% in the general population and 36.9% among persons between ages of 15 and 35 (City of Ekurhuleni, 2013, 2014). In 2013, 8% of the people living in Ekurhuleni reported that they did not have any source of income and 27.9% were considered to be living below a nationally defined minimum living standard (City of Ekurhuleni, 2013). The South Africa District Health Barometer of 2013 estimated a TB case notification rate of 336 per 100 000

for Ekurhuleni (Massyn *et al.*, 2014). According to a national HIV prevalence, incidence and behaviour survey, the HIV prevalence for Ekurhuleni was 14.3% (10.3% - 19.5%) in 2012 (Simbayi *et al.*, 2014).

Study design and baseline data collection

This was a cross-sectional study nested within a cluster randomised trial – the MERGE trial. The MERGE trial evaluated the effect of implementing an intervention to optimise/improve TB/HIV integration on morbidity, mortality and retention in care at public primary health care clinics (PHC clinics) (Kufa *et al.*, 2014). A total of 18 PHC clinics, the study clinics, were randomly allocated to the intervention or control arm. To be eligible for inclusion in the trial, the clinics had to meet the following criteria: no conflicting research study in progress at the clinic, clinic has at least 40 TB cases per year, and the clinic has available TB data.

Participation in the MERGE trial was not a requirement for inclusion in the patient costs study. Instead MERGE trial participants had an equal chance of also being enrolled in the patient costs study if eligible. Cost data were collected using structured questionnaires at the 18 study clinics between April and October 2013. Participants were selected consecutively and enrolled if they met any one of the following criteria: i) received a TB diagnosis 3-5 months prior to interview AND had a positive HIV test at any time ("TB/HIV"); ii) received a TB diagnosis 3-5 months prior to interview and was HIV negative at time of enrolment ("TB-only") iii) tested HIV positive for the first time 3-5 months prior to interview and was not on treatment for TB at the time of enrolment ("HIV-only"). The time period was informed by previous research which showed that participant recall becomes diminished at around 4 months onwards (Mauch *et al.*, 2011). All participants reported a known positive or negative HIV status. Unlike TB, HIV positive reporting was not confirmed with clinic records. Participant numbers were capped at 50 per site, although only 3 of 18 sites reached this cap due to low participant numbers at the facilities.

Questionnaires

Questionnaires were adapted from the Tool to Estimate Patients' Costs that was developed by the Tuberculosis Coalition for Technical Assistance (TBCTA) and the United States Agency for International Development (USAID) (USAID *et al.*, 2008). Separate questionnaires were developed for people being treated for TB (regardless of HIV status) and for HIV-positive people not being treated for TB to accommodate different pathways of care. Both questionnaires captured similar level of detail on the different events in the pathway of care. Questionnaires focused on the period in the first 3-5 months after

participants knowing or being told they had TB ('post-diagnosis') to understand the costs of accessing integrated services.

Demographic characteristics such as gender, age, ethnicity and nationality, levels of education, marital status, employment at the time of receipt of diagnosis, and the impact of illness on normal productive patterns were collected. Questionnaires also included detailed questions on the number of visits made to a range of providers, including the participant's local PHC clinic (our study clinic), other public facilities, general practitioners, hospitals, traditional healers and pharmacies. A distinction was made between integrated visits and stand-alone visits for TB and/or HIV services at the study clinic. We define 'integration' as physical and temporal integration, or receipt of both TB and HIV services at the same facility, on the same day (Mayhew *et al.*, 2016).

It was not feasible to measure costs for every visit made by participants; questions therefore elicited estimates of direct costs, time spent and income loss for the most recent visit to each provider, and the number of visits made to each provider type during the treatment period. The questionnaires also captured information about strategies adopted by participants to cope with costs of illness. Coping strategies enquired of include: taking interest-bearing loans from lenders, borrowing money from friends or relatives, selling personal goods, and receipt of grants or charitable donations.

Data analysis

The data were captured in a secure electronic database and exported into Stata 14 and Microsoft Excel for analysis (Microsoft, 2014; Stata and Stata Corp, 2015). An 'available case analysis' assumed unavailable data values were missing at random. All costs were converted to an average monthly cost to facilitate comparison across participants who had received diagnosis between 3-5 months prior to interview.

Direct costs were defined as medical and non-medical expenses paid out-of-pocket (OOP). Medical expenses included consultation fees and any OOP payment for medicines and diagnostics paid at any provider. Direct non-medical expenses included the travel costs of participants and guardians if any, food costs incurred while in hospital, money spent buying any special foods or dietary supplements due to illness, and any interest incurred on loans taken out to meet the costs of OOP payments. Direct medical and non-medical costs were determined as the product of the reported expense for the most recent visit to each provider type and the number of visits made to that provider during the post-diagnosis period; these were then divided by the number of months in the post-diagnosis period.

We use reported income loss as our primary measure of indirect costs for participants. To facilitate comparison with other patient cost studies, we also report separately on time the participants spent seeking care or were unable to work. We estimated the mean time spent per month using the total time reported for the most recent visit to each provider time, multiplied by the total monthly visits to each provider. Indirect costs for guardians and carers were defined as the opportunity cost of time spent away from their daily productive routine, including travel to health facilities, consultation time, and covering household chores usually done by the participant. As guardians and carers were not interviewed directly about their income loss, the opportunity cost of this time for guardians and carers was estimated using median income of elementary occupations in South Africa, R 1517 per month (Statistics South Africa, 2010) multiplied by the mean time loss. Loan costs were calculated as the difference between the borrowed amount and the amount paid back.

We also estimated catastrophic costs incurred due to TB and/or HIV. Catastrophic costs are calculated as a proportion of total costs (direct and indirect) to an income (personal or household). The principle of catastrophic costs is rooted in identifying when patients and their households involuntarily reduce expenditure on basic household needs such as food, clothing and education in order to pay for health care (Ranson, 2002). According the World Health Organization (WHO) approach, costs are defined as catastrophic when total costs incurred (direct and indirect combined) exceed a given threshold of household income (World Health Organization, 2015). In the absence of reliable data on household income, we adopted a threshold of 10% of individual participant income (Barter *et al.*, 2012). This threshold has been a widely used benchmark for catastrophic costs in many patient costing studies (Xu *et al.*, 2003; Russel, 2004; Tanimura *et al.*, 2014; Wingfield *et al.*, 2014; Foster *et al.*, 2015), due to the challenges of measuring household rather than individual income. An alternative 20% threshold of household income is also being increasingly used in the case of TB, due an observed association between this level of cost and negative health outcomes in Peru (Wingfield et al. 2014). We varied the catastrophic cost threshold in our analysis from 5-25% to understand the impact of this arbitrary threshold (Russell 2004, Ukwaja, Alobu & Hopewell 2013). To avoid mathematical errors associated with division by zero, an arbitrary value of USD1 was assigned to income for those participants who reported zero income or where income was a missing value (Foster *et al.*, 2015).

We adopted a descriptive cost analysis due to the small sample size of some of the comparison groups. Prior to analysis, all costs were converted from the South African Rand (ZAR) to the United States dollar (USD) using the average rate during the period of data

collection in 2013; ZAR 9.62= USD 1 (OANDA, 2016). Despite skewness and non-normality of cost data, arithmetic means were used in all calculations as was done in previous studies (Wingfield et al. 2014) and in line with the principles of economic evaluation (Bill and Melinda Gates Foundation *et al.*, 2014). Standard deviations were used as measures of dispersion for cost data and inter-quartile ranges for continuous descriptive data.

Ethical considerations

Ethical approval was obtained from the authors' institute. The study was also registered in the clinical trials register for South Africa (registration number DOH-27-10113846) and additional permission to conduct the study was sought from the Ekurhuleni health department.

RESULTS

We invited 475 participants meeting the inclusion criteria to participate in the study, and 463 consented to participate. The most common reason for non-inclusion was receipt of diagnosis outside of the window of 3-5 months prior to interview. Of the 463 enrolled, 454 participants from 18 PHC clinics were included in the analysis, with nine participants excluded because data on their gender were missing at analysis stage. The majority of the participants included in the analysis had received a diagnosis of HIV only (n = 298; 66% of sample). Forty TB-only participants and 116 TB/HIV participants were recruited. Of the TB/HIV participants, 20 received both TB and HIV diagnoses on the same day, and an additional 46 received both diagnoses within two months of each other.

Descriptive characteristics

Characteristics of the study population are presented in Table 5-1. The majority of participants were unmarried (58%). Most participants were female (64%), and educated above grade 8 (84%). Participants born in South Africa and those of African origin made up 83% and 97% of the study population respectively. Unemployment was very high across all participant groups; 45% of enrolled participants were unemployed at the time of receiving their diagnosis, as compared to a national unemployment rate of 25% (Statistics South Africa, 2011). Median monthly income was $128 at the time of diagnosis of TB and/or HIV. Of those who were employed at the time of diagnosis, 6% had a monthly income below the national poverty line of $52 per month (Statistics South Africa and Statistics SA, 2014). The highest income at the time of diagnosis was reported by the TB/HIV group (median $150 per month), while the TB-only group had the lowest average income ($88 per month).

Table 5-1 Demographic characteristics at time of interview, by participant group

		TB/HIV [n=116]		TB only [n=40]		HIV only [n=298]	
Female n (%)		63	22%	16	6%	210	73%
Age n (%)	18-24	10	9%	5	13%	22	7%
	25-34	43	37%	21	53%	131	44%
	35-44	48	41%	6	15%	96	32%
	≥45	13	11%	8	20%	43	14%
South African n (%)		100	86%	32	80%	244	82%
Black/African n (%)		111	96%	38	95%	291	98%
Grade 8 and above n (%)		95	82%	34	85%	251	84%
Unmarried n (%)		69	59%	24	60%	169	57%
Employed at diagnosis n (%)		60	52%	20	50%	168	56%
Had informal carers in post-diagnosis period n (%)		56	48%	22	55%	111	37%
Missed work in post diagnosis period n (%)		36	31%	11	28%	37	12%
Median CD4 count at last test (IQR)		125	275			244	216
Median monthly income at diagnosis (2012 USD) (IQR)		$150	381	$88	342	$135	312
Median days from diagnosis to interview (IQR)		115	28	119	32	115	33

A large proportion of participants had informal carers; 55% of those with TB, 37% of those with HIV and 48% of those with TB/HIV. The impact of illness and care-seeking had variable effects on participants' and household members' income-earning activities. Across all participant groups, 19% of participants missed work due to illness and 21% of participants were unable to complete their normal household duties in the post-diagnosis period. People with TB were more likely to miss work with the highest proportion being 31% among TB/HIV participants.

Health service use

All study facilities offered integrated care for both TB and HIV as defined in the methods section. Actual practice at study facilities varied considerably; in some facilities visits were integrated at the provider level where both services delivered by the same provider or the consultation level where both services delivered within the same consultation, though the latter was rare. Table 5-2 shows the overall mean number of clinic visits and by visit type, for each participant group. TB/HIV participants on average made 5 'integrated' visits in the post-diagnosis period. TB only participants also received integrated visits when for HIV

testing and collecting test results – on average this was 0.8 visits per person across study facilities.

In the post-diagnosis period, all participants made relatively few visits to providers outside the public health system. The average total number of visits to other facilities and providers ranged from 0.6 in the TB only group to 0.2 in the HIV only group. The total number of participants accessing other types of health provider, and mean number of visits by those participants, is presented in Supplementary Table 5-1. The largest proportion of participants accessing care from providers outside the public health system was among the TB/HIV participant group, at 23.28%. Fifteen percent of TB-only participants and 14% of HIV-only participants reported use of providers outside the public health system respectively. Thirteen TB/HIV participants were hospitalized, as compared to 2 HIV-only participants and zero TB-only participants.

Table 5-2 Visits to any health care provider in the post-diagnosis period, by participant group

Patient group	**TB/HIV (n=116)**			**TB only (n=40)**			**HIV only (n=298)**		
Visit type	**TB/ HIV visits**	**TB visits**	**HIV visits**	**TB/ HIV visits**	**TB visits**	**HIV visits**	**TB/ HIV visits**	**TB visits**	**HIV visits**
Study clinic visits, mean (SD)	5.0 (4.6)	10.9 (14.2)	2.2 (4.6)	0.8 (.6)	14.5 (14.6)	0.1 (.2)	0	0	4.4 (2.0)
Visits to other providers, mean (SD)**		0.3 (0.7)	0.2 (0.7)		0.6 (2.6)	0.1 (0.2)		0	0.2 (0.7)
Subtotal, all providers, mean	**5.0**	**11.2**	**2.2**	**0.8**	**15.1**	**0.1**	**0**	**0**	**4.6**
Total Visits, all visit types, all providers			**18.4**			**16.0**			**5.1**

SD standard deviation

**Other public clinic, pharmacy, general practitioner, hospital-outpatient, hospital-inpatient and traditional healers

All people with TB visited the study health facilities at least 4 times per month in the post-diagnosis period. HIV only participants made the fewest visits to study facilities over the study period (mean 1 visit per month).

Patient costs

Table 5-3 presents patient-incurred costs in the post-diagnosis period. The highest total costs in the post-diagnosis period were reported by TB/HIV and TB-only participants; $74.07 and $68.33 per month respectively. Costs for the HIV-only group ($40.41 per month) were substantially lower. Indirect costs contributed the majority of the total costs, at 71% of total cost for TB/HIV participants, 86% of total cost for TB-only participants, and 55% of total cost for HIV-only participants.

Table 5-3 Monthly direct and indirect costs (USD 2013), by participant group

	TB/HIV (n=116) mean	(SD)	TB only (n=40) Mean	(SD)	HIV only (n=298) mean	(SD)
Direct costs						
Patient medical						
Study clinic	0.00	0.00	0.00	0.00	0.00	0.00
Any other facility	1.71	10.23	0.07	0.42	0.87	4.12
Patient travel						
Study clinic	4.12	8.91	1.69	3.31	1.25	3.07
Any other facility	0.63	2.89	0.05	0.20	0.24	1.37
Guardian travel						
Study clinic	0.43	2.37	0.00	0.00	0.27	2.78
Any other facility	0.51	3.11	0.00	0.00	0.17	1.52
Food						
Hospital	0.26	1.31	0.00	0.00	0.04	0.47
Special foods	13.14	17.33	8.06	11.05	9.76	14.91
Loan interest	0.93	9.78	0.00	0.00	5.68	89.11
Total direct costs	**21.72 (29%[1])**		**9.86 (14%[1])**		**18.28 (45%[1])**	
Indirect costs						
Patient income loss						
Job loss income loss	15.40	126.17	17.78	76.69	2.99	24.30
Care-seeking income loss	30.45	105.56	34.60	98.99	13.81	59.03
Opportunity costs of time						
Guardian						
Study clinic	1.13	2.37	0.23	0.00	3.92	2.78
Any other facility	0.94	6.16	0.04	0.24	0.22	1.24
Carer	4.42	11.35	5.81	13.52	1.19	5.77
Total indirect costs	**52.34 (71%[1])**		**58.47 (86%[1])**		**22.13 (55%[1])**	
Grand total	**74.07**		**68.33**		**40.41**	

SD standard deviation

[1] percentage of the overall total

Direct OOP costs incurred by participants ranged from $9.86 per month for TB-only participants to $21.72 per month for TB/HIV participants (Table 5-3). Detailed costs incurred at all facility types are listed in Supplementary Table 5-2. Direct costs were largely driven by costs of special foods purchased as nutritional supplements for the illnesses in question. Monthly costs of special foods ranged from $8.06 to $13.40 per month, representing 53% of direct costs for HIV-only participants, 60% of direct costs for TB/HIV participants, and 82% of direct costs for TB-only participants. Expenditure on special foods alone represented an average of 30%, 13%, and 27% of total income for HIV-only, TB-only, and TB/HIV participants respectively. None of the interviewed participants incurred direct medical costs at the study clinic, or at any other PHC clinic. Participants who sought care from health facilities outside the public health system, particularly those with TB/HIV, incurred some direct medical costs; an average of $1.71 per month was observed for

TB/HIV participants. The highest direct medical costs from providers outside the public health system were incurred by participants accessing care from traditional healers, however this was driven by one participant reporting a very high cost of $415.

Indirect costs were high for all participant groups, particularly those participants being treated for TB. Job loss and other income losses were major drivers for indirect costs; accounting for 62% of cost in the participants with TB/HIV and 77% of cost for TB-only participants. Participants with TB (both TB-only and TB/HIV) lost an average of $32.53/month in income due to time spent seeking care. HIV-only participants lost substantially less income due to seeking care on average than other participant groups, at an average of $2.99 /month.

About 4% of participants with TB and 3% of those with HIV their job entirely due to illness. Among those who lost their jobs due to illness, the mean and median income losses were $321.62 and $207.90 respectively. The average income loss due to job loss across all participants was $17.78/month for TB-only participants, $15.40/month for TB/HIV participants, and $2.99/month for HIV-only participants. The monetary value of time lost by guardians was particularly high for HIV-only participants. Table 5-3 shows the monthly guardian opportunity costs of time varying from $2.07 in the TB/HIV group to $4.14 in the HIV-only group. In contrast, the cost of informal caregiving was particularly high for participants with TB (regardless of HIV status); this cost averaged $5.81 per month for TB-only participants and $4.42 per month for TB/HIV participants.

Patient time loss

The time that participants lost while travelling to health facilities and accessing (and waiting for) care in the post-diagnosis period is presented in Table 5-4. TB/HIV participants lost the most time, averaging 91 hours per participant over the post-diagnosis period. This was more than the combined time loss of TB-only and HIV-only participants (33.8 hours and 23.4 hours respectively). The time lost by TB/HIV participants was driven by long hospitalisations for 11 out of 116 (9.4%) participants who were hospitalised for an average of 17.7 nights over the post-diagnosis period. The average time loss for TB/HIV participants not hospitalized was 50 hours over the post-diagnosis period. Travel time, particularly for visits to the study clinic, was also substantial. TB/HIV participants lost an average of 20 hours travelling, while TB-only and HIV-only participants lost an average of 15 and 6 hours travelling, respectively.

Table 5-4 Total time loss in post-diagnosis period (hours), by participant group

		TB/HIV (n=116)		TB only (n=40)		HIV only (n=298)	
		mean	(SD)	Mean	(SD)	mean	(SD)
Study clinic	Consulting	28.2	27.7	17.5	17.3	13.9	11.7
	Travel	20.7	20.7	15.4	17.3	5.6	6.4
	Subtotal	48.9 (54%)		32.9 (97%)		19.6 (83%)	
Other clinic	Consulting	0	0.2	0.3	1.0	0.1	0.5
	Travel	0.1	0.5	0.5	1.4	0.2	1.3
	Subtotal	0.1 (0%)		0.8 (2%)		0.2 (1%)	
Pharmacy	Consulting	0	0.2	0	0.1	0	0.4
	Travel	0	0.3	0	0.1	0.1	0.4
	Subtotal	0.1 (0%)		0 (0%)		0.1 (0%)	
General practitioner	Consulting	0.1	0.7	0	0.3	0.3	1.8
	Travel	0.2	1.2	0	0	0.2	0.8
	Subtotal	0.3 (0%)		0 (0%)		0.4 (2%)	
Hospital-inpatient	Consulting	40.3	146.8	0	0	2.9	25.5
	Travel	0.3	1.0	0	0	0.1	0.7
	Subtotal	40.6 (45%)		0 (0%)		3.0 (13%)	
Hospital-outpatient	Consulting	0.2	1.0	0	0	0	0
	Travel	0.5	3.2	0	0	0	0
	Subtotal	0.7 (1%)		0 (0%)		0 (0%)	
Traditional healer	Consulting	0	0.3	0	0	0	0.2
	Travel	0.1	0.8	0	0	0.1	0.9
	Subtotal	0.1 (0%)		0 (0%)		0.2 (1%)	
Grand total			90.8		33.8		23.4

SD standard deviation

Catastrophic costs

Figure 5-1 illustrates the percentages of participants facing catastrophic cost, varying thresholds from 5% to 25%. All participants had high rates of catastrophic expenditures, across thresholds. The results show that more than 60% of all participants face catastrophic costs at the 10% threshold. TB/HIV participants show the highest proportions facing catastrophic costs, with 73% of participants encountering catastrophic costs at the 5% threshold and 61% at the 25% threshold. More than 70% of HIV-only participants experienced catastrophic at 5% threshold, however this proportion dropped at higher thresholds. Considering only direct costs reduced the proportion of participants encountering catastrophic costs to 68-50% of TB/HIV participants, 46-31% of TB-only participants, and 54-33% of HIV-only participants depending on threshold (Supplementary Figure 5-1)

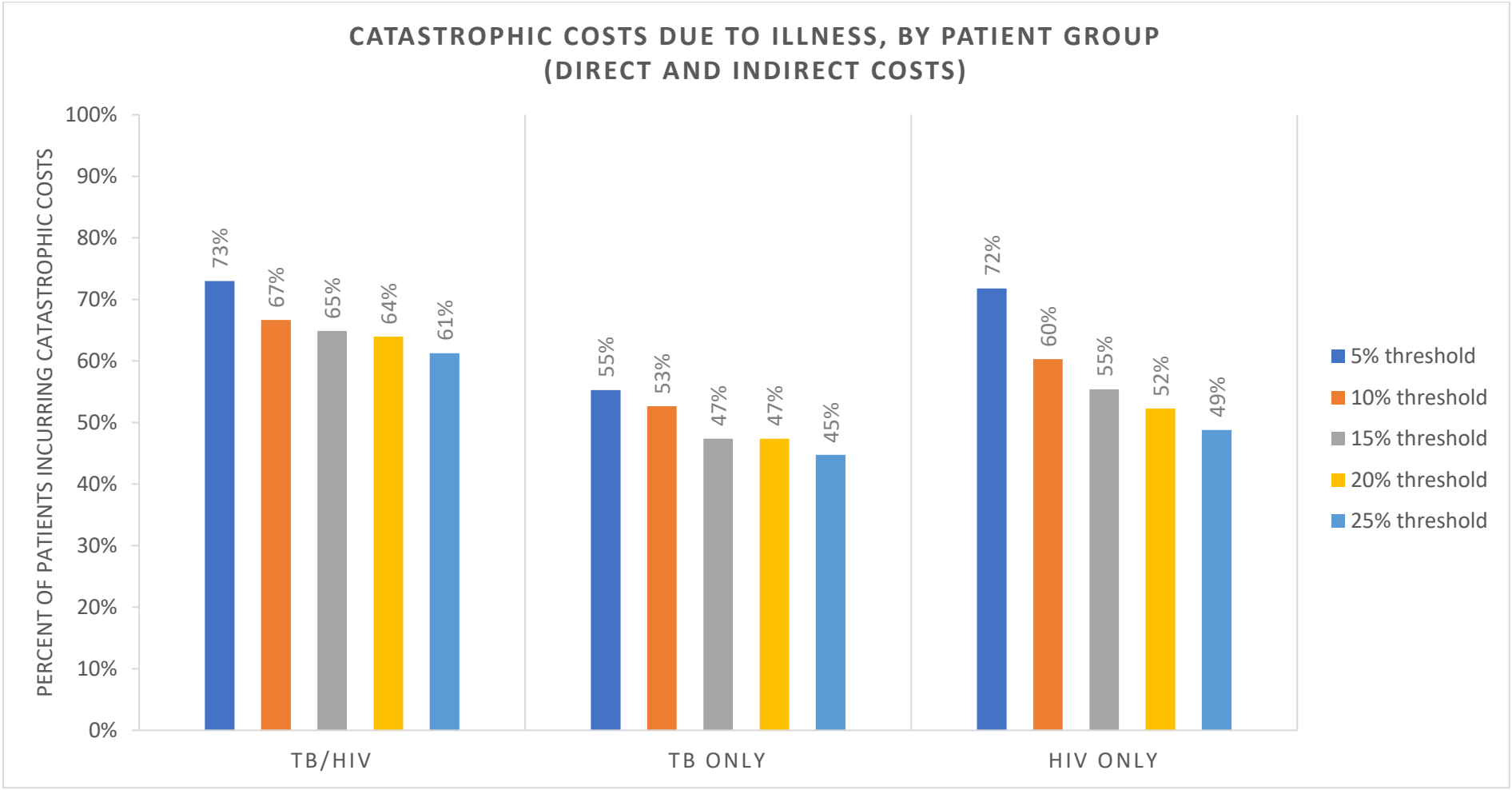
Coping Strategies

Table 5-5 shows the range of strategies adopted by participants and their households to cope with income loss and/or direct out of pocket payments incurred due to TB and/or HIV (Table 5-5). Fifteen percent of HIV-only participants, 6% of TB/HIV participants, and 8% of TB-only participants adopted at least one coping strategy. The most common coping strategy was loan-taking, which was done by 11% of HIV-only participants, 8% of TB-only participants, and 3% of TB/HIV participants. Interest charged on loans to the TB/HIV and HIV-only group were relatively high, at 27% and 22% of the initial value respectively. In contrast, TB-only participants were able to source loans at zero interest from friends or family. Government grants and charitable donations were rarely accessed across all participant groups. Similarly, asset sales were not used by the majority of participants as a means to cope with TB and/or HIV-related costs.

Table 5-5 Coping strategies, by participant group

	TB/HIV (n = 116)	**TB only (n = 40)**	**HIV only (n = 298)**
Grants and donations			
Patients receiving government grants n (%)	1 (1%)	0	5 (2%)
Patients receiving charitable donations n (%)	0 (%)	0	4 (1%)
Asset Sale			
Patients selling assets n (%)	3 (3%)	0	7 (2%)
Mean value of assets sold (USD)	$11.54	-	$9.15
Loans			
Patients taking loans n (%)	4 (3%)	3 (8%)	34 (11%)
Mean interest on loans (% of initial withdrawal)	27%	0%	22%
Total adopting any coping strategy	**7 (6%)**	**3 (8%)**	**46 (15%)**
Total adopting multiple strategies	**1 (1%)**	**0**	**4 (1%)**

Figure 5-1 Catastrophic costs due to illness, by participant group



DISCUSSION

All participants interviewed in this study encountered high costs associated with HIV and/or TB. Over 45% of all participants experienced catastrophic costs even at thresholds as high as 25% of individual income. People with both TB and HIV on average face higher levels of post-diagnosis catastrophic costs than those with TB-only or HIV-only, especially at higher thresholds.

In principle, integration has the potential to reduce the overall number of visits. We found many participants were receiving integrated care, defined as receiving multiple services within one visit. TB/HIV participants received an average of 5 'integrated' TB/HIV visits in the post-diagnosis period, where both TB and HIV services were delivered on the same day. As a result, participants received fewer TB-only visits than the TB-only group, and fewer HIV-only visits than the HIV-only group. However, the total time loss for TB/HIV participants was still considerably higher than time loss for other participants. Similarly, travel costs for people with TB/HIV were substantially higher than all other participants. Given the high costs faced by those with TB/HIV, further gains may be achieved by ensuring that 'integrated' visits are delivered by the same provider or within the same room, reducing waiting periods between multiple visits in a day.

The gain in reduced visits observed for people with both TB and HIV may be extended by further integration, where services are provided by one provider, minimising the need for separate appointments. However, given the existing level of integration in terms of numbers of joint TB/HIV visits, it is unlikely that catastrophic cost can be averted by integration alone, and our results point to the need for timely social protection schemes such the government temporary disability grant, particularly for HIV-positive people starting TB treatment.

To some degree, patients are able to cope with the costs of care, for example through taking loans with little or no interest from family and friends. However, where costs are particularly high or where patients lack social capital, coping strategies may place patients at risk of worsened long-term economic burden. For example, access to loans in some instances can show a level of credit worthiness; particularly where loans are taken from family or friends with no interest they have been regarded in the literature as an indicator of social capital and a possible way for households to reduce the economic burden of illness (Chuma *et al.*, 2007). However, where loans are taken out with high interest rates or

where productive assets are sold, households face the risk of long-term economic hardship (Madan *et al.*, 2015; Squire *et al.*, 2015). The extent of loan-taking at high interest in order to meet the costs of health care suggests that people with HIV may be at high risk of long-term economic hardship. People with HIV were also more likely to sell assets in order to pay for care; this may also translate to diminished financial status because assets may have been sold for less than their replacement values.

In addition to loans and asset sale, some people received grants as well as donations to deal with costs of illness. Currently, the South African government offers a temporary social relief of distress grant for patients who at the discretion of a doctor are deemed unfit to undertake remunerative work (Department of Social Development, 2006). However, access to these were consistently low, with 1% of participants overall accessing government grants. People with TB in particular had little access to the temporary disability grant, even when they were encountering catastrophic costs. This may be due to difficulty accessing the required certifications of disability within a rapid time frame. Access to charitable donations was similarly low, with only 4 of the 454 participants interviewed accessing a donation. This notable absence of donations and grants for all participants, and TB participants in particular, shows a policy implementation gap for the most vulnerable TB patients. Further research on the reasons for this implementation gap is needed, and the South African government should thus consider alternative social protection mechanisms, such as unconditional immediate cash transfers to TB patients to close this gap (Boccia *et al.*, 2011).

Participants with HIV (both HIV-only and TB/HIV) encountered relatively high costs due to accompaniment by guardians to the study facility. South African HIV treatment policy encourages use of a 'treatment buddy' to support adherence, however this is not considered a requirement for initiation onto treatment (South African Department of and South African Department of Health, 2010). Nearly all HIV-only participants reported that a guardian accompanied them to their most recent PHC clinic visit. Participants with TB-only were not as frequently accompanied to the PHC clinic, and therefore had relatively lower costs.

Our study supports previous findings that the primary drivers of TB patient costs are income and job loss associated with time spent care-seeking and inability to work due to illness (Muniyandi *et al.*, 2005; Aspler *et al.*, 2008; Ukwaja *et al.*, 2013; Chimbindi *et al.*, 2015). All people with TB had high numbers of health facility visits and these were reflected

in time and travel costs. Study participants with TB also had a high rate of job loss, no matter their HIV status. South Africa is currently scaling-up community based approaches to treatment supervision that may reduce these costs in the future.

Our study also supports previous findings that supplementary food is an important driver of TB patient costs in South Africa (Bond *et al.*, 2008; Foster *et al.*, 2015), raising the question of whether patients are getting appropriate education regarding nutrition and TB. Previous studies have indicated that patients may perceive that TB and HIV drugs must be supplemented with higher food intake, often including foods outside of the normal South African diet including eggs, fruit, soft drinks, and meat (Bond *et al.*, 2008). Improved nutrition counselling for people with TB and/or HIV is needed to help households meet dietary needs within their normal spending capabilities.

As with any patient-level costing effort, this study faced several methodological limitations. Primarily, our comparisons are made on a small sample and the participant groups we compared did not have equal numbers of participants because eligible participants were recruited consecutively, and the MERGE study had fewer participants with TB. Methodological choices taken in this study, and the potential limitations of these are discussed in detail by Sweeney et al (Sweeney *et al.*, 2016). In practice, when conducting patient cost interviews alongside intervention studies and trials, analysts are faced with either obtaining comprehensive costs of a smaller sample or limited costs (usually OOP) from a larger sample. Due to the importance of indirect costs as highlighted by previous studies, we chose the former. We chose a recall period of 3 to 5 months; this poses some risk of recall bias, which we weighed against the potential to miss costs. Second, the patient costs questionnaire was time consuming taking up to 60 minutes. The long survey times required also pose some risk of survey fatigue for interviewees, as well as interviewers. A number of training sessions were conducted with the interviewers and a number of recruitment guides were developed to make the recruitment process more feasible. Finally there is considerable debate in the literature surrounding the measurement of indirect costs, and the approach taken in previous studies is inconsistent (Zhang *et al.*, 2011; Krol *et al.*, 2013; Krol and Brouwer, 2014; Laurence *et al.*, 2015). We chose to report income loss as our primary measure of indirect cost in order to avoid double-counting and possible bias against people with zero income, and report on time loss separately to facilitate comparison with other studies (Wingfield *et al.*, 2014; Chimbindi *et al.*, 2015). Further methodological research on measurement of indirect costs would facilitate future analyses of patient costs.

CONCLUSIONS

Given the catastrophic costs associated with TB and HIV, even in settings where TB and HIV treatment are provided for 'free', social and income protection policies are likely to be required to protect these patients if global targets on catastrophic cost reduction are to be met. Integration of services has potential to reduce the number of visits to the health facility, and our data shows patients are receiving this care already in South Africa. However, we also find that those with TB/HIV suffer the highest costs, and integration should be further extended to ensure that both the economic burden of ill-health and that of treatment are minimised for vulnerable households.

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CHAPTER 6. METHODOLOGICAL ISSUES TO CONSIDER WHEN COLLECTING DATA TO ESTIMATE POVERTY IMPACT IN ECONOMIC EVALUATIONS IN LOW-INCOME AND MIDDLE-INCOME COUNTRIES

PREAMBLE FOR RESEARCH PAPER #2

The production of Research Paper #1 included several methodological choices in data collection and analysis, for example: which costs were included, the survey design and implementation, and the most appropriate measure of income. These decisions were made based on guidelines, learning from previously published studies, the experience of the senior author, and practical feasibility. Research Paper 2 systematically reflects on these methodological choices used in patient costing studies and presents a framework for considering the impact of methodological choices in estimating catastrophic costs.

We present and discuss the different methodological challenges incurred by four patient costing studies, and place these within the broader context of existing literature on survey methods. We discuss the impact of methodological decisions taken due to limitations of time, budget, or study setting to enable researchers to make informed decisions about the impact of their choices.

This paper was part of a supplement published by the journal Health Economics on economic evaluation in low- and middle-income countries. The supplement shows the increasing implementation and sophistication of economic evaluation in LMICs. In this context of increasing estimation of disease-specific catastrophic costs for economic evaluation, we challenge researchers to address fundamental data gaps for measuring the impact of illness on economic vulnerability through stronger reporting of methods and further methodological work.

This was a multi-authored work based on the experiences of several practitioners collecting patient cost data. All co-authors contributed comments and edited the paper. NF, GK, and DM provided data and valuable feedback on their experiences in collecting costs. VS provided a helpful perspective on sampling. All other work, including the design of the

analytical framework, analysis, and writing the first and consecutive drafts of the paper, was my own.

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Student ID Number	238062	**Title**	Ms.
First Name(s)	Sedona		
Surname/Family Name	Sweeney		
Thesis Title	Improving the estimation of patient costs for TB		
Primary Supervisor	Anna Vassall		

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SECTION E

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METHODOLOGICAL ISSUES TO CONSIDER WHEN COLLECTING DATA TO ESTIMATE POVERTY IMPACT IN ECONOMIC EVALUATIONS IN LOW-INCOME AND MIDDLE-INCOME COUNTRIES

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ABSTRACT

Out-of-pocket spending is increasingly recognized as an important barrier to accessing health care, particularly in low- and middle-income countries (LMICs) where a large portion of health expenditure comes from out of pocket payments. Emerging universal health care policies prioritize reduction of poverty impact such as catastrophic and impoverishing health care expenditure. Poverty impact is therefore increasingly evaluated alongside and within economic evaluations to estimate the impact of specific health interventions on poverty. However, data collection for these metrics can be challenging in intervention-based contexts in LMICs due to study design and practical limitations. Using a set of case studies, this letter identifies methodological challenges in collecting patient cost data in LMIC contexts. These components are presented in a framework to encourage researchers to consider the implications of differing approaches in data collection and to report their approach in a standardised and transparent way.

INTRODUCTION

As universal access to health care becomes a greater international priority, interest has grown in reducing the level of financial catastrophe and impoverishment caused by health-related expenditure (Sixty-fourth World Health Assembly, 2011). As a result, there is increased recognition that the impact of health interventions on poverty and equity should be incorporated into economic evaluations (Bill and Melinda Gates Foundation, Nice International, University of York Centre for Health Economics, & Health Intervention and Technology Assessment Program (Thailand), 2014) – particularly in low- and middle-income countries (LMICs) where out of pocket (OOP) expenditures make up a large proportion of total health expenditure (World Health Organization, n.d.). This is evidenced by the growing popularity of 'extended' economic evaluations, which incorporate assessments of the potential financial risk protection impact of an intervention or technology (Asaria, Griffin, Cookson, Whyte, & Tappenden, 2015; Verguet, Laxminarayan, & Jamison, 2015). In the context of this growing importance of poverty impact metrics in health planning and decision-making, there is need for high quality data to estimate the impact of health expenditures on poverty and vulnerability. To date, the majority of research reporting the poverty impact of health expenditures has drawn on data from large cross-sectional surveys such as the Living Standards Measurement Survey (LSMS) or World Health Survey (WHS). While these datasets facilitate equity analyses evaluating the distribution of health impacts or financial pooling mechanisms across socioeconomic status analysis at the national level, for example in the context of insurance reforms (Lu, Chin, Li, & Murray, 2009; Xu et al., 2003), they cannot be easily used to capture the impact of a specific health intervention on poverty and may not always include detail on indirect costs or income loss, which can be key aspects of the poverty impact of illness.

Collecting this type of data within a smaller-scale study setting can substantially increase the time and cost of data collection. Many studies therefore avoid collecting data for a poverty impact analysis altogether. Furthermore, where poverty impact data are collected as part of intervention evaluations there are notable inconsistencies in data collection methods. Systematic reviews of existing patient cost studies in LMICs highlight a lack of standard approaches across cost ingredients, data sources, sampling methodologies and recall periods, even where the same measure of poverty impact is used (Alam & Mahal, 2014; Barter, Agboola, Murray, & Bärnighausen, 2012; Kankeu, Saksena, Xu, & Evans, 2013; McIntyre, Thiede, Dahlgren, & Whitehead, 2006; Tanimura, Jaramillo, Weil, Raviglione, &

Lönnroth, 2014). This can lead to challenges in assessing the comparability, quality and accuracy of results. In part, this heterogeneity may stem from limited practical guidance or standards on collecting patient-incurred cost data. Reporting guidelines for economic evaluations largely cover provider perspectives (Drummond & Jefferson, 1996; Husereau et al., 2013), and are neither updated to reflect information necessary for poverty impact metrics, nor provide guidance when constraints in data collection require compromise, such as limiting the sample size or restricting the length of the questionnaire.

The aim of this letter is to highlight challenges faced in collecting data on patient costs within economic evaluation platforms in LMICs. We discuss practical issues around collecting patient-incurred cost and household income data, including comprehensiveness of the survey instrument, timing of interviews, sampling, and survey administration. To illustrate these issues, we use four case studies from our own research as examples (Foster et al., 2015; P. G. C. Ilboudo, Greco, Sundby, & Torsvik, 2014; Kufa et al., 2014; Mfinanga et al., 2015) (see Table 6-1). Finally, we present a framework of methodological choices in planning research on poverty impact metrics (Table 6-2) to encourage researchers to report their approach in a standardised and transparent way, and to consider potential implications of varying approaches in data collection (Figure 6-1).

COMPREHENSIVENESS OF SURVEY DESIGN

There is a rich theoretical literature on the measurement of affordability in health care. The most common indicators of poverty impact are catastrophic expenditure (defined where health spending exceeds a threshold percentage of household income) and impoverishing expenditure (defined where health spending pushes a household below the poverty line) (Russell, 1996; Wagstaff, 2008; Wagstaff & Eozenou, 2014; Wagstaff & van Doorslaer, 2003). A number of theoretical challenges are associated with estimating the poverty impact of illness which are not addressed in detail in this letter, including the choice of threshold for analysis and assessing the long-term impact of health spending (Chuma, Thiede, & Molyneux, 2006; Flores, Krishnakumar, O'Donnell, & Van Doorslaer, 2008; Kruk, Goldmann, & Galea, 2009; McIntyre et al., 2006; Moreno-Serra, Millett, & Smith, 2011; L M Niëns, Brouwer, Niens, & Brouwer, 2013; Laurens M Niëns et al., 2010; Onoka, Onwujekwe, Hanson, & Uzochukwu, 2011; Pal, R., & Pal, 2012; Sauerborn, Adams, & Hien, 1996; Wagstaff & Eozenou, 2014; Wagstaff & van Doorslaer, 2003; Wingfield et al., 2014; Xu et al., 2003). The data required is defined by the metric of poverty impact chosen, but can include data on direct out-of-pocket expenditures for health care, any indirect costs of time

associated with being ill or accessing care, and any further economic impact measures such as income loss.

The main challenge in survey design is the representation of complex patient experiences within a manageable survey length. Survey length is of particular concern when a patient cost questionnaire follows a lengthy clinical investigation, as it increases the risk of survey fatigue and participation refusal and increases resources required to conduct the survey. Our four case studies had a range of survey durations; this is largely a function of the complexity of the patient pathways in question. MERGE and XTEND attempted to cover the overall costs of a complex illness episode over a range of different providers, whereas ECONPOP covered only a recent hospitalization and REMSTART covered only the current visit. Survey durations for each study are detailed in Table 6-1.

Disaggregation of cost ingredients will also affect survey length, and researchers may need to prioritize certain aspects to cover in depth. However, it is known that major drivers for patient costs can vary by setting and across income quintiles (Saksena, Xu, & Durairaj, 2010; Tanimura et al., 2014), making it difficult to pre-suppose any exclusions or the relative attention placed on each aspect of expenditure or income measured. Surveys should be adapted to accurately represent the setting of interest, and researchers must be clear about which ingredients they do include, and how ingredients are disaggregated.

Another widely recognized challenge is measurement of permanent income in LMICs, where informal employment is common and income is often seasonal (Deaton, 1997; Ferguson, Tandon, Gakidou, & Murray, 2003). Income data is difficult to collect in a small survey setting; as interviews in an intervention evaluation are conducted individually, accurate estimation of household income is often impossible. Researchers will need to decide whether personal income is an appropriate proxy for household income in their study context, and be clear about the limitations of such a decision.

Table 6-1 Study characteristics

	MERGE (Kufa et al., 2014)	XTEND (Foster et al., 2015)	ECONPOP (P. G. C. Ilboudo et al., 2014)	REMSTART (Mfinanga et al., 2015)
Country	South Africa	South Africa	Burkina Faso	Zambia & Tanzania
Aim of study	Implementation and evaluation of an optimized model for scaling up TB/HIV integration at primary care clinics	Evaluation of the implementation of a new TB diagnostic, XPert MTB/RIF	Multidisciplinary study to estimate costs and consequences of abortion	Trial assessing a complex intervention to reduce mortality in ART-naive patients beginning ART
Study Design	Cluster-randomized trial	Cluster-randomized trial	Cross-sectional survey	Individually randomised control trial
Timeframe	Cross-sectional	Cohort	Cross-sectional	Longitudinal
Sampling for cost data	Convenience sample at study facilities	Random sub-sample of study-enrolled patients	Convenience sample at study facilities	All participants at study clinics. Clinics chosen for convenience
Location of interview	Facility	Facility	Facility	Facility
Sample size	459 for costs 3478 total for trial	351 for costs 4656 total for trial	304 for economic study	1375 for costs 1999 total for trial
Subgroups (n)	TB only (n=41) TB/HIV (n=119) HIV only (n = 299)	No TB treatment (n = 302) Started on treatment (n = 49)	Induced (n=37) Spontaneous (n=267)	Intervention (n=684) Control (n=691) Tanzania (n=870) Zambia (n=505)
OOP cost ingredients	Transport for individual & companion, medicines & consumables, diagnostics, consultation fees, special foods / supplements, inpatient accommodation	Transport for individual & companion, medicines & consumables, diagnostics, consultation fees, special foods / supplements, inpatient accommodation	Medicines & consumables, consultation fees, ultrasound, informal payments, pre-referral costs, hospitalisation	Transport and 'other' costs
Recall period (costs)	The last visit to each provider (variable; max 5 months)	The last month	~1 day (interviewed on discharge)	1 day (cost of visit only)

Household / individual costs	Individual and companion	Individual and guardian/ caregiver	Individual	Individual and companion
Average length of interview	~ 60 minutes	~ 45 minutes	~ 20 minutes	~ 25 minutes
Diary/Recall	Recall	Recall	Recall	Recall
Indirect cost measurement	Human capital approach	Income loss	None	Human capital approach
Additional health services costed	Pharmacy, GP, outpatient hospital, inpatient hospital, traditional healer	Pharmacy, GP, outpatient hospital, inpatient hospital, traditional healer	None	None
Income data? (proxy)	Individual income before diagnosis (3-5 months prior to interview)	Annual individual income	None (GDP per capita)	Individual level income in last month
Interviewers used	Research assistants	Nurses and Research assistants	Trained female interviewers	Trained field workers
Medium of recording	Paper survey	Electronic survey	Paper survey	Paper survey
Mean cost (95% CI)	Monthly OOP expenditures: $25.82 ($16.33 - $35.33) Monthly opportunity costs of time: $43.36 ($32.64 – $54.08) Monthly income loss: $13.70 ($12.03 – $15.38)	Total OOP expenditures: $111.83 Total loan interest: $43.32 Reported income loss: $54.82 Total guardian costs: $32.11 Total carer costs: $81.99 Total episode cost: $324.07	Total OOP expenditures associated with abortion: $52.80 ($47.36 – $58.24)	OOP expenditures for one visit to study facility: $1.96 ($1.80 – $2.13)
Average annual income (95% CI)	$ 2,564.96 ($2,224.90 - $2,905.03)	$1,237.44 ($1,000.88 - $1,474.00)	Not measured (GDP per capita used as proxy)	Tanzania: $244.24 ($212.25 – 276.23) Zambia: $218.88 ($198.94 – 238.82)
Nationally-defined poverty line (annual income)	$773.39	$773.39	$183.60	Tanzania: $233.60 Zambia: $266.45

GDP per capita (annual)	$6.617.91	$6.617.91	$530.50	Tanzania: $694.77 Zambia: $1,844.80
Frequency of catastrophic expenditure (20% threshold)	40% (36% - 45%)	59% (54% - 65%)	10% (6% - 14%)	4% (3% - 5%)
Minimum sample size required to estimate proportion of catastrophic expenditure with 95% confidence	Error margin 5%: 2,282 Error margin 10%: 570 Error margin 15%: 254	Error margin 5%: 1,057 Error margin 10%: 264 Error margin 15%: 117	Error margin 5%: 13,689 Error margin 10%: 3,422 Error margin 15%: 1,521	Error margin 5%: 36,504 Error margin 10%: 9,126 Error margin 15%: 4,056

In the XTEND and MERGE case studies, respondents consistently reported themselves to be the primary breadwinners in the household; personal income was therefore collected, with the limitation that these analyses may have underestimated the economic burden on the family as they did not account for the fact that income is shared amongst household members. On the other hand, within the ECONPOP sample respondents were often not the primary breadwinners and often could not estimate household income. The decision was therefore made to use an assumption of gross domestic product (GDP) per capita as a proxy rather than risk breaking the confidentiality of the interview by asking family members. This decision has implications for the metrics used, as in this case we did not have a firm understanding of where households lay in relation to the poverty line at baseline – and therefore would not have been able to report on impoverishing expenditures.

Where a trial is unable to collect income directly, researchers may also use asset indices as a proxy measure of household socio-economic position. Information on assets can be simpler to collect than income or consumption, but result in ordinal data. In order to convert an asset index into monetary terms (Ferguson et al., 2003), necessary for the denominator of threshold metrics such as catastrophic or impoverishing expenditures, these data need to be mapped to an absolute wealth metric (Howe et al., 2012; Hruschka, Hadley, Gerkey, & Hadley, 2015). This may pose issues if income diversity in the population of interest is substantially different from that of the national population.

TIMEFRAME

Deciding on the appropriate timing for the survey may also be difficult in a study where survey timing is based primarily on outcome measurement. The clinical pathways for some types of illness (for example TB) can be long and complex, making recall bias a significant concern. This is illustrated in the XTEND survey; where patients enrolled in the trial could only be interviewed at the end of the 6 month follow-up date. To accommodate this, an additional sample of those on TB treatment outside the trial enrolees were also surveyed to increase sample size and allow for shorter recall periods between interviews. When capturing income loss as a result of illness in the case of complex clinical pathways, researchers will also need to weigh the risks of recall bias against the anticipated benefit of soliciting information on income before the illness.

There is also the potential for cost truncation in chronic illness or conditions with complications. The long-term economic impact of illness can be substantial (P. Ilboudo, Russell, & D'Exelle, 2013). This can be captured by following a cohort along the clinical pathway (as in the XTEND study), or with follow-up surveys conducted later (P. Ilboudo et al., 2013). However, it is a particular problem for lifelong treatments such as anti-retroviral therapy.

Finally, dissaving or other coping strategies can also be an important reflection of the long-term impact of illness (Wilkes et al., 1997), and where possible it may be helpful to include questions on coping strategies in the survey. Surveys may directly ask how households mobilized payment for health care services (Flores et al., 2008), or longitudinal surveys may be able to conduct repeated asset surveys, capturing any depletion of assets caused by illness (P. Ilboudo et al., 2013). This is only a partial measure of the economic impact of illness on households, however it is a useful proxy where income measurement is impossible or the poverty line unknown.

SAMPLE SIZE AND REPRESENTATIVENESS

Sample size considerations are key in the planning stages of a study, and will depend on the aims, nature, and scope of the study, and the degree of precision (confidence interval and margin of error) deemed appropriate (Lwanga & Lemeshow, 1991). Household surveys generally follow United Nations guidelines of a 5-10% margin of error at the 95% confidence interval, with further adjustment to account for clustering and non-response (United Nations Statistical Division, 2008). However this degree of precision may be difficult to achieve in an intervention-based context and researchers need to be pragmatic. Some trade-off in error margin will likely need to be made in the interests of practicality of the survey; this is especially true for outcomes which are particularly rare in the population of interest, as illustrated in Table 6-1. This decision should also be taken within the context of the larger uncertainty associated with the survey – for example, spending more time in the interview to avoid recall bias may produce more reliable results than spending additional time interviewing a great many more patients.

In each of our case studies, the sampling for OOP expenditures was restricted due to practical considerations of the study – for MERGE, XTEND and ECONPOP a sub-sample of the study population was taken, while in REMSTART the number of follow-up visits was limited. Table 6-1 shows the sample size for each case study, and the ideal sample sizes

necessary for various specifications of relative precision to estimate catastrophic expenditure.

Sampling considerations pose particular issues for the estimation of impoverishing expenditures when most patients are already below the poverty line – for example where targeting those already in poverty may be a desired feature of interventions or where investigating diseases such as HIV and TB, which disproportionately affect those below the poverty line (Bates et al., 2004). When this is the case, impoverishment becomes infrequent, making power to detect the true proportion of impoverishment very low; a different metric of poverty impact should be used in these cases. All three case studies estimating income had a large proportion of poor patients: 64% of XTEND patients, 45% of MERGE patients and 70% of REMSTART patients had a pre-diagnosis income below the national poverty lines (Chibuye, 2014; Laokri et al., 2013; OECD, 2013; Statistics South Africa, 2014).

DATA SOURCES AND SURVEY ADMINISTRATION

Finally, researchers will need to identify data sources and plan administration of the survey. DIRUM researchers working in a high-income country setting (Ridyard, Hughes, & DIRUM Team, 2015) propose a taxonomy for methods of resource use measurement (RUM) including: the source of data, who completes the RUM, how it is administered, how it is recorded, and the medium of recording. Work in LMICs requires some additional consideration, described below.

Cost diaries are considered to be the gold standard in patient cost collection (Goossens, Rutten-van Molken, Vlaeyen, & Van Der Linden, 2000; Wiseman, Conteh, & Matovu, 2005), but they can be time- and cost-intensive for researchers, especially where there is high illiteracy; patient recall is more common in low-income settings (Beegle, De Weerdt, Friedman, & Gibson, 2012). This can be supplemented with geographic information system (GIS) or other mapping data to facilitate estimation and verification of travel costs where patients are unable to estimate distances (Siedner et al., 2013), and retrospective records review can also combat recall bias in the case of frequent health facility visits (Das, Hammer, & Sánchez-Paramo, 2012). Information on resource use can also be matched with price data to minimize recall bias, however in LMIC there is much wider variation in price and market prices may not accurately reflect the economic value of resources (Hutton & Baltussen, 2005).

There may also be a distinction in survey quality depending on the interviewer and where the interview takes place. Independent research assistants may be preferable to nurses if the subject material is sensitive. Individual income and spending can be sensitive, and patients may be inclined to under- or over-report income if the purpose of the interview is not well understood (Morris, Carletto, Hoddinott, & Christiaensen, 2000). Using interviewers who understand the principles and rationale for collecting patient costs also substantially affects the quality of the data; for example the MERGE study initially experienced poor data quality, which improved after retraining interviewers. Similarly, the location of the interview will affect data quality; perceived privacy will impact patient recall and willingness to disclose details on income and spending.

Finally, the medium of recording will require particular consideration in LMICs. Electronic or telephone surveys may facilitate survey completion (Walther et al., 2011), but will require some further training of interviewers in data entry and security, and planning for power and connectivity issues in fieldwork.

DISCUSSION

Using the four case studies above, we have highlighted important considerations in measuring patient costs and income in order to estimate the impact of illness on economic vulnerability in intervention-based contexts in LMICs.

Poverty impact metrics are currently data-hungry and are therefore often excluded from study surveys due to time- and budgetary constraints in a research study. Going forward in these settings, economists first and foremost have a responsibility to communicate data requirements in the study design phase and advocate for the collection of patient cost data as an essential part of the economic evaluation. Additional information on patient costs and the poverty impact of health spending is more costly to collect, but these forms of analysis are increasingly important to policy makers and programme planners and therefore have a high value of information.

Inevitably some degree of variation in methods will occur across studies where context and data availability vary. Economists therefore also must communicate with each other where different approaches are possible, or where compromise as to the gold standard of data collection may be managed. Robust reporting of data collection methods can help other researchers understand and interpret findings, and facilitates standardization of methods.

Our recommendations for reporting data collection methods for patient costs are summarized in Table 6-2.

Finally, it may be possible to minimize the additional cost of collecting patient cost and poverty impact data, through restricting data needs and clarifying where alternative methods are acceptable. Several alternative methodological approaches are available, and researchers must weigh the limitations of potential alternatives in their own setting. The potential advantages and limitations of various methodological approaches are described in Figure 6-1. We advocate for further methodological work to investigate the means to minimize the impact of cost ingredient aggregation, cost truncation, and other forms of compromise when planning poverty impact studies in LMICs, and investigate the external validity of results that parallel effect estimates particularly in clinical trials.

This supplement confirms the increasing implementation and sophistication of economic evaluation in LMICs (Harker & Others, 2015; Pitt & others, 2016). Going forward in these settings, evaluations need to tackle policy concerns around equity and poverty. Researchers should be challenged to address fundamental data gaps for measuring the impact of illness on economic vulnerability through stronger reporting of methods and further methodological work.

Table 6-2 Framework for planning/reporting data collection

STUDY PLANNING COMPONENT	ITEMS FOR CONSIDERATION
COMPREHENSIVENESS OF SURVEY DESIGN	• Which OOP expenditures are included? • What is the level of disaggregation in cost ingredients and how long is the survey? • Are any context-specific variables included? • How is income measured, and whose income is collected (i.e. personal or household income)?
TIMEFRAME & RECALL PERIOD	• What is the recall period for the survey? Is it appropriate to capture all economic outcomes? • What is the complexity of the disease pathway? Is there resulting potential for recall bias? • Is there a potential for cost truncation in the context of chronic disease and/or future complications? • Are coping strategies used to estimate the long-term economic impact of health spending? • What is the recall period for income measurement (i.e. current vs. pre-diagnosis)?
SAMPLE SIZE	• What is the confidence interval and margin of error deemed acceptable? • If estimating impoverishing expenditures, what is the distribution of pre-diagnosis income below the poverty line? • Are any adjustments to sample size required to account for clustering, or non-response?
DATA SOURCE & ADMINISTRATION	• Is a cost diary or recall used to capture expenditures? • Is data supplemented with any additional data sources, such as retrospective records review or GIS data? • Where is the interview conducted, and by whom? • What is the medium of collecting and recording data (i.e. electronic, paper, or telephone surveys)

Figure 6-1 Potential Advantages & Limitations of Alternative Approaches in Data Collection

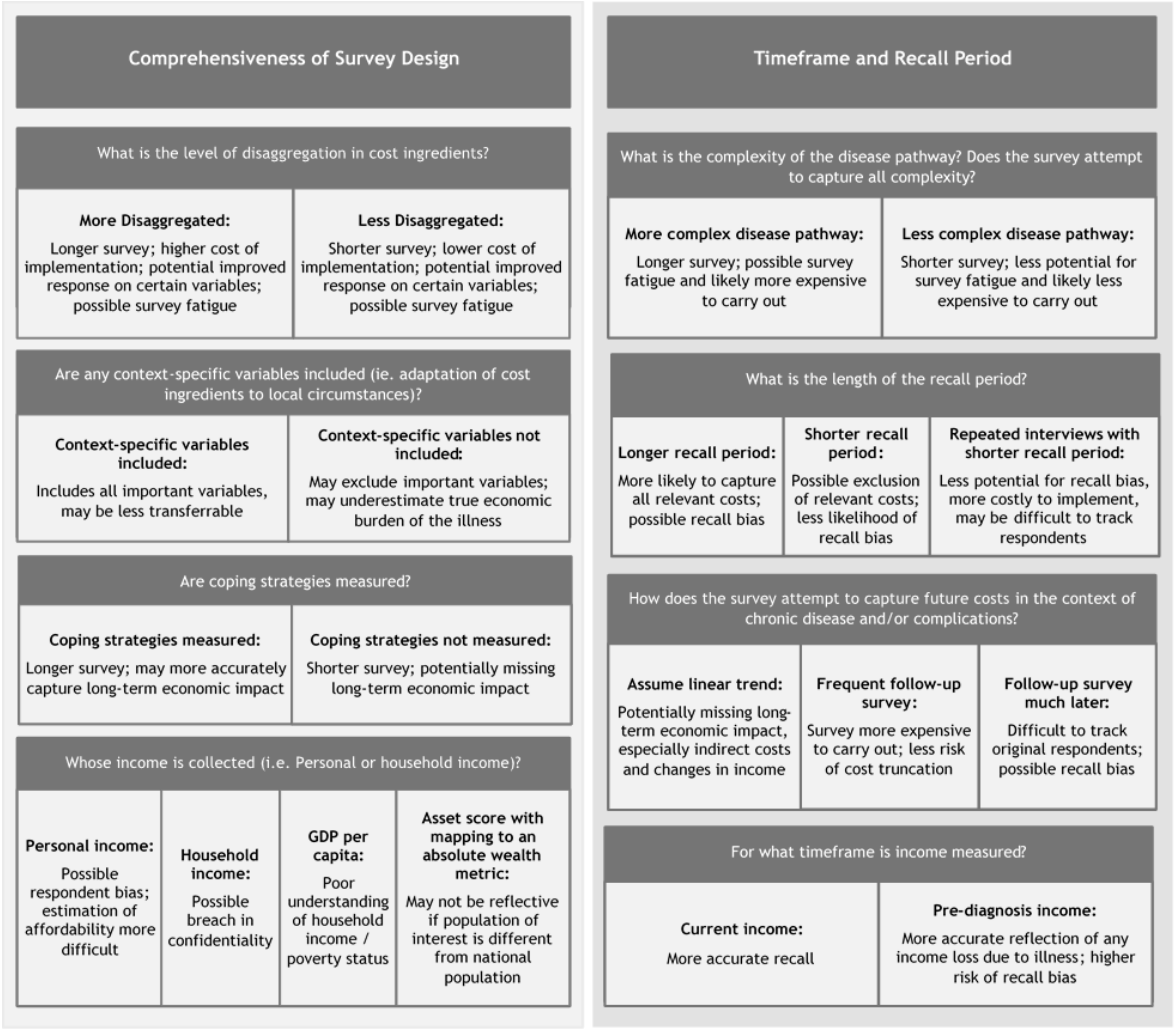
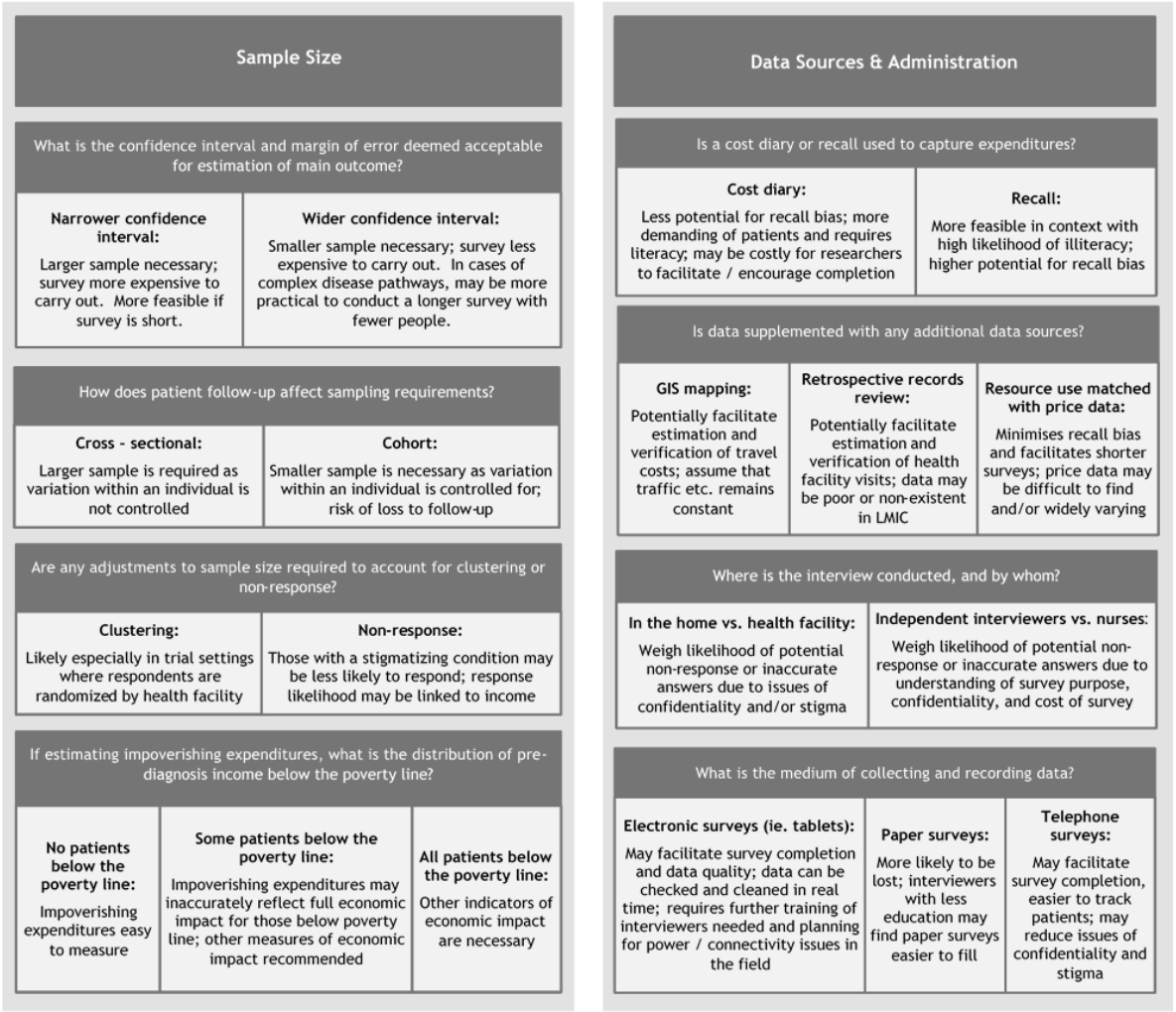


Figure 6-1 (cont)



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DECLARATIONS

This work draws on experience from case studies which have been previously published, however all methodological recommendations and other work associated with this letter are original, and have not previously been published.

The authors declare no conflicts of interest.

No ethical approval was required for this work, as it draws only on secondary data. All case studies presented in this letter obtained ethical approval for data collection; ethics statements for these studies can be found in their corresponding research articles. All case studies gave approval for their findings to be included in this letter.

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CHAPTER 7. MEASURING AND VALUING PATIENT COSTS IN GLOBAL HEALTH: BIBLIOMETRIC REVIEW

PREAMBLE FOR CHAPTER

Research Papers #1 and #2 show that the process of estimating patient costs in LMIC settings comes with particular challenges, and therefore requires guidance which is relevant to this setting. As part of my work as a Research Fellow at LSHTM, I conducted a scoping exercise to evaluate the extent of existing guidance on collecting cost data in 2016 for the Global Health Cost Consortium. This work helped to justify and set the frame for the GHCC Reference Case for Estimating the Costs of Global Health Services and Interventions.

This chapter expands the searches conducted in the above-described exercise to focus specifically on guidance for estimating patient cost, and its applicability and accessibility to researchers working in LMIC settings. This chapter aims to answer many of the same questions that the original exercise addressed, evaluating to what extent current guidance is meeting the needs of researchers collecting patient costs, particularly those researchers working in LMICs.

Good costing guidance would facilitate researchers to achieve these desirable properties in their work, through a process that is fit for purpose and efficient given the funding and data available. Guidance would ideally reflect a consensus in the topic, drawing together methodological findings by a community of researchers in order to facilitate methodological choices in designing a costing study. Finally, and importantly, guidance must be available and accessible to researchers operating in the field and reflected in the methods used for costing studies.

This chapter focuses on four characteristics to evaluate the current guidance: availability, accessibility, relevance and use. I conducted a systematic search and bibliometric analysis of any existing published literature on methods for estimating patient costs. I found that although there were a large number of papers, there were few that were accessible or relevant to a low- or middle-income setting or available to researchers working in LMIC settings. I highlight a need for improved discussion on methods for patient costing across the different institutions and agencies working on the topic. I also call for improved

accessibility to methodological guidance for researchers working in low- and middle-income countries.

MEASURING AND VALUING PATIENT COSTS IN GLOBAL HEALTH: A BIBLIOMETRIC REVIEW

INTRODUCTION

Chapter 2 of this thesis has described the current understanding of the state of the art in estimating costs and capacity to pay for health care, drawing on the available guidance in the literature on methods for estimating health-related costs from the household perspective. As noted in the GHCC Reference Case for Estimating the Costs of Global Health Services and Interventions, several properties are desirable in a 'good' cost estimate [1]. These include accuracy, precision, generalizability, transferability, comparability, and reliability.

However, as noted in Chapter 6, practical constraints for many studies prevent the implementation of 'gold standard' methods. For example, the diary method is considered the 'gold standard' for the estimation of direct costs. However, it is rarely used in patient costing studies in LMIC settings as it is expensive, requires literacy, and participant fatigue is likely [2]. Recall is more commonly used, introducing the potential for bias in measurement. Large sample sizes are also often not possible as they may increase the cost of data collection and deviate from the main study design; researchers therefore often need to make a trade-off between sample size and interview length and depth.

This is often exacerbated in LMIC settings. As noted by Briggs [3], there are often differences in methodology adopted by researchers working in LMIC settings as compared to those working in high-income country (HIC) settings, resulting from different contexts. For example, in an LMIC context, out-of-pocket payments for health services often account for a higher percentage of total health financing and there is often insufficient infrastructure for routine data collection to track out-of-pocket spending on specific health conditions. Concerns about recall bias in estimation of resource use are more pertinent in LMIC settings where retrospective records review often isn't an option, and where the diary method of estimating resource use is difficult to implement due to low levels of literacy [2,4]. Valuation of patient time for indirect costs may be different in LMIC settings, where informal employment is common and income is often seasonal. Wider variation in market prices in LMIC settings may make it more difficult to accurately reflect the economic value of resources [5]. Finally, the economic impact of household spending on

health care may need to be understood differently in LMIC settings as compared to HIC settings. There is lower access to risk pooling mechanisms and other forms of *ex-ante* limitation of exposure to income shocks, increasing the need for coping strategy use.

As discussed in Chapter 6 of this thesis, in some cases researchers collecting patient cost data as part of studies evaluating costs and impacts of health treatment and interventions in LMIC settings will need to make compromises in methodology because of cost concerns and convenience. These compromises in methods are often unavoidable, and if taken appropriately they do not necessarily introduce bias into cost estimates. However, it is important that researchers understand and describe the impact of any methodological compromises made on the likely bias of the data. Transparency in data collection for economic evaluation is critical, and presentation of cost data should be accompanied with a full, detailed description of how the data were estimated to prevent misuse or misapplication of the data for other purposes [1]. It is essential that these choices are made with a full understanding of how the chosen approach might introduce bias into cost estimates.

As discussed in Chapter 2, this is often not the case with patient costing studies. Numerous literature reviews have highlighted difficulties in synthesizing findings across published patient cost estimates due to differences in methods, or lack of transparency in methods used [6–12]. This raises the question of whether current costing guidance is meeting the needs of researchers. As noted by the DIRUM project, methods for collecting economic data are disparate, mostly un-validated, and challenging to obtain – causing health economists in all settings to repeatedly "reinvent the wheel" in development of questionnaires and tools to estimate costs of health-related services [13]. Good costing guidance would facilitate researchers to achieve these desirable properties in their work, through a process that is fit for purpose and efficient given the funding and data available. Guidance would ideally reflect a consensus in the topic, drawing together methodological findings by a community of researchers in order to facilitate methodological choices in designing a costing study. Finally, and importantly, guidance must be available and accessible to researchers operating in the field and reflected in the methods used for costing studies.

The aim of this paper is to understand which, if any, methodological resources are available, accessible, and relevant to researchers estimating disease-specific patient costs in LMIC settings, to what degree the evolution of costing methods has involved the LMIC

context, and to what degree the available guidance has been used in collecting disease-specific patient cost data in LMIC settings with specific reference to TB. The objectives were twofold: to conduct a bibliometric review of patient costing guidance and to evaluate the use of patient costing guidance for TB in LMICs.

METHODS

In order to address the aim of this paper, I took a bibliometric approach rather than conducting a systematic review. Bibliometric methods allow researchers to quantify and examine patterns in the generation, propagation, and use of large bodies of literature [14,15]. I do not seek to summarize the guidance to date or make recommendations on which methods are most appropriate, as several previous reviews have provided excellent summaries of the current state of the art for various steps in the costing process [Supplementary References 189-214]. I combine this with a critical review of guidance used in TB patient costing studies as a case study to evaluate the use of guidance in patient costing in this field and to inform the aims of the PhD.

Bibliometric analysis

Literature Searches

Searches were structured to capture any guidance on methods for collecting patient- or household-incurred costs associated with poor health and included both peer-reviewed and grey literature sources. The search process involved two steps. In the first step, publications were drawn from a database of references compiled in order to inform the development of the GHCC Reference Case for Estimating the Costs of Global Health Services and Interventions [1]. This database was developed through a systematic search of six databases (Econlit, Global Health, Pubmed, Embase, IBSS, and Web of Science) as well as extensive snowball and manual searching for grey literature including Google Scholar and the websites of DIRUM, WHO, UNAIDS, and the World Bank. Searches used keywords relating to costing, cost collection, or cost estimation; combined with keywords relating to methods, guidance, standards, generalizability, validity, or comparability. This search aimed to capture any guidance on costing from any perspective for any disease, in any setting; guidance in this database was not necessarily specific to patient costing. There were no date or language restrictions placed on the search.

Preliminary analysis of this database revealed that several papers relating specifically to patient costing and estimation of productivity costs were not captured in the first search. I therefore conducted additional 'patient-cost specific' searches, using different keywords in the same databases and grey literature sources listed above. In this second search, I used keywords that were more specific to patient costing, including terms relating to: out of pocket, productivity, direct, indirect, cost, loss, burden, or expenditure. Search terms were adapted for each database, to account for differences in use of Boolean search terms and other factors. Additional health-related search terms were added for the Econlit database. There were no date or geographical restrictions made on searches, and articles written in languages other than English were included in the results. The full search terms and strategy is detailed in Appendix 1. Initial searches were also presented to a group of experts, who provided input on further references to include.

Selection

Article abstracts were screened for inclusion. In the abstract review stage, I included any references that were relevant to the collection of cost data from any perspective. I included any references containing original research or guidance applicable to researchers collecting costs for specific diseases. Publications not presenting original research or guidance in written format, including commentaries, conference abstracts, errata, protocols, costing tools without any accompanying documentation or guidance, and literature reviews were not included during the abstract review process. Existing literature reviews summarizing methods in costing or summarizing the current 'state of the art' in costing methods were not included if they did not add anything new in terms of methods or guidance for future work, although they were used for snowballing to ensure all relevant references were captured.

References from the bibliometric review were imported into Excel and a second abstract review was conducted. On the second abstract review, guidance on methods estimating overall household expenditure, including articles from the topics of labour economics, agricultural economics, or other economic topics, were excluded unless they were directly related to health. Articles on methods for national household expenditure surveys (including DHS and WHS surveys and World Bank LSMS) were also excluded. I excluded references that gave guidance only on cost analysis, conducting economic evaluation or estimation of catastrophic or impoverishing cost if they did not also give guidance on collecting cost data. This includes a number of references amounting to an ongoing debate

between the Erasmus group and the Washington Panel as to whether productivity costs are included in the numerator or denominator within a CEA; see for example [16–25]. It also includes a number of papers about estimating the cost of illness – for example recommending whether to measure cost of illness through a net cost approach (counting specific disease-related costs of those known to have the disease) or a regression-based approach (counting all costs for all population, and factoring in disease as an explanatory variable); see for example [26–31].

Extraction and analysis

Bibliometric data for all included references were extracted using Web of Knowledge data where possible, and manually where reference details were unavailable on Web of Knowledge. Bibliometric data included: publication date, authors, title, journal name, author organization, and author country. All analysis was conducted in Microsoft Excel.

Availability of guidance

To understand the availability of methods guidance, I used information in study abstracts to sort references into five 'topics'. Topics were defined following the broad structure of the GHCC reference case and conceptual framework described above, as: 1) broad costing guidance (articles which include guidance on multiple topics including study design, measurement, valuation, analysis, and/or reporting); 2) study design (including sampling, selection, type of cost, and/or costing perspective); 3) measurement of quantities of resources; 4) valuation of direct costs; 5) valuation of indirect costs; and 6) reporting cost estimates.

I used information in study abstracts to extract information on study methods. I identified whether authors had used any form of analysis to support recommendations, or whether recommendations were theory-based alone. Types of analysis included: empirical comparison, case study, literature review, survey, and expert consultation. I summarized the number of references by method to indicate the degree to which methods development is driven by primary research vs theory alone.

Accessibility of guidance

To measure the accessibility of methods, I identified whether journals were 'open access' using the Directory of Open Access Journals. It was assumed that all grey literature and 'institutional' publications (e.g. guidance developed and published by the World Health Organization or other similar institutions) were freely accessible online. Journals were

assigned to three classifications from Pitt, et al. [32]: biomedical journals; health economics, policy, services, and/or social science journals; and 'other' journals.

Relevance of guidance

Where possible, I used the study abstract to identify the study setting to determine if recommendations were particular to a high- or low-income country. For several papers, the study setting was not explicitly named in the abstract but all authors were from one country; in cases like these, the country of affiliation for authors was assumed to be the study setting.

I used the full author list and affiliations for each paper to evaluate the degree to which each 'topic' was dominated by certain institutions, or by researchers in high-income vs low-income settings. Institution names were cleaned where possible to allow for aggregation and counting of high-output institutions. On multi-author papers, each author was given equal credit for the paper. Similarly, each institution of author affiliation was counted equally – for example in papers with three authors all working at the same institution, that institution would be counted three times.

Use of guidance in the development of costing methods

To examine how the literature is being used, I then conducted a citation analysis based on the assumption that "the usage given a scientific periodical in any field may be measured by the number of times it is cited in the literature of the field" [33]. Citation information was drawn from two sources in order to understand how methods have developed and evolved over time. First, I gathered the total number of citations per reference per year using Google Scholar and Scopus. These reflect the impact that methods papers have had on the overall literature, including the degree to which certain methods recommendations have been adopted by practitioners in patient costing; these are referred to as 'total citations'.

Next, I gathered information on the number of times each reference was cited by other methods-focused papers on the same topic in order to understand the influence of different contributions on the evolution of ideas about methods for estimating costs. This data was extracted using the programme CitNetExplorer [34] or manually where this information was not available electronically. I termed these 'methodological citations', and used them as indicators of the degree of discussion between authors thinking about methods, and the degree to which particular authors and institutions influence the conversation about methods development.

I compared 'total' and 'methodological' citations to identify the correlation between the papers that have been widely adopted by practitioners and those which have contributed to further methods development. Where high 'methodological' citations and low 'total' citations are seen, this is an indication that while a paper may have had a high degree of influence on economic theory, this may not have been taken up by practitioners actually collecting cost data. Where high 'total' citations and low 'methodological' citations are seen, this is an indication that recommendations may be frequently adopted by practitioners of costing, but have not been recognized in the methodological literature or contributed to the progression of the economic theory behind the methods.

I also used the programme CitNetExplorer to create a visualisation of a 'citation network'. Citation networks display a field of citations arranged by publication, with lines representing the citation relations between publications. This depiction of citation relations helps to illustrate the development of the field over time. Citation networks are presented with papers classified by topic and by country income group.

Use of guidance in practice: TB patient cost methods review

Literature search and selection

In order to understand the uptake of existing guidance by practitioners on estimating of disease-specific patient costs for TB, I conducted a review of all studies presenting patient costs for TB that have been published in the last 10 years (since 2008). These references were obtained from the GHCC Unit Cost Study Repository [35,36].

Extraction and analysis

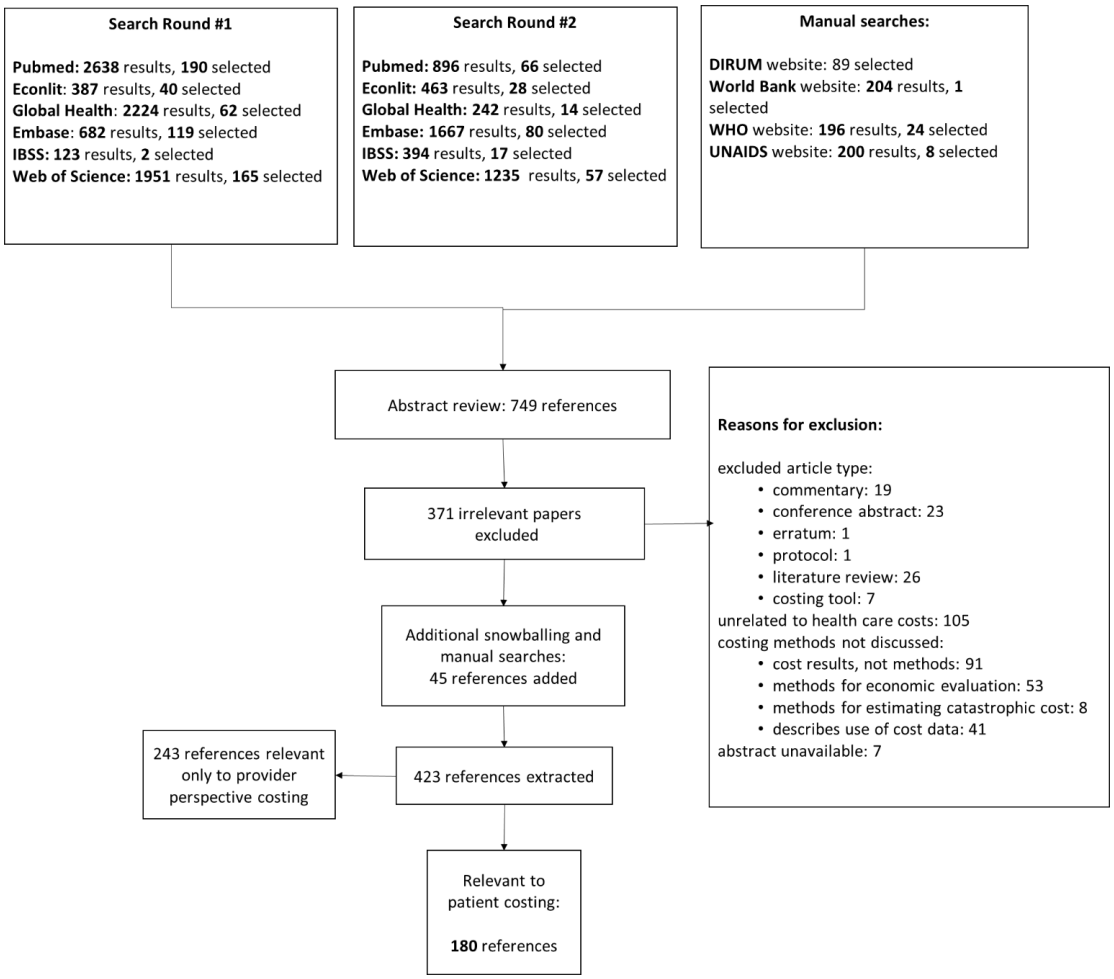
For each study, I extracted any references made in the methods section relating to methods for data collection or analysis. Any guidance used in these studies were then documented and classified according to their source. Where authors stated that their costing methods were an adaptation of a previously used questionnaire with developed by the same authors but no other methods were cited, this was recorded as 'adaptation of previously used questionnaire'. It was also noted whether the reference was relevant to patient costing. Any references identified were then classified according to the methodological area in which they provided guidance, including: study design / sampling, estimation of resource use for patient costs, valuation of direct costs, valuation of indirect costs, estimation of capacity to pay, and defining a threshold of affordability.

RESULTS

Literature Search Results

Searches returned a total of 9,912 titles, and I selected 749 papers for the abstract review. The full search and selection procedure is illustrated in Figure 7-1 (37). The abstract review excluded 372 references: 7 references were impossible to locate, 105 were irrelevant or unrelated to health costs, 76 did not discuss costing methods, and 77 were an excluded article type (literature review, commentary or conference abstract). Of the 422 papers extracted, 239 (57%) were excluded as they were relevant to costing only from a provider perspective, and 180 (43%) were deemed relevant to costing from a patient perspective and included in this review.

Figure 7-1 Search and selection process



Availability of guidance

The literature on methods for patient costing has seen enormous growth over time, and particularly over the last twenty years (Figure 7-2). The earliest article included was published in 1976. By the year 2016, there were 180 references providing guidance relevant to patient costing.

I found 17 references which provided broad guidance for disease-specific costing [Supplementary references 1-17] and 11 references providing broad costing guidance that was relevant to any disease or service [Supplementary references 18-28]. I identified 87 references giving guidance on estimating resource use [Supplementary references 29-115], 45 references focused on valuation of indirect costs [Supplementary references 116-160], and 14 references focused on estimation of direct cost or solicitation of information about health-related expenditures [Supplementary references 172-185]. Only 2 references provided guidance on study design which was relevant to a patient perspective [Supplementary references 161, 162] and 2 references provided guidance on reporting patient cost data [Supplementary references 163, 164].

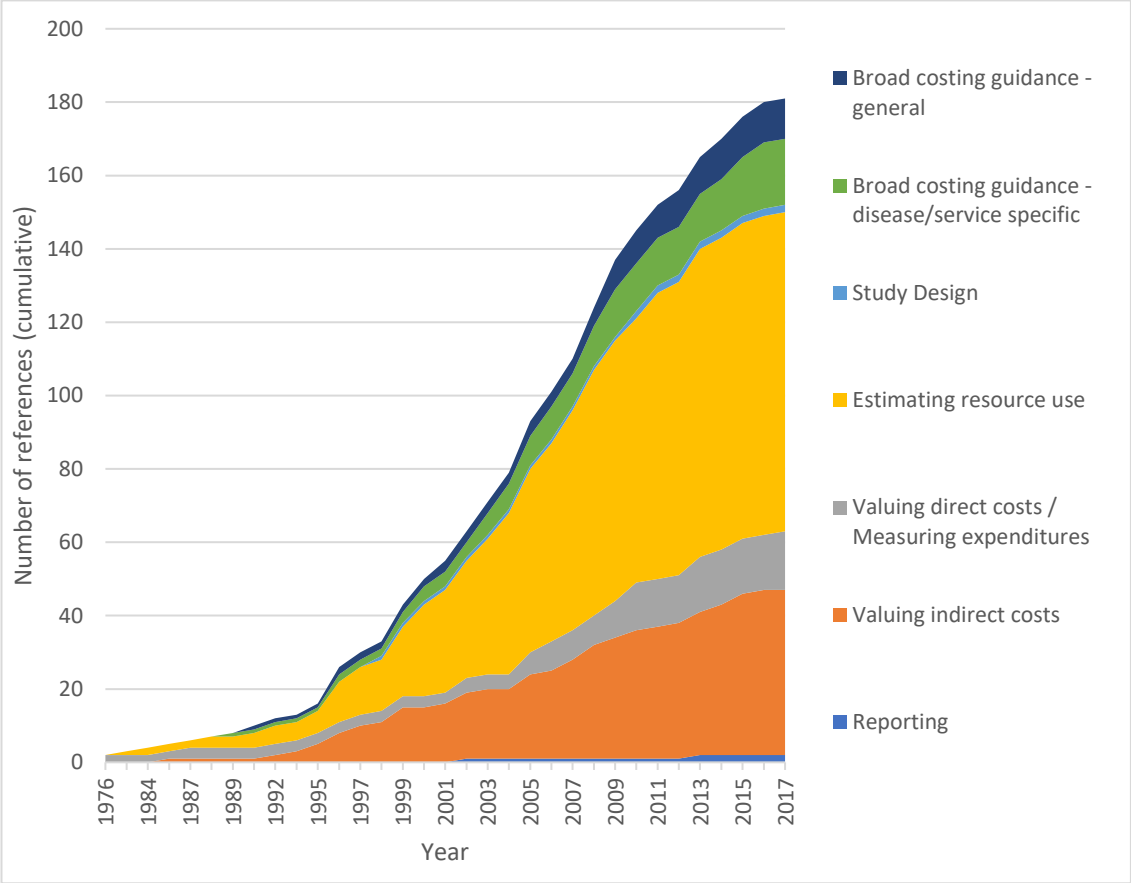
The majority of references (139 of 180; 77%) were methodological papers focused on one single aspect of costing, for example investigating recall bias using different measurement approaches; all but one of these of these were peer-reviewed journal articles. Twenty-five (14%) of the papers included were purpose-written costing guidelines or guidelines associated with costing tools, focused on providing practical costing guidance to researchers collecting cost data; of these 7 were grey literature published by international agencies and available online, 16 were peer-reviewed journal articles, and 2 were book chapters. Eleven reports of costing studies with some methodological commentary and 5 reviews of differences in costing methods across studies were also included; all of these were peer-reviewed journal articles.

Broad costing guidance

Broad costing guidance covering multiple topics (including study design, measurement, valuation, analysis and/or reporting) has been published in increasing numbers over the years. I found 28 references which provided broad guidance on multiple issues including study design, measurement, valuation, analysis and/or reporting of cost estimates [Supplementary references 1-28] (Further detail in Supplementary Table 7-1). The earliest reference in this topic was published in 1989 [Supplementary references 9]. Of these, 17 were disease- or service-specific and 11 were general. Diseases included cystic fibrosis,

dengue, diarrheal diseases, HIV, malaria, mental health, and TB, while services included immunization, laparoscopic surgery, and vaccines. Twenty-six (93%) of the references were theory-based or based on the expertise of the authors; one provided empirical analysis underlying guidance on methods, one was based on a literature review.

Figure 7-2 Availability of costing guidance over time



Searches returned four references providing disease-specific guidance on estimating the patient- and household-incurred costs of TB, all of which were classified as 'broad costing guidance' [Supplementary references 12, 14, 16, 17]. Of these, three were grey literature references published by international agencies (e.g. WHO, UNAIDS, and the Bill and Melinda Gates Foundation) and freely available online [Supplementary references 14, 16, 17], and one was published in a biomedical journal [Supplementary references 12].

Study design

I found two references relating to study design which were applicable to patient costing (Further detail in Supplementary Table 7-2). Both used a systematic review of the literature to comment on current practice in study design; one focused on sampling / statistical issues in economic evaluations [Supplementary references 161] and one focused on the selection

of the population for estimating costs of illness [Supplementary references 161]. Both were focused on high-income country settings.

Estimating resource use (visits / time)

I found 87 references addressing estimation of visits, time, or other resources used by the patient [Supplementary references 29-105, 107-114, 159, 165]; the earliest of these was published in 1979 [Supplementary references 55] (Further detail in Supplementary Table 7-3). All 87 references on estimating resource use were published in academic journals; of which 54 were published in biomedical journals, 25 were published in health economics and/or social science journals, and 5 were published in other journals.

When estimating quantities of health visits or resources used, the most commonly recommended options are self-reported resource use (recall), self-recorded resource use (diary), use of routinely collected administrative data, or use of expert panels [Supplementary references 166-171]. The large majority of references (68 of 86; 79%) compared self-reported health service utilization data with administrative data [Supplementary references 29, 32, 33, 36-38, 41-51, 54, 58, 60-64, 68, 70-75, 77-86, 88, 90-94, 98-101, 105, 107, 108, 110-114]. Two references gave summaries of the current state of the art in estimating quantities of health service use; one published in 1999 [Supplementary references 66] and one published in 2013 [Supplementary references 103]. Finally, 6 references provided guidance on estimating productivity loss [Supplementary references 31, 69, 97, 109, 159, 165], and 12 were on other topics.

Within those references comparing self-reported resource use with other approaches, findings varied substantially. Twenty two references (32%) concluded that self-reported data was unreliable [Supplementary references 36, 43, 44, 48, 50, 61, 68, 74, 77, 80, 82, 84, 85, 88, 90-93, 105, 108, 110, 114]; of these, 5 state in the abstract that patients over-report utilization [Supplementary references 50, 74, 88, 90, 92], and 9 state in the abstract that patients under-report utilization [Supplementary references 36, 44, 61, 80, 84, 91, 93, 108, 110]. In contrast, 18 studies (26%) state in the abstract that self-reported data was reliable [Supplementary references 45-47, 49, 51, 62, 64, 72, 75, 78, 79, 83, 86, 98, 99, 101, 111, 113], and 19 (28%) concluded that reliability varied by service type [Supplementary references 29, 32, 33, 37, 38, 41, 42, 54, 58, 60, 63, 70, 71, 73, 81, 94, 100, 107, 112]. Sixteen of these studies were included in a systematic review in 2016 (38). The review found that within the six studies determined ‘high-quality’, self-reported resource use tended to be lower as compared to administrative data. Fifteen of the studies were

summarized in a second systematic review (39), which found that the validity of self-reported resource use as compared to administrative data varied by instrument and by type of health resource.

The vast majority of references concerning estimation of resource use (78 of 86 references; 91%) use empirical comparison or validation to identify the most appropriate approach to measure quantities of health care visits. Supplementary Table 7-3 shows the total number of references for estimating resource use by analysis type and by the average number of internal and external citations per reference for each type.

Valuation of direct cost / estimation of expenditures

I found 14 papers providing some guidance on valuing direct costs from the patient perspective [Supplementary references 172-185] (Further detail in Supplementary Table 7-4). Papers present guidance on data sources [Supplementary references 173, 175], measurement error associated with recall bias or survey design [Supplementary references 172, 177, 178, 180-185], allowing for market distortions when valuing cost in LMIC settings [Supplementary references 186], and survey timing [Supplementary references 176, 187].

Of the 16 studies providing guidance on valuing direct out-of-pocket health spending, 8 contained some empirical comparison or validation, 2 presented results from an expert consultation, 1 presented results from a literature review, and 5 contained no analysis (Supplementary Table 7-4).

Valuation of indirect costs

I found 45 references addressing valuation of costs [Supplementary references 115-123, 125-158, 160, 186], with the earliest reference published in 1985 [Supplementary references 152] (Further detail in Supplementary Table 7-5). All references but one [Supplementary references 186] discuss the valuation of lost productivity or indirect costs in high-income settings. All references were published in peer-reviewed academic journals.

The three most frequently recommended measurement approaches include the human capital approach (HCA), the friction cost approach (FCA), the willingness to pay approach (WTP) [Supplementary references 132, 136, 138, 142, 145, 146, 157]. The HCA model takes account of indirect costs of illness by measuring the monetary value of lost productivity – for example by measuring income loss due to a lost job or lost days of work, less uptake of

paid work, and the opportunity cost of time spent by caretakers providing informal care. The FCA, proposed by Koopmanschap in 1995, limits productivity costs to the 'friction period' before the ill person is replaced, and includes any lost productivity through presenteeism, lost productivity before a replacement is hired, and the costs of hiring and training a replacement worker. Finally, the WTP approach uses contingent valuation to solicit preferences of patients and their households. There is substantial literature devoted to the controversy surrounding choice between these methods for economic evaluation purposes [Supplementary references 123, 126, 127, 129, 130, 133, 135, 137, 144, 147, 150, 153, 158]. There is also discussion in the literature around methods for valuing the time of housemakers [Supplementary references 116, 149] or informal caregivers [Supplementary references 119, 121, 125, 128, 148, 154, 156, 188], and valuing productivity loss without absence from work [Supplementary references 115, 120, 122, 131, 139, 140, 143, 160]. Finally, there are several references which summarize the current state of the art [Supplementary references 132, 136, 138, 142, 145, 146, 157].

Of the 45 references, discussing methods for indirect costs, 24 are supported by some form of empirical analysis. An additional 7 conduct some other form of analysis; 5 show a worked example or case study, two are based on a literature review, and one reports results from an expert consultation. Thirteen references are theory-based.

Reporting

I found two studies providing guidance on reporting which was relevant to patient costing [Supplementary references 163, 164] (Further detail in Supplementary Table 7-6). Both were focused on reporting for economic evaluation in clinical trials, and both presented results from a literature review to illustrate their points.

Accessibility of guidance

References included two book chapters, 10 grey literature references published by international agencies (e.g. WHO, UNAIDS, and the Bill and Melinda Gates Foundation), and 168 journal articles. Overall, only 20 of 180 (11%) references were published either in an open access journal or accessible as grey literature online; of these only one provided guidance specific to a LMIC setting.

The majority of references were peer-reviewed, published in biomedical journals (81 references) health economics, policy, services, and/or social science journals (78 references), or other journals (9 references) (Table 7-1). The majority of journal articles

(103; 65%) provided some form of empirical comparison or validation; of these 8 were published in open-access journals [Supplementary references 10, 20, 54, 61, 68, 74, 86, 96, 102, 104].

Of the journal articles, 127 were specific to a high-income setting, 13 were relevant to any setting, and 9 were specific to a low- or middle-income setting. Of the 10 agency publications, 5 were relevant to any setting, 1 was specific to a high-income setting, and 1 was specific to low- and middle-income settings. None of the agency publications supported their recommendations with any empirical analysis.

Table 7-1 Accessibility of guidance

	Not open-access		Open-Access	
	Book chapter	**Journal article**	**Agency publication**	**Journal article**
What type of guidance exists?				
Methodological papers on one aspect of costing		132	1	6
Purpose-written guidelines	2	13	7	3
Costing study with methodological commentary		9		2
Reviews of cost methods		4		
What topics does guidance cover?				
Broad costing guidance	2	15	7	4
Estimating resource use		80		7
Reporting		2		
Study Design		2		
Valuing direct costs		15	1	
Valuing indirect costs		44		1
What setting is guidance relevant to?				
High income		135	1	9
Low- and middle-income settings		9	2	3
All income levels (not country specific)	2	14	5	
Does any analysis underlie guidance?				
Case study / worked example		11		
Empirical comparison / validation		103		8
Expert consultation		4		
Literature review		9		1
No analysis (theory-based)	2	31	8	3

The relevance of guidance to researchers in LMIC settings

Across the literature, the majority of references (145 of 180; 80%) were conducted in or otherwise specific to a high-income country setting; of these, 66 were specific to a European or Central Asian country, and 65 were specific to a North American country

(Table 7-2). A further 21 references were not country-specific and applicable to any setting, while only 14 references were conducted in or specific to a low- or middle-income country.

Of the 28 publications providing broad costing guidance, there were 18 authors from low- and middle-income countries, including Mexico, Brazil, Colombia, South Africa, El Salvador, France, Jamaica, Korea, Nigeria, Panama, Thailand, and Uganda. Twelve authors (10%) were from the Bill and Melinda Gates Foundation, and 7 (6%) were from the WHO. Other topics were dominated mainly by authors from high-income countries. Of the 58 authors providing guidance on valuing direct costs, 6 were from low- or middle-income countries, and of the 407 authors providing guidance on estimation of resource use, 1 was from a low- or middle-income country. All other authors were from high-income countries.

Table 7-2 Relevance of Guidance

	High-income settings	Low- and middle-income settings	All income settings (not country specific)
What type of guidance exists?			
Methodological papers on one aspect of costing	125	5	9
Purpose-written costing guidelines	6	8	11
Costing study with methodological commentary	11	0	0
Reviews of cost methods	3	1	1
What costing purpose does guidance cover?			
Economic evaluation / priority setting	91	7	17
Equity and poverty analyses	3	4	2
Financial planning / management	0	2	1
Purpose not specified / multiple purposes	51	1	1
What topics does guidance cover?			
Broad costing guidance	9	8	11
Estimating resource use	86		1
Reporting	1		1
Study Design	2		
Valuing direct costs	6	5	5
Valuing indirect costs	41	1	3
Does any analysis underlie guidance?			
Case study / worked example	10		1
Empirical comparison / validation	107	3	1
Expert consultation	2		2
Literature review	7	1	2
No analysis (theory-based)	19	10	16

Use of guidance in the development of costing methods

The mean number of 'total' citations for all references was 64; this amounted to a mean of 5 references per year (varying from 0 to 46.5). Articles providing insight into the valuation of indirect costs received the most citations per year (mean 6.5 citations per year), followed by broad costing guidance (mean 4.8 citations per year). The mean number of citations that articles received by other authors writing about costing methods ('methodological citations') was 2.19 (0.10 per year). The most 'methodological citations' were observed in papers on estimating resource use (mean 3.11; 0.18 per year) and valuation of indirect costs (mean 2.39; 0.17 per year).

On average, the overview guides to costing received 54 total citations, amounting to a mean of 4.73 citations per year from the time of article publication. The most frequently cited guidance was Brouwer's "Costing in Economic Evaluations", in Drummond & McGuire (2001) Economic Evaluation in Health Care [Supplementary references 19], with 517 total references or 32 per year. Twenty-one of the 28 references had zero methodological citations. The reference with the most methodological citations was the "Empirical standard costs for health economic evaluation in Germany" [Supplementary references 23], with 5 methodological citations, or 0.4 per year.

The top five papers on valuation of indirect costs with the most external citations were written by three authors (Koopmanschap 1995, 1992, 2008; Van den Hout 2010; Pauly 2008) [Supplementary references 133-135, 140, 157], from two countries (the Netherlands and the United States). The two papers with the most 'methodological' citations (Koopmanschap 1995; Krol 2012) [Supplementary references 133, 136] are also both written by authors from Erasmus University in the Netherlands. References relying on a case study or worked example received the most citations overall and the most 'methodological' citations.

Of the top five papers on the topic of estimating resource use with the highest total citations, 2 were applicable to a low- or middle-income setting (Kessler (2003); Goossens (2000)) [Supplementary references 53, 69] and 3 applicable to a high-income setting (Roberts (1996); Bhandari (2006); Ritter (2001)) [Supplementary references 29, 92, 93]. Of references within this topic, those with some form of empirical comparison or validation received more 'methodological' citations than those with no analysis or with other forms of analysis, however higher numbers of total citations were observed for papers using a case study or worked example, or presenting results from expert consultation.

Articles on valuing direct cost received a mean of 4.43 citations per year. The majority of these citations received zero 'methodological' citations. Two papers received one 'methodological' citation each; both of these had some empirical analysis [Supplementary references 179, 185].

Neither paper providing guidance on reporting received citations from other authors writing about methods, but both received citations generally in the literature (mean 3.26 per year).

Figures 7-3 and 7-4 illustrate the citation network for the top 100 references, grouped by guidance topic and country income group, respectively. As illustrated in Figure 7-3, the majority of 'methodological' citations occurred between different articles publishing on the same topic. Many of the references providing disease-specific broad costing guidance cite previous works on the estimation of resource use but do not cite any references on the valuation of indirect costs. One reference providing broad costing guidance cites references from both fields [Supplementary references 23]. There were four references providing guidance on estimating the quantity of patient time or productivity lost due to illness [Supplementary references 69, 97, 109, 159] – these references were not cited by other papers on estimating resource use but were cited by papers on valuation of indirect costs.

As illustrated in Figure 7-4, the vast majority of 'methodological' citation between references occurred amongst papers set in high-income settings. Most papers set in a low- or middle-income setting, as well as most papers that were not country-specific, did not cite any pre-existing guidance and were not cited by any following guidance. The only exception to this is Hutton's "Cost valuation in resource-poor settings" (2005) [Supplementary references 186], which cites a paper on the valuation of indirect costs [Supplementary references 135].

Figure 7-3 Citation network by guidance topic

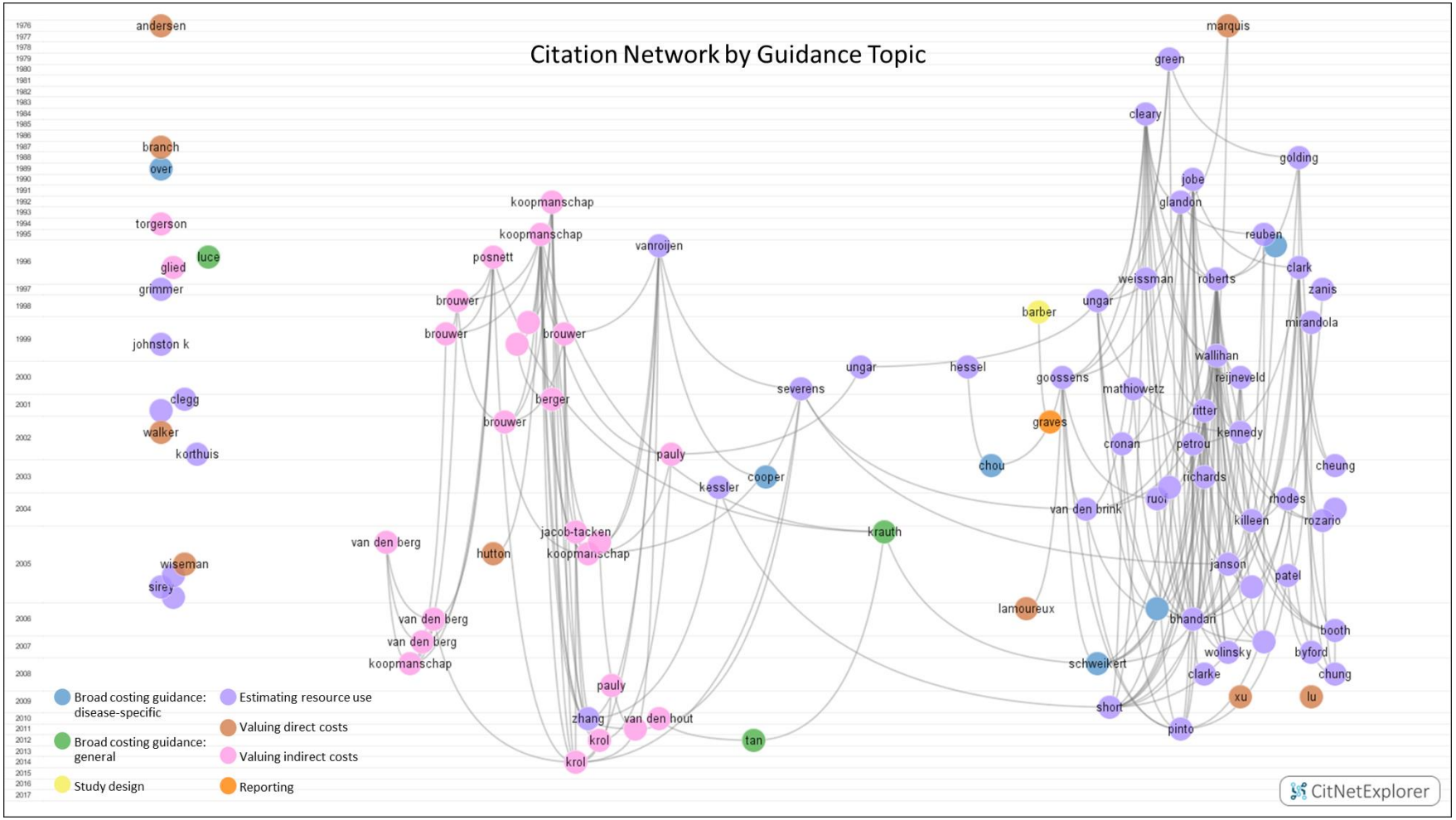
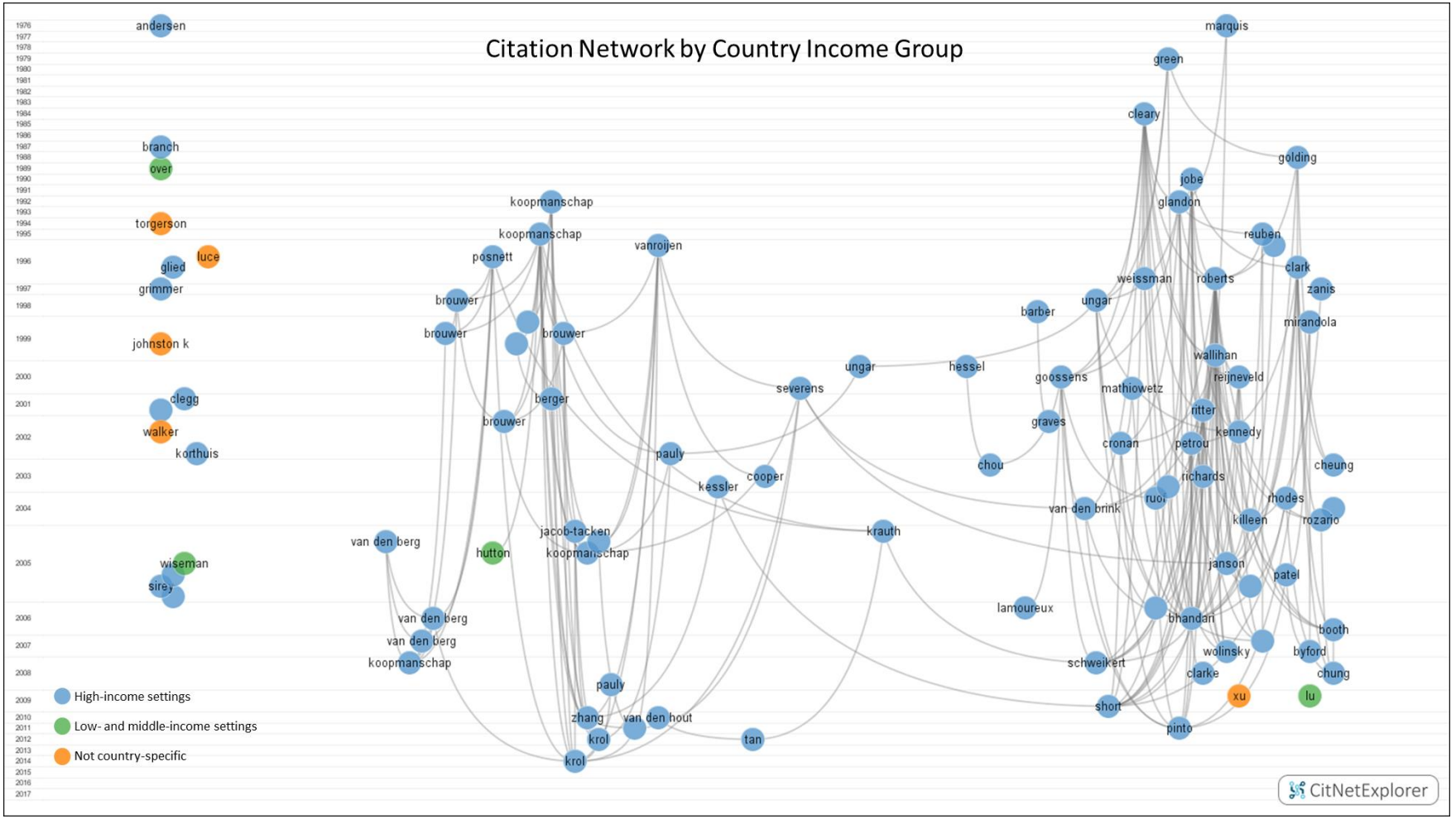


Figure 7-4 Citation network by country income group



Use of guidance in patient cost data collection (TB case study)

Table 7-3 summarizes the available TB-specific costing guidance, as well as any other guidance cited by articles on the patient costs of TB published since 2008.

The detail of guidance available for TB-specific costing varied. One article briefly mentions patient costs but contains no direct guidance on collecting or analysing patient costs [Supplementary references 12]. Three agency publications provided more detailed guidance on TB specific costs, giving a detailed breakdown of the types of costs likely to be incurred by TB patients and their households and sample questions to estimate these costs [Supplementary references 14, 16, 17]. Sample questions for estimating direct costs consistently ask patients to recall their actual expenditure; none of the guidelines discusses the alternative approach of measuring resource use and valuing those resources separately. None of the three guidelines describes likely sources of bias associated with estimating direct costs (such as recall bias, desirability bias, or respondent bias), nor do they reference any empirical evidence on ways to counteract this bias through data collection methods. Where sample questions for estimating indirect costs are given, methods appear to follow the human capital approach. The benefits and drawbacks of alternative approaches to estimating productivity costs are not discussed, and no methods for using the FCA or WTP approaches are described or referenced. Finally, guidance on study design is minimal in all four TB-specific references. The three agency publications mention that patient/family/lay-person costs should be generated from a random sample of interviewees, but they do not provide guidance on methods for sampling or selection. Logistics for the survey are also not addressed; none of the tools indicates appropriate timing of the survey or which questions may be cut if practical constraints restrict the time available for the interview (40–42).

Of the 63 TB patient costing papers reviewed, 30 provided no references in the methods section. Of those that did provide a reference in the methods section, 16 referred to a previous costing study conducted by their team, reporting that they had adapted a previously used questionnaire.

Twenty-three articles made some reference to published costing guidance. Of these, 13 referred to the Tool to Estimate Patient Costs (43). No other TB-specific costing guidance was cited by any articles. Several articles were cited which provide general high-level guidance on economic evaluation but do not provide any specific guidance on methods for estimation or valuation of resource use from the patient perspective (44–50). Three articles

Table 7-3 TB-specific costing guidance availability and uptake by costing practitioners

Reference type	Open access?	Number of references citing guidance	Guidance on study design / sampling?	Guidance on estimation of resource use for patient costs?	Guidance on valuation of direct costs?	Guidance on valuation of indirect costs?	Guidance on estimation of capacity to pay?	Guidance on defining a threshold of affordability?
Adaptation of previous questionnaire		28	n/a	n/a	n/a	n/a	n/a	n/a
TB-specific costing guidance								
WHO (1999)	Yes	0	No	Yes	No	HCA only	No	No
USAID (2008) (43)	Yes	13	Partial	Yes	No	HCA only	No	Partial
Sohn (2009)	No	0	No	No	No	No	No	No
WHO (2015)	Yes	0	Yes	Yes	Yes	HCA and outputs	Yes	Yes
Other Costing guidance								
Drummond (1997) (49)	No	2	No	No	No	HCA only	No	No
Creese and Parker (1994) (50)	Yes	1	No	No	No	No	No	No
Rice (1967) (31)	No	1	No	No	No	HCA only	No	No
Luce (1996) (46)	No	1	No	Yes	Yes	HCA and WTP	No	No
WHO (2002) (47)	Yes	3	No	Partial	Partial	HCA and others	No	No
Pizzi (2006) (48)	No	1	No	No	No	No	No	No
Guidance unrelated to health		2						
No guidance cited		32	n/a	n/a	n/a	n/a	n/a	n/a

cited a reference which did not provide any specific guidance on patient costing (45,48,51). Two articles cited references which were unrelated to health. None of the articles referred to any stand-alone guidance on specific methodological issues such as sampling, recall, data collection methods, or valuation of time.

DISCUSSION

This paper has presented a bibliometric review of the literature base on methods for estimating patient costs, in order to determine the availability, relevance, accessibility, and use of costing guidance for researchers estimating disease-specific catastrophic costs in low- and middle-income settings.

Overall, the availability of guidance was strong. I found a large literature base on methods for estimating patient costs, amounting to 180 publications in total. Availability of guidance varied somewhat by topic. For some methodological questions (for example, estimation of resource use), there has been a good deal of research published on the validity of different approaches. In contrast, there were only 2 references containing guidance on study design and 2 references providing guidance on reporting patient cost estimates.

Although there were a large number of references, I found that the literature base contained few references that were accessible to researchers in a low- or middle-income country. Most references were published in peer-reviewed journals, and the majority of references (88%) were not published in open-access journals. The literature was also diverse, and difficult to find using standard keywords and searches. Several rounds of searches and snowballing were required to produce this dataset. For most topics, I found piecemeal and inconsistent recommendations from individual studies. Where literature reviews were conducted, they were mostly not accurate representations of the existing literature base. There is a clear need for consolidation of the literature into one easily accessible place to enable researchers to make informed choices about methods and for more consistent use of keywords and/or MeSH terms to identify costing guidelines.

Many studies with methodological recommendations may also not have been relevant to a low- or middle-income setting. Some topics, such as estimation of resource use or valuation of indirect costs, had almost no papers relevant to a LMIC setting. For example, most papers discussing the estimation of resource use evaluated self-reported service use against administrative records. Administrative records are currently not suitably robust in many low-income settings; while this provides an excellent argument to encourage better

record-keeping, until this happens records may not be a viable option for researchers working in LMIC settings. Similarly, it is unclear whether the approaches to value indirect costs which were developed for a high-income country setting are also relevant to a low-income setting where the labour market operates very differently. The friction cost approach has not been tested in a low- or middle-income country to date, and the value of time for informal caregivers may be valued differently in settings where there is high unemployment. There is a great need for further consideration of how to apply the lessons learned in a high-income country setting to LMICs.

Throughout the literature base, the concern of much of the literature seems to be focused on estimating patient cost as part of economic evaluation, rather than estimating costs to the household in order to capture the effect of illness on equity or vulnerability. For example, at least 28 references were about the friction cost method of valuing indirect costs reflects the impact of illness on the economy, which fails to capture the increased vulnerability within the household that arises from lost time and productivity due to health issues. Similarly, all of the references on study design consider sampling for economic evaluation purposes, rather than any sampling to capture increased vulnerability. This is a reasonable approach for some settings such as the UK, where universal access to health care minimizes the likelihood of impoverishment due to health-related spending. However, in settings such as the US or in LMIC settings where there is not yet universal access, this limitation of methods may mean that important losses of welfare are not captured accurately. Improved guidance on the appropriateness of different methods for different uses of patient cost data is much needed.

This review included 28 broad patient costing guides, published by international organizations and available freely online. These references were identified as receiving some of the highest 'total' citations, implying that they are some of the most commonly used sources of costing guidance cited by costing practitioners. In the relatively high level of use of these broad guides, there appears to be an assumption that these references draw on the existing literature base in order to draw conclusions as to the best approach. However, on closer examination of citation networks, I found many of these 'broad' costing guides do not currently draw on the substantial literature base. While a few 'broad' costing guidelines cite references on the estimation of resource use, they largely do not refer to the existing literature on other topics such as valuation of direct or indirect costs, study design, or reporting. References which provide guidance relevant to low- and middle-

income settings do not draw on existing guidance at all, nor do those references that are not country-specific or those published by international agencies.

The impact of the limited accessibility and relevance of methods for low- and middle-income settings can be seen in the limited uptake of costing guidance as exhibited in the review of the TB costing literature. The review of the methods employed by existing patient cost studies has shown that remarkably little of the available literature base is cited by patient costing practitioners within the existing TB patient costing studies. No TB patient costing studies cited individual methodologically-focused studies with recommendations based on an empirical comparison of the validity of different approaches. The majority of authors do not cite any costing guidance in the methods sections of their papers, often relying instead on institutional knowledge within their own teams. The guidance that authors do reference in the methods section is often high-level and often does not provide any specific guidance on methods for estimation or valuation of resource use from the patient perspective.

Overall, although guidance on estimating patient costs is available to some degree, this review has shown that the accessibility, relevance, and use of this guidance leaves much room for improvement. This review has highlighted a lack of discussion between authors making costing accessible to practitioners working in LMIC settings, where it could be said that the issue of patient costs is more critical than in HIC where there is often universal coverage, and those working at the 'cutting edge' of methods development. This limited discussion leads to an increased dependence on institutional knowledge, raising barriers to access for new researchers in the topic and leading different teams to take different methodological approaches. This results in reduced confidence in cost estimates, and limited comparability across estimates made by different teams. For cost estimates to be useful to policymakers, it is essential that cost estimates collected for different interventions and in different settings are comparable and that the potential sources of bias in cost estimates are clear. If estimates of cost in economic evaluations are not comparable between interventions within a country, this makes planning and decision-making difficult for policymakers. In addition, if estimates of the prevalence of catastrophic cost are not comparable across countries, this diminishes the ability of international organizations such as the WHO to monitor country progress towards international targets.

Limitations

This review has some limitations. Firstly, for practical reasons, I needed to constrain the review at some point. I excluded references from topics not relevant to health – for example, several references from labour economics, agricultural economics, and development economics were excluded despite offering some relevant guidance on valuing the time of people in low- and middle-income settings or measuring expenditures within LMIC households in the context of a household survey. This may have resulted in an under-representation of the resources available to health economists considering patient cost in LMIC settings, as they could draw on this wider literature in developing methods.

Secondly, the search process, as described in the Methods process and in Figure 7-1, was complex. The literature base on estimating patient costs is diverse – this is compounded by poor use of keywords throughout the literature, and by the fact that many key references are not published in economic journals. The extensive snowballing process used in the review helped to facilitate capture of relevant references, however there is still a chance that some relevant references were not included.

Finally, the review included a number of references in the form of grey literature or publications by international agencies (for example WHO, UNAIDS, and USAID). Grey literature is usually not included in the Google Scholar or Web of Science databases. The number of 'methodological' citations for this literature base was counted manually, to ensure accurate estimates of the degree of internal discussion for grey literature. The 'citations' search tool in the Scopus database was used for these references, giving a good approximation of the number of articles citing these references; however, citation data is less reliable for these references.

Conclusions

This review highlights the need for improved discussion and consensus for patient costing methods, and the need for improved accessibility to methodological guidance for researchers working in low- and middle-income countries. The database created in the process of writing this paper will be published online through the Global Health Cost Consortium. A central repository for patient costing guidance would facilitate access to the materials as well as discussion around methodologies.

The increasing movement towards Universal Health Care has great significance for the topic of economic evaluation. Now more than ever, health economists are tasked with

providing policy-makers information on the impact of specific illnesses on economic vulnerability within the household. If further consideration were given in the methodological literature as to how these critical issues can most accurately be reflected, research could lead to better policy lessons surrounding economic vulnerability in the context of illness – not only in LMIC settings but also in high-income countries. Further research on appropriate methods for disease-specific patient cost measurement is essential in order to help answer important policy questions as countries look to expand access to health care.

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CHAPTER 8. MEASURING INCOME FOR CATASTROPHIC COST ESTIMATES: LIMITATIONS AND POLICY IMPLICATIONS OF CURRENT APPROACHES

PREAMBLE FOR RESEARCH PAPER #3

Chapters 5 and 7 describe some potential reasons for widely varying methods observed across estimates of costs encountered by patients and their households. Methods can differ across studies due to practical constraints such as time and budget, and due to a lack of standardized guidance on appropriate methods. It is vitally important to recognize that these practical decisions can have a substantial impact on study results.

The same issues can also impact the estimation of household income, which can lead to inconsistency in estimates of the prevalence of catastrophic costs. I assess this potential impact in Research Paper #3, using the example of individual income (used in the valuation of time lost as a result of TB) and household income (used in the estimation of capacity to pay for TB-related costs). Household and individual income are both notoriously difficult to estimate (Beegle, De Weerdt, Friedman, & Gibson, 2012; Howe, Hargreaves, & Huttly, 2008). The costing literature, however, largely ignores this issue – with most costing guidelines suggesting only one or two questions to obtain income (eg. "How much do you estimate was the average income of your household per month BEFORE the TB illness?" and "How much do you estimate is the average income of your household per month NOW?" from the Tool to Estimate Patient Costs).

Using data from a recent clinical trial conducted in South Africa (TB FastTrack), I compared six different approaches to estimate catastrophic costs. I explore the variation arising from different income estimation approaches and compared the number of households encountering catastrophic cost estimated through each approach. I found that the income estimation approach is critical in estimating catastrophic costs; results varied from 0% to 36% of households encountering catastrophic costs depending on the estimation method. I conclude that the rapid methods for estimating income among patients attending a health facility are currently inconsistent, and advocate strongly for further development of methods for measuring income.

This was a multi-authored paper based on cost data collected during the TB FastTrack study (Fielding et al., 2015). SC designed the questionnaire with input from myself. SC and RM collected the data. All authors input on a final version of the paper. All other work, including paper approach, analysis, and writing the first and consecutive drafts of the paper, was my own.

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

SECTION B – Paper already published

Where was the work published?	Social Science and Medicine		
When was the work published?	2018		
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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)	SC designed the questionnaire with input from SS. SC and RM collected the data. All authors input on a final version of the paper. All other work, including design of the analytical framework, analysis, and writing the first and consecutive drafts of the paper, was the candidate's.

SECTION E

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MEASURING INCOME FOR CATASTROPHIC COST ESTIMATES: LIMITATIONS AND POLICY IMPLICATIONS OF CURRENT APPROACHES

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Abstract

There is increasing global policy interest in estimating catastrophic costs incurred by households because of ill health, and growing need for information on disease-specific household cost data. There are several methodological approaches used to estimate income and no current consensus on the best method for estimating income in the context of a survey at the health facility. We compared six different approaches to estimate catastrophic cost among patients attending a health facility in South Africa. We used patient cost and income data collected June 2014–March 2015 from 66 participants enrolled in a clinical trial in South Africa (TB FastTrack) to explore the variation arising from different income estimation approaches and compared the number of households encountering catastrophic costs derived for each approach. The total proportion of households encountering catastrophic costs varied from 0% to 36%, depending on the estimation method. Self-reported mean annual income was significantly lower than permanent income estimated using an asset linking approach, or income estimated using the national average. A disproportionate number of participants adopting certain coping strategies, including selling assets and taking loans, were unable to provide self-reported income data. We conclude that the rapid methods for estimating income among patients attending a health facility are currently inconsistent. Further research on methods for measuring income, comparing the current recommended methods to 'gold standard' methods in different settings, should be done to identify the most appropriate measurement method

Keywords: South Africa, Catastrophic cost, Coping, Tuberculosis, Methods, Income

HIGHLIGHTS

- Rapid methods for estimating income for catastrophic TB costs are inconsistent
- Depending on income estimation approach, 0-36% households faced catastrophic TB costs
- Quantitative indicators of catastrophe did not reflect extent of coping strategy use

1. INTRODUCTION

Costs incurred as a result of ill-health can aggravate household vulnerability (Alam and Mahal, 2014; Wagstaff and Lindelow, 2014). They can also contribute to delays in diagnosis, reduced adherence, and poorer health outcomes (Wingfield et al., 2014). Tuberculosis (TB) patients often encounter substantial costs in the form of out-of-pocket payments and lost income. In recognition of the impact of these costs, the End TB Strategy introduced a TB-specific indicator of financial risk protection; this is labelled "catastrophic total costs due to TB", and includes non-medical direct costs and income losses (Lönnroth et al., 2014). The End TB Strategy targets specify that no patient encounters catastrophic total costs due to TB by the year 2020 (World Health Organization, 2015).

The indicator of 'total catastrophic costs due to TB' is relatively new and requires a different measurement approach and definition of 'catastrophic' compared to that used for general catastrophic health expenditure measured in the context of health financing. This paper aims to inform guidance on the measurement of catastrophic total costs due to TB from a sample of patients as part of a facility-based survey. We compare estimates of the prevalence of catastrophic cost using six approaches. We highlight the implications of these measurement approaches on the identification of catastrophic costs and resulting policy.

1.1 Background

To support countries seeking to meet the target of zero catastrophic costs due to TB by 2020 (World Health Organization, 2015), the World Health Organisation (WHO) TB Programme established a Task Force in 2015 to develop a generic protocol for estimating the prevalence of catastrophic costs, building on methods used in previous studies of patient costs to provide guidance to countries on estimating catastrophic cost (World Health Organization, 2017). The aim of the 'catastrophic total cost' measure as described in the WHO handbook is to capture where health-related costs are likely to have a substantial

impact on the household's ability to pay for basic subsistence needs; this is represented in terms of total costs as a proportion of household capacity to pay. For global monitoring of the End TB Strategy catastrophic cost indicator, the WHO has chosen to use a threshold of 20% of annual household income. This threshold is currently used by National TB Programmes (NTP) implementing the WHO survey for annual reports to WHO (World Health Organization, 2018), however countries are also encouraged to undertake sensitivity analyses around the threshold.

In the context of health financing, the numerator for the "catastrophic expenditures" equation has been traditionally measured as direct out-of-pocket expenditure (Xu et al., 2005). However, over half of the economic burden encountered by households during an episode of TB comes in the form of lost income and lost productivity due to illness or time spent care-seeking (indirect costs) (Tanimura et al., 2014). The indicator of 'catastrophic costs due to TB' therefore includes indirect costs. Indirect costs are most commonly estimated through two approaches: first, household income can be estimated before and after the TB episode; any direct income loss due to TB is then captured by taking the difference. Second, the number of hours spent seeking care or otherwise unable to work due to TB can be estimated, and the value of these hours approximated with an estimate of the earning capacity of the patient for that time (e.g. hourly income). The first approach captures only the loss of paid work, while the second approach captures all time off work necessitated by symptoms and treatment seeking (but may not include any household mitigation of that loss).

There are several potential indicators of household capacity to pay for health care, including: permanent income, current income, and wealth [Supplementary File 1]. The indicator of 'catastrophic costs due to TB' is intended to capture where costs associated with TB impose an economic burden that is non-recoverable, beyond typical day-to-day wealth management. Theoretically, permanent income is the best comparator to reach this aim. Measures of permanent income will more appropriately reflect the impact of health costs on the total resources available to the household, thus capturing any potential long-term depletion in financial wellbeing in the household. According to the permanent income hypothesis, permanent income can be captured through consumption expenditure (Friedman, 1957), as consumption stays relatively constant according to one's socio-economic status (Garvy, 1948). A consumption expenditure module should therefore appropriately capture ability to pay for health-related costs.

However, pragmatically most surveys estimating catastrophic costs for specific diseases are conducted with patients attending a health facility, as disease prevalence is often too low to make household surveys efficient. Interviewing at the facility, often as part of clinical trials, introduces substantial time and cost restrictions on the survey. Short-form consumption expenditure questionnaires are not available for many contexts, and the limited time available often prevents full consumption expenditure surveys. The risk of survey fatigue for patients interviewed at a health facility is also much higher and large sample sizes are often not possible (Sweeney et al., 2016). Researchers have therefore opted to take various approaches to estimate 'capacity to pay', with the large majority using self-reported current annual income in the denominator of the catastrophic costs equation (Barter et al., 2012) WHO recommendations currently suggest equivalence between current income and annual household expenditure.

Estimates of current income are subject to variation arising from different methods of measurement (diary vs. recall), recall periods, levels of detail in questions soliciting income, and level of respondent (individual vs. household). There is some evidence that each of these factors can lead to bias in income measurement. Bias can manifest in the form of error in reporting (i.e. due to recall error, telescoping, rounding error, cognitive errors, survey fatigue or misreporting), or in the form of non-response (Beegle et al., 2012; Browning et al., 2014; Deaton, 2001; Deaton and Grosh, 1999; Foster and Lound, 1993; Gibson, 2016; Jolliffe, 2001; Moore et al., 2000; Pudney, 2008; Winter, 2002, 2004). While it is possible to adjust analysis for partially observed data (i.e. through multiple imputation, mean imputation, or other assumed values) (Brick and Kalton, 1996; Sinharay et al., 2001), income data is susceptible to non-response not at random, making many forms of imputation likely inappropriate. Survey design is key in efforts to limit the amount of missing data.

Another potential solution to the problem of bias in small facility-based surveys is using a proxy for income, either by assuming the national average income for all participants or by using household assets as a proxy for permanent income. Where national survey data exist, it is possible to use principal components analysis or multiple correspondence analysis (MCA) to compute factor weights at the national scale, which can then be applied to asset data for a smaller survey. This approach allows researchers to estimate permanent income without the large expense of conducting a national survey (Gwatkin et al., 2005; McKenzie, 2005; Standards, 1997). There are some limits associated with this approach, however; assets are slow-changing and therefore may not capture changes in household economics

accurately, particularly for the lowest quintile (Booysen et al., 2008; Harttgen and Vollmer, 2011).

Finally, the issue of income measurement can be avoided entirely by adopting an indicator of financial catastrophe which is not dependent on estimating TB-related costs as a proportion of capacity to pay. Following indications that financial catastrophe is linked with coping strategies (Madan et al., 2015), presence of these strategies could be used as an indicator of catastrophic cost.

2. METHODS

2.1 Study Design

We present and compare estimates of catastrophic cost using a range of existing methods to represent household capacity to pay for TB services, in the absence of a full consumption questionnaire. We use data from a patient costing study nested within the TB FastTrack study, a pragmatic, cluster randomised trial with 24 primary healthcare clinics randomised to implement algorithm-guided empirical TB treatment for ambulant HIV-positive adults who had a low CD4 count and were not yet on TB or HIV treatment (Fielding et al., 2015). Patients in the intervention arm were started on TB treatment if indicated by the study algorithm, and ART initiation was promoted either two weeks after the start of TB treatment, or at the earliest opportunity if TB treatment was not indicated; in the control arm, clinic staff initiated TB treatment and / or ART according to routine practice. Patient cost data was collected between June 2014 and March 2015. The patient cost study was not designed to draw any conclusions on the impact of the TB Fast Track intervention on income or cost. Ninety-nine participants were recruited from a pragmatic sub-selection of 17 study facilities in Bojanala Platinum (28 participants), City of Ekurhuleni (9 participants), City of Tshwane (48 participants), and Greater Sekhukhune districts (14 participants). Bojanala Platinum and Greater Sekhukhune are both rural districts, located in North West and Limpopo provinces respectively. City of Tshwane and City of Ekurhurleni are peri-urban districts, both located in Gauteng province. All municipalities had high unemployment rates in 2011, ranging from 24.2% in City of Tshwane to 50.9% in Sekhukhune (Statistics South Africa, 2014).

Participants were interviewed for this study at their 6-month follow-up trial visit. Questionnaires were adapted from the USAID Tool to Estimate Patient Costs for TB (USAID et al., 2008), and included a series of questions about patient demographics, asset

holdings, health care seeking behaviour, costs associated with seeking care, and income [Supplementary File 2]. Questionnaires included detailed questions on visits made to a range of providers, including the trial clinic, other public facilities, general practitioners, hospitals, traditional healers, and pharmacies. Questionnaires were designed to exclude visits that were made solely for research purposes. Data on household size from the survey was unreliable, as data was only available for 49 participants. To maintain consistency in the analysis we used the mean household size by municipality as obtained from Statistics South Africa as a measure of household size rather than individual household estimates.

Data were entered into an Excel spreadsheet, and analysed using a combination of Excel and Stata 14. All cost and income data were inflated using the local inflation rate to reflect prices in October 2015, and then converted to USD using the average conversion rate in October 2015, R 13.08 = 1 USD (XE, n.d.). Participants were interviewed in a private space and all data were anonymised prior to analysis. The trial, including the costing study, was approved by the Research Ethics Committees of the University of Witwatersrand (approval number: R14/49 M111177), the London School of Hygiene and Tropical Medicine (approval number: 6099), and the Provincial Research Committees of Gauteng, North West and Limpopo.

2.2 Components of Catastrophic Cost Estimates

We estimated the proportion of households encountering catastrophic costs for each income estimation approach, following WHO definitions of catastrophic costs (World Health Organization, 2017):

$$\frac{Episode\ direct\ cost + Episode\ indirect\ cost}{Household\ 'capacity\ to\ pay'} > THRESHOLD\ VALUE\ (\%)$$

Methods of estimation for each of these components is detailed below. For comparison of catastrophic cost incidence across estimation approaches, we use a threshold value of 20% as a base case, but also illustrate the impact of varying threshold on the total proportion of participants encountering catastrophic cost. We also considered the presence of coping strategies as an indicator of catastrophic cost.

2.2.1 Estimation of household 'capacity to pay'

We estimated the annual household income using four different approaches, described below. We did not attempt to estimate household consumption or expenditure, as at the

time of study design there were no validated short-form consumption questionnaires for use in South Africa.

2.2.1.1 Approach #1: Self-reported current income (prompted ranges)

On trial enrolment, we asked participants to self-report their monthly household income using a single question with prompted ranges of: less than $62, $62-$104, $104-$208, $208-$415, greater than $415, or not known. Households in each range were assigned the mid-point income for that range (i.e. $31 for those stating income less than $62, $83 for those with income $62-$104, and so forth).

2.2.1.2 Approach #2: Self-reported current income (detail)

During the patient costing questionnaire at the 6-month follow-up visit, we asked participants to recall the monthly income of the household with respect to 4 time-points: prior to symptom onset, at trial enrolment, at the start of TB treatment (or HIV treatment if not treated for TB), and at the 6-month follow-up visit. The onset of symptoms was self-identified by participants as the date when they "first felt unwell". Income was solicited this time with detailed questions surrounding the salary and non-salary income of the participant and that of other household members; questions included monetary income, non-monetary income (e.g. food), grants and remittances. Household income prior to symptom onset was used for the denominator of the catastrophic cost equation.

2.2.1.3 Approach #3: Estimated permanent income based on asset scoring

At trial enrolment, we asked participants about a range of assets held by the household and household characteristics, including: a stove, DVD player, motorcar, washing machine, satellite television, computer, radio, television, refrigerator, cell phone, bicycle, and indicators of housing quality (toilet facilities, source of water, wall materials, floor materials, and dwelling type). We used the same asset questions as the National Income Dynamics Survey (NIDS) in South Africa (Leibbrandt et al., 2009), a national panel survey of households. Coding for these questions was mapped to coding for the same questions from the NIDS.

We conducted a multiple correspondence analysis (MCA) on NIDS survey data to estimate weights for each of the above-described assets and characteristics as reported in the most recent round of the survey, conducted in 2015 (Wave 4) (Booysen et al., 2008; Howe et al., 2008). The first dimension explained 78% of variation in the dataset. Weights from the first dimension were applied to the TBFT dataset, and households were classified into five socio-economic quintiles. For each income quintile, mean monthly expenditures were taken from

the NIDS dataset and assumed to represent the mean household permanent income for that quintile. This was used as the denominator for catastrophic costs.

2.2.1.4 Approach #4: Estimated income based on the average net disposable income

We compared the above income measures against a broad assumption that all households earned the average net adjusted after-tax income in South Africa, as estimated in the OECD Better Life Index (USD 8,712 per year) (OECD, 2017). Income estimates were inflated from the 2013 reference year given by OECD to October 2015.

2.2.2 Estimation of direct costs

We estimated direct medical and non-medical costs for the numerator of the catastrophic cost equation. Direct medical and non-medical costs were estimated for the period from the onset of symptoms to the 6-month follow-up visit. If participants had no symptoms, costs were estimated for the three months prior to enrolment to ensure all related care-seeking costs were included. To standardize costs, we assumed a minimum 6-month follow-up period after enrolment for all participants. In cases where participants were interviewed before 6 months, we estimated an average monthly cost and then extrapolated this to six months. The 6-month recall period is longer than typically recommended to estimate costs; as the patient cost study was not designed to provide definitive conclusions on the cost of the TB Fast Track intervention we accepted some risk of bias in order not to interfere with the intervention implementation.

Direct costs were defined as medical and non-medical expenses. Medical expenses included consultation fees and any out-of-pocket payment for medicines and diagnostics paid at any provider type. Direct non-medical expenses included any travel costs of participants and guardians, food costs incurred while in hospital, money spent buying any special foods or dietary supplements due to illness, and any interest incurred on loans taken out to meet the costs of out-of-pocket payments. Direct medical and non-medical costs were determined as the product of the reported expense for the most recent visit to each provider type and the number of visits made to that provider.

2.2.4 Estimation of indirect costs

We estimated indirect costs for the numerator of the catastrophic cost equation using two approaches. First, indirect costs were defined as the opportunity cost of time spent away from the daily productive routine. The number of hours included time spent travelling to health facilities and waiting and consultation time, excluding any extra visits made for

research purposes alone; any time spent by household members caring for the participant or covering household chores usually done by the participant was also included. The total time was multiplied by the estimated household income per person per minute, which was derived from each of the four respective measures of household income estimated as described above using the mean household size by municipality from Statistics South Africa and self-reported working hours per day (approaches #1-4).

Next, we estimated the indirect cost using the self-reported income loss during the period from symptom onset to 6 months after study enrolment. Any gain or loss in income during this time which the participant attributed to illness were multiplied by the duration of the pre-enrolment, trial entry, and treatment periods respectively to come to a total indirect cost. This is labelled as approach #5.

2.2.5 Coping strategies

Finally, we consider use of coping strategies as an indicator of economic catastrophe (approach # 6). Participants were asked about their use of several coping strategies to meet the costs of TB, including asset sales, taking loans, reducing food consumption, and changes in household labour use (e.g. pulling children out of school to work).

2.3 Analysis

To facilitate comparison between different income measurement approaches, we began our analysis by dropping all participants for whom a household income was not calculable using any of the income estimation approaches described below due to missing data (n = 33) and conducted a complete case analysis for the remaining participants (n = 66). We tested the reliability between different approaches of income measurement using Cohen's kappa statistic (McHugh, 2012). Finally, we illustrate the resource implications of varying methods using the example of South Africa's temporary disability grant, which is a monthly cash transfer providing income support to all South African citizens who are unable to work due to disease or disability (typically R1010 ($67.23) per month). We estimate the total cost of a years' access to the temporary disability grant ($806.76) for each household identified as encountering catastrophic cost by each approach. This type of grant could protect households from the negative economic ramifications of catastrophic TB costs and reflects the potential cost of reducing catastrophic costs.

3. RESULTS

3.1 Data and Demographics

Ninety-nine people in total participated in the patient costing survey. Of these, we excluded 33 participants (33%) from the full analysis due to missing data for one or both self-reported income questions. Twenty-seven participants responded, "Don't know" to the question "On average, what is your monthly household income: zero or less than R600 ($62), R601-1000 ($62-$104), R1001-2000 ($104-208), R2001-4000 ($208-415), or greater than R4000 ($415)". When responding to more detailed income questions, two participants were unable to report their own income, and eight were unable to report the income of other household members.

Table 8-1 Demographic characteristics of study participants, comparing those included vs. excluded in the main analysis

Variable	Participants included in analysis (n = 66)	Participants excluded due to missing income data (n = 33)	Difference
Female n (%)	45 (68%)	19 (58%)	chi^2 = 1.08; p = 0.30
Mean age (Std Dev)	37 (8.0)	40.8 (11.9)	t = -1.76; p = 0.08
Black/African n (%)	66 (100%)	33 (100%)	n/a
Grade 8 and above n (%)	59 (89%)	27 (82%)	chi^2 = 1.11; p = 0.29
Unmarried n (%)	40 (61%)	21 (64%)	chi^2 = 0.09; p = 0.77
Employed at symptom onset n (%)	35 (53%)	9 (27%)	chi^2 = 5.91; p = 0.02*
Employed at trial enrolment n (%)	32 (48%)	10 (30%)	chi^2 = 2.98; p = 0.08
Receiving any government grants n (%)	51 (77%)	24 (73%)	chi^2 = 0.25; p = 0.62
Receiving disability grant for HIV/TB n (%)	1 (2%)	0 (0%)	chi^2 = 0.51; p = 0.48
Median CD4 count at last test (IQR)	90 (58)	73 (60)	t = 0.57; p = 0.57

Asset quintile distribution (mapping to national asset index) n (%)	Quintile 1: 3 (5%) Quintile 2: 7 (11%) Quintile 3: 27 (41%) Quintile 4: 18 (27%) Quintile 5: 11 (17%)	Quintile 1: 6 (18%) Quintile 2: 2 (6%) Quintile 3: 8 (24%) Quintile 4: 6 (18%) Quintile 5: 11 (33%)	chi^2 = 10.23; p = 0.03*
Coping strategies	Coping: 24 (36%) Took loans: 20 (30%) 0-25% interest: 6 (9%) ≥ 25% interest: 14 (21%) Reduced food: 10 (15%) Sold assets: 2 (3%) Multiple strategies: 8 (12%) No coping: 42 (64%)	Coping: 15 (45%) Took loans: 12 (36%) 0-25% interest: 7 (21%) ≥ 25% interest: 5 (15%) Reduced food: 0 (0%) Sold assets: 4 (12%) Multiple strategies: 2 (6%) No coping: 18 (55%)	chi^2 = 0.76; p = 0.38

IQR interquartile range

Table 8-1 shows the demographic data for those participants included in the analysis (n = 66), and for those excluded (n = 33). Most participants included in analyses were female (n = 45), and between the ages of 30 and 44 (n = 47). All participants were of black African ethnic origin, and 89% were educated to grade 8 and above (n = 59). The majority (n = 40) were unmarried. Only 53% (n = 35) of participants reported being employed at the time of symptom onset (or 3 months prior to enrolment if no symptoms); this had dropped to 48% (n = 32) by the time of trial enrolment. Excluded participants were significantly more likely to be unemployed at symptom onset than those included in the analysis.

Table 8-2 Mean number visits, direct costs, and time spent seeking care from start of illness to 6-month trial visit (n=66)

Facility type	Mean total number visits	Mean total direct medical cost	Mean total direct non-medical cost	Mean total hours care-seeking
Main clinic	12.98	$0.00	$27.32	70.01
Other clinic	0.12	$0.00	$0.31	1.03
Pharmacy	1.44	$4.60	$0.86	1.51
General practitioner	0.35	$7.56	$0.86	1.27
Hospital-inpatient	0.12	$0.80	$4.49	8.25
Traditional healer	0.21	$8.95	$0.69	1.56
Specialist	0.57	$0.57	$1.19	1.97
Radiologist	0.00	$0.00	$0.88	1.02
DOT	0.00	$0.00	$0.00	0.00
Total	**15.80**	**$22.48**	**$36.60**	**86.62**

All costs in 2015 USD

Many households undertook coping strategies to meet the costs of illness. Several households reported reducing food consumption (n=10), selling assets (n=2) or taking out loans (n=20), but no households reported taking children out of school to work. Some participants who were excluded from the analysis due to missing income data sold assets (n

= 4) or took loans (n = 12) to meet costs related to illness. The median CD4 count reported at enrolment was 90.

3.2 Total direct costs

Mean direct medical costs for all providers per episode were $23 and mean costs for travel and food during this period were $37 (Table 8-2). Sixteen participants visited general practitioners at least once at an average cost of $24 per visit, and seven participants were hospitalized at least once. No patients in this cohort received daily clinic-based directly observed treatment (DOT). Eight participants visited a traditional healer at least once, with consultation fees per visit ranging from $5 to $97 per visit. Direct non-medical costs were highest for participants' main clinic – this reflects travel and food costs for participants and their guardians during the many visits to these facilities. Supplementary File 3 shows the visit and direct cost data for excluded participants.

3.3 Total resources available to the household

Table 8-3 shows the mean and standard deviation of the estimated resources available to the household, and the number of participants falling below the nationally defined lower-bound poverty line of $43 per person / month for each of the four income estimation approaches (Statistics South Africa, 2014).

The two methods with the highest correlation coefficient (0.373; p = 0.002) were approach #1 and approach #2. The mean monthly income per household measured using prompted ranges (approach #1) was $242 (median $156), and the mean income reported in response to detailed questions (approach #2) was $317 (median $222).

Table 8-3 Monthly household income estimates using different approaches (n=66)

Income estimation approach	Households below poverty line	Mean monthly income per household	Median monthly income per household	Standard Deviation
Approach #1: current income (prompted ranges)	40	$241.70	$156.00	221.03
Approach #2: current income (detailed)	33	$317.71	$221.80	340.88
Approach #3: permanent income (MCA)	2	$497.33	$339.23	289.92
Approach #4: national mean income	0	$760.70	$760.70	-

All income in 2015 USD

Weights for assets and household characteristics from the NIDS MCA exercise are listed in Supplementary File 4. All durable assets had positive factor loading scores while indicators of poor housing had negative loading scores. Durable asset ownership was moderately correlated with permanent income in the NIDS dataset ($r = 0.40$; $p < 0.00$). More participants in the TBFT dataset reported ownership of some durable assets and high-quality housing characteristics, placing more participants in higher income quintiles than lower quintiles. Permanent income estimated using the MCA approach (approach #3; mean $497) was significantly higher than self-reported current income (approaches #1 and #2) ($p < 0.002$).

The highest mean income was estimated using approach #4 (mean $761); income estimates for approach #4 were also significantly higher than those for approaches #1 and #2 ($p < 0.00$). Depending on the approach taken to estimate income, as few as zero or as many as 40 of the 66 (61%) households were estimated to fall below the poverty line.

Table 8-4 Indirect costs for all estimation approaches from start of illness to 6-month trial visit (n=66)

Indirect cost estimation approach	Mean indirect cost	Standard deviation	Indirect cost as % total cost
Approach #1: current income (prompted ranges)	$33.33	53.16	34%
Approach #2: current income (detailed)	$43.55	53.80	41%
Approach #3: permanent income (MCA)	$74.75	77.62	54%
Approach #4: national mean income	$113.77	95.96	64%
Approach #5: self-reported income loss	$85.85	744.08	57%

All costs in 2015 USD

3.4 Total indirect costs

Indirect costs were a function of income and followed the same pattern as that of income. The highest indirect costs were estimated using approach #4, and the lowest indirect costs were estimated using approach #1. Depending on the income estimation approach taken, mean indirect costs for the episode varied from a mean of $33 to $113. Differing approaches in income estimation therefore had wide-ranging impact on cost drivers overall. Indirect costs account for 64% of total cost when using approach #4 for income estimation, and 34% of total cost when using approach #1 (Table 8-4). Self-reported income loss (approach #5) was roughly double that of time loss valued in terms of current income

(approaches #1 and #2), and had a much larger standard deviation than any other approach – this was due to a few participants reporting substantial income loss as a result of job loss due to illness, and a few reporting substantial income gains (e.g. in grants or remittances) as a result of their illness.

3.5 Catastrophic costs

Figure 1 illustrates the proportion of participants in the study encountering catastrophic costs across a range of thresholds, by approach. Across thresholds and particularly at lower thresholds, the choice of income measure lead to very large differences in the proportion of catastrophic cost. Approaches #3 and #4 had the fewest participants encountering catastrophic costs, dropping to zero at thresholds above 10%.

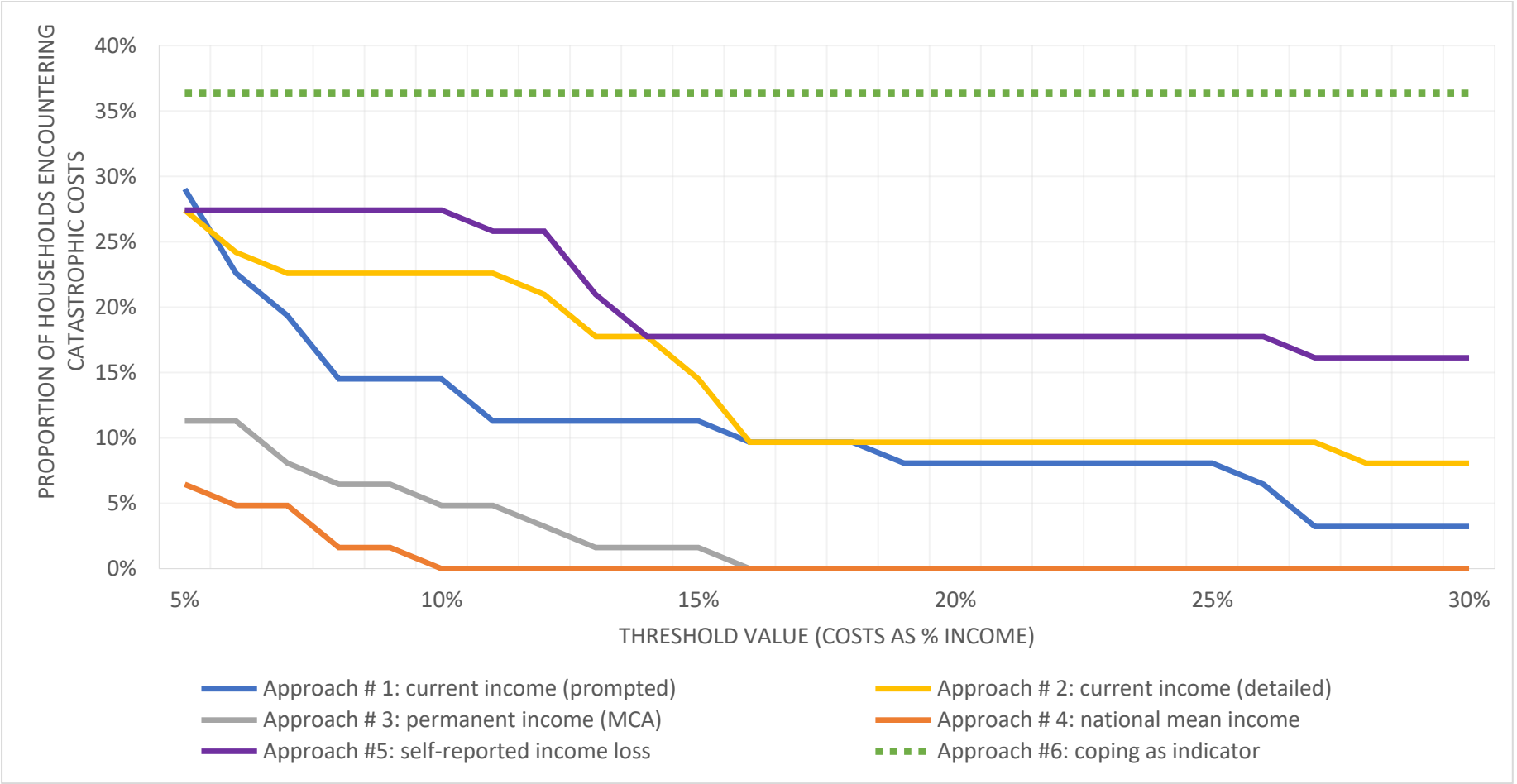
Table 8-5 presents the estimated prevalence of catastrophic cost for each of the six estimation approaches, and the potential cost of providing a disability grant to those encountering catastrophic costs. Under the national average income assumption, zero participants encountered cost over the 20% threshold. Using self-reported income data, six participants (9% of those included in analysis) encountered catastrophic costs. Using coping as an alternative indicator of catastrophic costs, 24 (36%) encountered catastrophic costs. There was minimal agreement between the five income measurement approaches in identification of catastrophic cost (Kappa = 0.2711, $p < 0.000$). Participants who reduced food consumption to meet costs were largely not classified as encountering catastrophic costs under approaches #1-4, however approach #5 reflected catastrophic costs for some of these participants.

Table 8-5 Policy impact of catastrophic cost estimates

	Number participants with catastrophic cost (total n = 66)	Total cost of providing one-year disability grant to all households with catastrophic cost
Approach #1: current income (prompted ranges)	6 (9%)	$7,997.23
Approach #2: current income (detailed)	6 (9%)	$7,997.23
Approach #3: permanent income (MCA)	0 (%)	$0.00
Approach #4: national mean income	0 (%)	$0.00
Approach #5: self-reported income loss	11 (17%)	$14,661.58
Approach #6: coping strategies	24 (36%)	$31,988.90

Catastrophic threshold for Approaches #1-#5: 20%
All costs in 2015 USD

Figure 8-1 Prevalence of catastrophic cost, by income estimation approach and threshold value



Of all patients interviewed, only one was in receipt of a disability grant related to their HIV/TB status. If all those undertaking coping strategies were assumed to encounter catastrophic costs, the cost of providing disability grants to those people would be $31,988. In contrast, if the national average income is used to estimate income, zero participants would be found to encounter catastrophic costs and there would be zero cost to providing disability grants.

4. DISCUSSION

This paper illustrates the uncertainty around measuring income accurately when estimating disease-specific catastrophic costs. The gold standard for estimating permanent income is through a consumption expenditure questionnaire. In this setting, as in many real-world situations, it was not possible to conduct such a questionnaire due to time limitations and the lack of a validated short-form questionnaire. In the absence of such a gold standard, we illustrate the implications of alternative approaches. The four income measurement methods we employed gave substantially different estimates of the frequency of catastrophic costs with vastly different policy implications; different approaches in estimating income amongst the same population resulted in estimates varying from 0 to 36% of respondents encountering catastrophic costs.

It is clear from our results that all potential alternatives presented are problematic in some way. Self-reported current income, as estimated through approaches #1 and #2, is a poor proxy for permanent income. In addition, these data were the most difficult to collect amongst the five approaches. We lost 33 participants from our analysis due to missing data for one or both self-reported income estimation approaches. We lost a disproportionate number of participants who were unemployed and who adopted certain coping strategies, including selling assets and taking loans to meet the costs of TB, potentially biasing our results to reduce the estimated prevalence of catastrophic costs. This loss of data is not unusual for this kind of survey. The practical difficulties of collecting reliable income data are widely acknowledged (Deaton and Zaidi, 2002; Filmer and Pritchett, 2001), and it is often particularly difficult for participants to estimate income outside the purview of the survey respondent, which is critical for estimation of household income. It is crucial when estimating catastrophic costs to ensure that the analysis is not biased against capturing those who encounter serious difficulty in meeting the costs of illness.

Income quintiles were estimable using the MCA approach (approach #3) for all 99 participants; however, there are several potential limitations with this approach as

illustrated in this paper. Our sample had relatively high levels of durable asset ownership, placing many participants in the upper two quintiles and resulting in only two households being defined as below the poverty line using approach #3. This indicates that approach #3 may have substantially overestimated household socioeconomic position, as consistent evidence indicates that both TB and HIV are most prevalent among lower income quintiles (Lonnroth et al., 2009; Steinert et al., 2017; Wabiri and Taffa, 2013). This approach also assumes that expenditure patterns of TB-affected households are similar to the national average, which is unlikely to be the case. Although theoretically promising, we must therefore draw the conclusion that asset indices are likely a poor proxy for consumption expenditure in the South African setting. This is consistent with indications that asset indices are poor proxies for consumption expenditure across a range of settings (Howe et al., 2009). Asset indices also may not be the best option available to researchers - asset questionnaires can be very lengthy in themselves, and mapping to a national dataset is not always possible. Researchers looking to use asset mapping to proxy permanent income should first check whether there is a national dataset that can be mapped to assets in a facility survey and whether there is a high correlation with permanent income in their setting. Increasing the number and range of indicators may help to improve agreement.

As expected, the use of a mean national income in the denominator (approach #4) was highly problematic. The approach likely substantially overestimated household socioeconomic position and provided no real sense of the relative impact of TB costs across socioeconomic quintiles. This approach does not achieve the aim of the indicator of 'catastrophic costs due to TB' and adds no value to a blunt estimate of total costs due to TB.

Given the limitations of methods to estimate catastrophe quantitatively in absence of consumption expenditure, we also explored the use of alternative measures such as adoption of coping behaviours (approach #6) as an indicator of catastrophic costs. Unlike some quantitative measures explored, this information was easily collected for all households. Coping strategies may be a good indication of long-term financial hardship in the context of health-related costs. Health shocks are often costlier than other types of shocks, and households are often less able to recover following a health shock as compared with agricultural, natural, or legal shocks (Dhanaraj, 2016; Heltberg and Lund, 2009). This is especially the case when illness is repeated, or in the case of chronic illness, such as HIV and TB (Gertler and Gruber, 2002; Kenjiro, 2005; Wagstaff and Lindelow, 2014). Our data indicates that several households reduced food consumption to meet health-related costs,

which can lead to under-nourishment, increase susceptibility to infectious disease, reduce quality of life, and damage long-term productivity. Many households also took loans at high interest, potentially leading to unmanageable debt. Most of these participants were not classified as encountering catastrophic cost using approaches #1-#5, despite the potential long-term effects of these coping strategies.

However, as noted by Collins et al., many households living near the poverty line frequently take loans and sell assets in their day-to-day management of resources (Collins et al., 2009). The high frequency of coping strategies employed by all households in the sample could reflect households using all the resources available to them in a dynamic process of managing assets to raise funds to pay for illness-related expenses, rather than an act of desperation. Indeed, the greatest long-term difficulty might be encountered by those households which do not have assets to sell, are not creditworthy or otherwise unable to take out loans, or cannot further reduce food intake. Further research linking use of coping strategies to long-term economic outcomes within households would help to better identify the potential usefulness of this metric.

This study was designed to illustrate and explore the challenges around measuring income at the facility level and has some clear limitations. Our sample size was small and was further limited by missing income data which led us to drop 33 participants from the analysis. While these limitations do not impact the validity of our observations about missing data and internal comparisons, results should not be taken as evidence surrounding catastrophic costs for people with TB/HIV in South Africa or any conclusions on the TB Fast Track trial. We did not include direct costs of childcare in our questionnaire, potentially underestimating direct costs. We used the average household size by municipality to estimate income per person, thereby introducing some uncertainty into our estimates. We did not collect information on which assets were sold, and therefore are unclear how asset sales may have impacted household placement in the asset index. We also were not able to compare against a gold standard of household income measurement such as a household consumption survey, and thus have no way to test the degree to which bias may have affected our findings. However, this paper highlights the extent of uncertainty around these measures and the need for greater clarity on the most appropriate measure of household resources for estimating catastrophic costs.

We did not explore here the approach of using consumption-based measures for patients attending health facilities, yet these may also be considered. Short-form consumption

questionnaires have been successfully used in surveys in the past (Wagstaff and Lindelow, 2014), although short-form questionnaires have not yet been validated for many settings. Further development and validation of short-form consumption questionnaires would greatly improve ability to measure permanent income in a facility-based setting. There should also be further investigation into whether short-form consumption questionnaires are needed at all, or whether a full consumption module might be preferable given the potentially high expected value of information associated with these surveys. In a recent implementation of the Living Standards Measurement Survey, the full consumption module took an average of only 25 minutes (Browning et al., 2014); it may therefore be feasible to implement full consumption modules in facility-based surveys if other questions can be reduced.

There is growing concern to provide social protection to those facing catastrophic costs due to TB (Boccia et al., 2011; Siroka et al., 2016). Improved social protection could help to mitigate long-term costs through improved TB and other health outcomes, reduced periods of time off work, and increased productivity. As demonstrated in this paper, the additional costs faced by countries which will be liable for social protection for those facing catastrophic costs are potentially substantial. In the absence of a gold standard to identify those needing social protection, the substantial uncertainty identified in this paper opens the possibility of gaming, or choosing a particular method for measuring income to minimize the frequency of catastrophic costs, for example to appeal to funders or to minimize the cost of social protection. It is also possible that some countries will be unfairly judged as performing worse than others when the estimation method is simply different.

Using existing data, this paper shows the potential implications of different measures of household resources in the denominator of the catastrophic cost equation. Further concerted research is needed to come to an acceptable recommendation for measurement of TB-specific catastrophic costs, and in the meanwhile countries and economic evaluators should use a range of approaches. New guidelines developed by the Global Health Cost Consortium (GHCC) highlight the importance of stating potential sources of bias clearly in cost estimates for health interventions (Vassall et al., 2017) for use in economic evaluation and more generally. We suggest that methods for estimating income, and potential sources of bias arising from these methods are clearly explained and discussed to facilitate interpretation. Our findings confirm the recommendation by the WHO Task Force to use multiple methods for income estimation, and stress that different approaches should not be used as substitutes for one another until these measures can be directly compared

against consumption modules. Further research is needed to evaluate the benefits and drawbacks of these different approaches, and to empirically validate rapid estimation methods which can be used in a facility setting.

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CHAPTER 9. ESTIMATING CATASTROPHIC TB-RELATED COSTS IN THE CONTEXT OF ECONOMIC EVALUATION IN SOUTH AFRICA

PREAMBLE FOR RESEARCH PAPER #4

Chapters 5-7 evaluated the reasons behind the substantial inconsistency in methods currently in use to estimate patient costs for TB, and discussed the potential impact of this inconsistency on study results. Chapter 8 evaluated the impact of methodological inconsistency on the estimation of household income, making estimates of the prevalence of catastrophic costs from different studies potentially incomparable.

WHO-TB have taken action to reduce this variability by developing standardized methods to estimate catastrophic costs as part of their End TB Strategy, using nationally-representative cross-sectional surveys. However, these surveys require ample resources and time to complete. In many settings, data on patient costs have been collected as part of trials or other smaller-scale projects. These data could provide a useful resource for countries looking for decision-making support without the substantial investment of implementing a national survey, however methods for using these data are not verified.

In Research Paper #4, we attempt to identify whether it is possible to overcome the substantial methodological differences discussed in previous chapters and use existing data from small-scale studies to come to a country-level estimate of the prevalence of catastrophic cost. We conduct a pooled analysis of existing primary studies estimating patient costs for TB in South Africa. We obtained three datasets from authors working in South Africa and pooled the data into one combined dataset. We used two approaches to estimate the national prevalence of catastrophic costs associated with TB using the pooled dataset: a regression analysis with multiple imputation, and a meta-analysis linked to a decision model. We encountered uncertainty in our estimates of both the numerator (costs) and the denominator (income) of the catastrophic costs equation, but found that conducting an individual-level analysis does not necessarily improve uncertainty in national estimates.

I designed the analytical framework, designed and conducted the analysis, and wrote the first and consecutive drafts of the paper. NC and DM collected the original data used in this pooled analysis. MS and GBG conducted the original systematic review of papers with patient cost estimates for GHCC. AV, GBG and MS provided input on analysis methods. All co-authors

contributed comments and edited the paper. We are also grateful to the following people who declined authorship: Nicola Foster (collected original data for the XTEND project), Carol Levin and Lorna Guinness (provided feedback on the draft paper), Carlos Jesus Pineda Antunez (developed a Stata program to facilitate data pooling, and advised on the analysis).

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Student ID Number	238062	**Title**	Ms.
First Name(s)	Sedona		
Surname/Family Name	Sweeney		
Thesis Title	Improving the estimation of patient costs for TB		
Primary Supervisor	Anna Vassall		

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

SECTION B – Paper already published

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Where is the work intended to be published?	Value in Health
Please list the paper's authors in the intended authorship order:	Sedona Sweeney, Anna Vassall, Mariana Siapka, Natsayi Chimbindi, Don Mudzengi, Gabriela B Gomez
Stage of publication	**Not yet 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)	SS designed the analytical framework, designed and conducted the analysis, and wrote the first and consecutive drafts of the paper. NC and DM collected the original data used in this pooled analysis. MS and GBG conducted the original systematic review of papers with patient cost estimates for GHCC. AV, GBG and MS provided input on analysis methods. All co-authors contributed comments and edited the paper. We are also grateful to the following people who declined authorship: Nicola Foster (collected original data for the XTEND project), Carol Levin and Lorna Guinness (provided feedback on the draft paper), Carlos Jesus Pineda Antunez (developed a Stata program to facilitate data pooling and advised on the analysis).

SECTION E

Student Signature	[redacted]
Date	13 February, 2019

Supervisor Signature	[redacted]
Date	13 February, 2019

ESTIMATING CATASTROPHIC TB-RELATED COSTS IN SOUTH AFRICA

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INTRODUCTION

Despite recent improvements in biomedical interventions for prevention and cure of TB, progress towards elimination of TB remains slow. TB remains a leading cause of death worldwide, with 9.6 million people falling ill and 1.5 million people dying from TB in 2014 alone [1]. South Africa has one of the world's highest incidence rates for TB, with an estimated incidence of 450,000 people in 2014. Often those who are most affected by TB are the most vulnerable in society, and households affected by TB can face substantial cost associated with the disease. A recent systematic review found that across countries globally, costs associated with TB represented an average of 58% of household income (range 5%-306%) [7].

In recognition of the potentially devastating impact of the costs of illness on households, the World Health Organization (WHO) has highlighted reduction of catastrophic costs due to TB as one of three priority targets for 2020 [1]. This is in line with, but distinct from, efforts to reduce catastrophic total health expenditures and improve access to Universal Health Care. The TB-specific measure includes direct non-medical and indirect costs in addition to the direct out of pocket costs captured in the measurement of catastrophic total health expenditures. From 2020, countries will be required to report on the number of patients encountering catastrophic total costs due to TB, and this will be one of three key metrics for monitoring country progress.

The Global TB Program at the World Health Organization has developed guidelines for nationally representative cross-sectional surveys to estimate catastrophic costs as part of their End TB Strategy [11]. However, these surveys require ample resources and time to complete, and will not be feasible for all 130 member states to carry out routinely. This leaves many countries searching for another source of these estimates.

The existing evidence on catastrophic costs due to TB in South Africa is minimal but highlights a significant burden. Evaluating a cohort of patients from a single study,

Mudzengi et al. [8] found that 31-46% of TB-only and 50-68% of TB/HIV patients encounter catastrophic cost depending on the threshold used. Verguet et al. [9] used modelled incidence and mortality for tuberculosis and patient-incurred cost estimates from one study, predicting that 16,848-24,278 households encounter catastrophic costs over 20 years in a scenario where current standard of care continues, equivalent to 16-25% of those with TB [10]. Although there are several other studies reporting costs, and several suggesting that costs are likely to be catastrophic, no other studies report the prevalence of catastrophic cost.

In many settings, data on patient costs have been collected as part of trials or other smaller-scale projects. This existing data could provide a useful resource for countries looking for decision-making support, in the absence of a national survey. As discussed in Chapter 4 of this thesis, there are several potential methods to combine information from existing studies, including a meta-analysis of summary data, and pooled analysis of primary data. There are a number of potential benefits associated with pooling primary data from multiple studies. It can increase the sample size and therefore improve statistical power [12], and improve the cultural and economic diversity of patient populations reflected in the data [13], which may increase the validity of extrapolations to different contexts. Increased diversity of patient populations in the dataset can help to reflect the full spectrum of economic backgrounds and responses to health shocks. However, it is often difficult to obtain access to primary data, and the pooling process can be arduous.

Following a request from the Global TB Program at the World Health Organization to investigate the potential of using existing data to estimate national prevalence of catastrophic costs, the aim of this analysis is to investigate approaches to parameterize a cohort model of TB cases in South Africa, to estimate the national prevalence of catastrophic costs due to TB in South Africa. We use two approaches to parameterize a model with existing data from three facility-based studies: a meta-analysis using summary data, and a regression analysis of pooled primary data.

METHODS

Model description

We created a nationally representative individual-level cohort model of TB disease which simulated progression through the course of illness in order to estimate both direct and indirect 'patient-incurred' costs and catastrophic costs for the entire treatment period, for

a representative population of South Africans with TB. The model contained a hypothetical cohort of 10,000 South Africans with drug-susceptible (DS) TB. HIV prevalence was modelled for each TB case based on the relative national prevalence of HIV-positive vs HIV-negative drug-susceptible TB [14]. Drug-resistant TB (MDR-TB) was not considered in this model due to a lack of data; this is discussed further below.

Each individual in the model was assigned into a household income quintile using data from Ataguba et al. on the distribution of TB cases across quintiles [15], and assigned a corresponding household income following the national income distribution, using the approach described by Harttgen and Vollmer [16], and income quintile cut-offs from Statistics South Africa [17]. We then used mean and standard deviation values from the most recent (2015) round of the South African National Income Dynamics Survey (NIDS) to assign each individual an employment status (differentially by income quintile) and household size (no significant difference between income quintiles) [18]. Individuals were then assigned an individual income corresponding to their household income, employment status, and household size; individual income took a value of zero if unemployed.

The TB care cascade was defined as containing four distinct periods: 1) from symptom onset until a diagnosis is received, 2) from the time diagnosis is received until treatment is started, 3) the intensive phase of treatment, and 4) the continuation phase of treatment. The likelihood of seeking care in each of the four periods for each TB case was then determined using data from a national study of the TB care cascade in South Africa [14]; applied to HIV and non-HIV subgroups. Costs were assigned to each period. Cost categories we specified as: direct medical costs (including out of pocket payments for consultation fees, medicines, diagnostics, etc.); direct non-medical costs (including costs for transportation and accommodation); costs of food supplements and special foods; and indirect costs (the value of time spent travelling to health facilities and in consultation with health providers). Direct costs per episode for those seeking care were estimated as the sum of direct medical, direct non-medical, and food costs in each of the four periods. For individuals not seeking care or lost-to-follow-up, it was assumed that only the costs of food supplements and special foods were encountered.

Total indirect costs were estimated as the sum of total hours spent travelling to health facilities and in consultation, multiplied by the hourly income of the individual (estimated assuming 20 working days per month and an 8-hour working day). Productivity loss due to illness was not included in the estimate of indirect costs due to a lack of data. Indirect costs

were assumed to be zero for those who were unemployed; this was tested in a sensitivity analysis. Total costs were defined as the sum of total direct and indirect costs per episode. Following the WHO handbook on estimating catastrophic cost [11], catastrophic cost was identified where the total cost of the TB episode (including direct and indirect costs) was greater than 20% of annual household income.

The cohort model was simulated 500 times, to give 500 unique estimates of the national prevalence of catastrophic costs. Estimates from the 500 model runs are summarized using the median value, as well as the 5^{th} and 95^{th} percentiles.

Model parameterization

The process of building a model involves characterisation of parameter uncertainty around costs, events and population characteristics, and choice of methods to address this. Two approaches are commonly used in evidence synthesis in order to produce summary estimates from existing data for input into a model: meta-analysis and regression analysis. A meta-analysis requires only summary statistics from pre-existing datasets, whilst a regression analysis requires the researcher to obtain the full dataset. We used both approaches in order to understand their limitations and to evaluate whether either is sufficient to predict the national prevalence of catastrophic cost given existing data.

Searches and data pooling

A list of all research articles presenting estimates of patient costs due to TB in South Africa was collated using a database constructed by the Global Health Cost Consortium. This database was constructed following a systematic search of scientific databases and grey literature of TB costs worldwide; full methods for construction of the GHCC database are described by Alexander et al. [14].

Twelve papers were identified as presenting patient costs for TB in South Africa. Of these, four were excluded because they presented costs for outdated models of care, and one was excluded because no original cost data was presented. Corresponding authors of the seven eligible studies were invited to participate in the analysis, and access to a predefined set of variables was requested. Four datasets were obtained and pooled [8,9,21]; the total sample size per study is listed in Table 9-1.

A data coding protocol, identifying variable names and formats to be included in the pooled dataset, was provided and discussed in depth with all authors who agreed to share data. Costs were distinguished by the type of healthcare provider, including: public facility (the

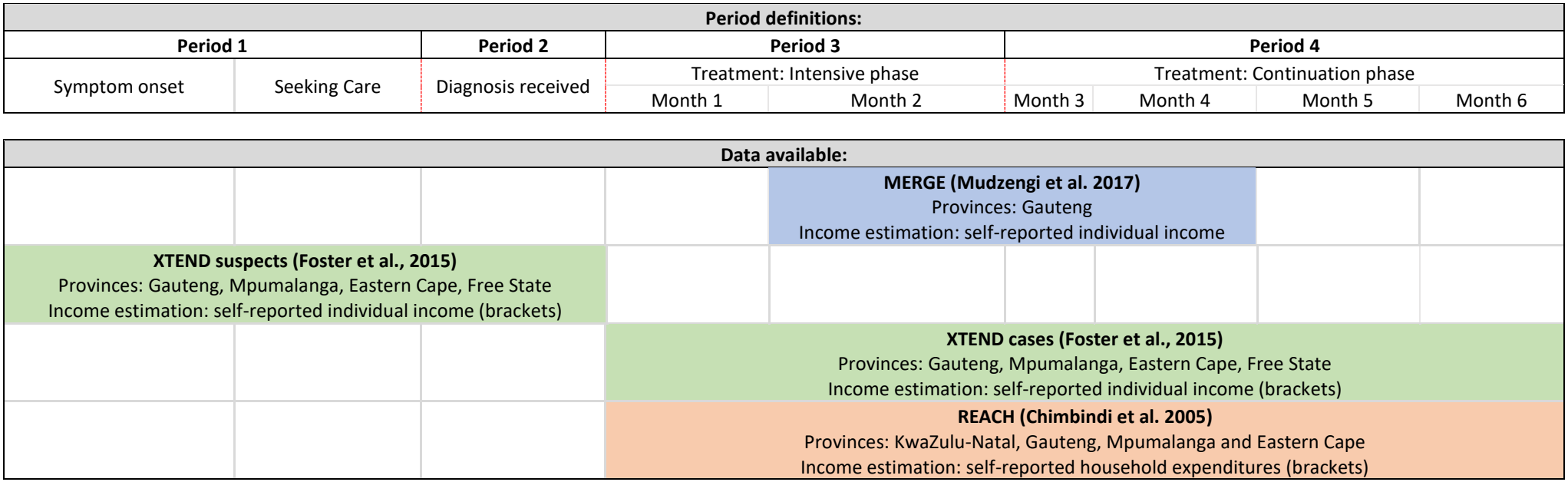
study site), another public facility, general practitioner, pharmacy, inpatient hospital, outpatient hospital, and traditional healer. Care was also taken to ensure that all studies defined relevant periods consistently (distinguishing particularly pre- and post-diagnosis). Data were collected for different periods during the TB episode for different studies, as illustrated in Figure 9-1.

Given the data available, the scope of the analysis was restricted somewhat. First, as there were only 35 observations for the pre-treatment periods, we were only able to estimate total costs for periods 3 and 4 of treatment, rather than the whole illness episode from symptom onset. As discussed above, we were unable to include DR-TB due to unavailability of data. As all studies were conducted within the health facility, we were not able to capture costs of those not attending a health facility. Finally, none of the studies collected data on lost productivity due to illness; this was also therefore not included in the analysis. These restrictions on the analysis are likely to result in an under-estimation of true catastrophic costs.

We conducted a descriptive analysis of sample characteristics and summary cost variables for each dataset and tested any between-study variance in the parameters of interest within the pooled dataset. Variables were summarized using the mean and standard deviation to reflect central tendency and dispersion of variables for each individual dataset and across the pooled dataset. We tested for significant differences in categorical variables (such as sex, level of education, and income quintile) using a chi-squared test, and tested for significant differences in continuous variables (such as visits to health providers, time, and cost) using a one-way analysis of variance (ANOVA).

All cost and income data were reported in USD. Because some primary data was provided in USD with no original exchange rate from South African Rand (ZAR) provided, data was inflated to November 2017 using the US consumer price index [22]. All datasets had obtained ethical approval for the original study. Ethical approval for the pooled analysis was granted by the London School of Hygiene and Tropical Medicine (reference 14486). All data was anonymized before transferring. All data was transferred using encrypted files and kept in a secure file.

Figure 9-1 Data availability



Identifying income quintiles

An advantage in pooling these datasets was that all datasets were collected using adaptations of the Tool to Estimate Patient Costs [23], and thus defined costs mostly in the same way, reflecting the definitions detailed above. However, methods for collecting data on income varied widely across datasets and were not reconcilable. As a first step in the analysis, it was necessary to assign households into income quintiles using a consistent estimation approach. We, therefore, dropped all collected income data and took a statistical approach to predict income for households in the dataset, using information that was consistent throughout the datasets including asset holdings, housing quality indicators, and basic demographics.

We conducted a regression analysis using data from the most recent NIDS round to obtain coefficients representing the relationship of household income to covariates: urbanicity (1 = rural), gender (1 = female), education level (1 = educated to grade 8 and above), marital status (1 = married or cohabitating), TB status (1 = current TB), employment status (1 = employed), asset quintile (quintiles 1-5), age group (1 = age 15-29; 2 = age 30-45; 3 = age > 45) and province. Two model structures were explored, including a generalized linear model (GLM) with a gamma distribution and a log link, and a quantile regression approach which allows regression on a specified quantile of the data (e.g. 25^{th} quantile, median, or 75^{th} quantile) (Supplementary Table 9-5). The quantile regression model was determined to be the more efficient of the two, and there was strong evidence that coefficients varied across income quintiles (Supplementary Figure 9-7). We, therefore, proceeded with coefficients from the quantile regression fit on the log of annual household income at the 25^{th} quantile, following evidence that the burden of TB falls overwhelmingly on those with lower socioeconomic status [15,24]. The regression model incorporated survey weights calibrated to the corresponding population totals as given in the mid-year population estimates released in 2015 [25].

Regression coefficients were then applied to observations on the same covariates in the pooled dataset to create a predicted household income for each individual. Methods for income prediction are further described in Appendix 2.

Identifying direct costs and time

In order to parameterize the model with cost data, a second step was to identify a mean and standard error value for direct medical costs, direct non-medical costs, food costs, and total hours by SES quintile and HIV status per period. This predicted household income was

used to partition observations from the pooled dataset into socio-economic quintiles [19,26], using income cut-offs defined by Statistics South Africa [17]. We tested two different approaches for this: a meta-analysis using summary statistics from each included study, and a regression approach using pooled individual data from all studies. Using the mean and standard error values obtained through each method, we then randomly drew cost estimates for each individual following a gamma distribution.

Meta-analysis

A meta-analysis was conducted on summary statistics from each study to obtain adjusted mean values for the above-described cost categories for each treatment period: direct medical costs, direct non-medical costs, food costs, and time spent travelling to health facilities and in consultation. Adjusted mean values were estimated by HIV status and SES quintile.

As depicted in Table 9-3, some studies did not collect cost data for certain provider types or periods. This data was not imputed for the meta-analysis. Data were log-transformed for the meta-analysis as they were highly skewed, and results were exponentiated following meta-analysis. Given that patient demographics varied significantly across datasets and assuming that patient costs vary according to demographics, we used a random effects meta-analysis approach, which does not assume that all studies investigate the same population [27]. Results from the meta-analysis are presented in Supplementary Figures 9-1 through 9-5.

Regression analysis

We then conducted a regression analysis on the patient-level data to obtain better-parameterized estimates to populate the model. The first step in the regression analysis was to address the missing values by using a multiple imputation of costs. As the datasets each studied a different period during the TB episode, there were no observations containing data on the total cost of the TB episode. These missing data could be a result of study design rather than the costs encountered, implying that data is missing completely at random (MCAR) and can be filled with mean imputation. However, there were significant differences in demographic characteristics across different datasets, including urbanicity, age, education, and SES quintile (Table 9-1). It is, therefore, more likely that data were missing at random (MAR) dependent on these observed factors. Some datasets had partial observations, where the number of visits to each provider type was observed, but costs for those visits were unobserved. In addition, the number of visits per month in both the

intensive and continuation phases varied as practice in the implementation of directly observed therapy (DOTS) varied substantially across facilities. In order to limit the uncertainty introduced by this variation, we used multivariate imputation with chained equations (MICE) as described in Chapter 4, using predictive mean matching (PMM) to fill unobserved data points for total visits, total direct costs and total hours spent seeking care by period and provider type, generating 20 imputations [28]. As discussed in Chapter 4, the non-parametric technique PMM is preferable to simple linear regression for cost data as it allows for skewness in the data [29,30]. Observed demographic variables including urbanicity, education level, HIV status, employment status, and income quintile, were used in the imputation; these variables were selected to maintain consistent specification for the imputation model and the final regression analysis. The total number of imputations for each data point is listed in Supplementary Table 9-2. As there were only two observations for the travel time associated with accessing a traditional healer, this data point was not imputed and travel time for traditional healers was assumed to be the same as travel time for the study clinic.

Following imputation, we conducted a series of regression analyses, using the following variables as dependent variables: direct medical costs, direct non-medical costs, food costs, and total time spent travelling to health facilities and in consultation. Regression analyses used a Generalized Linear Model (GLM) approach, assuming a gamma distribution and a log link to accommodate skewed data [31]. For each regression analysis, independent variables were defined as: urbanicity (1 = rural), education level (1 = educated to grade 8 and above), employment status (1 = employed), HIV status (1 = HIV positive), SES quintile (quintiles 1-5). These independent variables were identified following theory, as well as previous evidence that these factors are significant determinants of catastrophic cost [4,5,27–30].

Following the regression analysis, marginal estimates for each of the above-described cost variables were obtained by HIV status, income quintile, and employment status - with urbanicity and education values held constant at the mean observed among people with TB in the NIDS dataset (urbanicity = 0.327, education above grade 8 = 0.683). For input into the model, direct medical costs, direct non-medical costs, food costs, and total hours by SES quintile and HIV status per period were randomly drawn using a gamma distribution using the adjusted mean and standard errors from the marginal estimates.

To help us interpret the results of the pooled regression, we also tested the extent to which cost drivers varied across datasets by conducting a regression on the raw unimputed data

for each dataset separately. As there were insufficient observations to do this for Period 3, we conducted this test only on observations in Period 4.

RESULTS

Data and Demographics

The pooled dataset contained a total of 1,573 observations; this was made up of 1,219 from the REACH study [21], 148 from the MERGE trial [8], 171 TB cases from the XTEND trial [9]. Data for 35 TB suspects from the XTEND trial [9] was not included as the small sample size limited analysis capability for the pre-treatment periods. Table 9-1 shows the demographic data for each dataset, as well as the pooled dataset. Overall, 82 participants (51%) were female, and 908 (52%) were from an urban setting. Participants were well educated on average; 1,025 (65%) completed grade 8 or above. Just over one-quarter of participants overall (430; 27%) were married or cohabitating; the remainder were single, divorced, or widowed. Many households undertook coping strategies to meet the costs of illness. Overall, 266 participants (17%) took loans and 38 participants (2%) sold assets to meet the costs of their TB.

Several demographic variables, including urbanicity, age, education, and employment status, were significantly different across datasets. Although each dataset was randomly selected and should, therefore, be a representative sample of each respective study population, the datasets were not representative of the population of South Africa as a whole. For example, the MERGE trial only interviewed participants attending health facilities in urban areas. Some observations were also likely driven by the fact that TB affects certain populations more often than others; for example, the majority of observations in all datasets (1,058; 96% overall) were of black/African ethnicity, and only 351 (22%) participants were employed at the time of interview.

Table 9-1 Demographics

	REACH n = 1219	MERGE n = 148	XTEND n = 171	Pooled Dataset n = 1573	Difference between datasets Chi-Squared	NIDS Dataset people with current TB (n = 244)[a]	Difference between pooled dataset and NIDS dataset Chi-Squared
Total observations							
Period 1	0	0	0	0			
Period 2	0	0	0	0			
Period 3	103	1	169	273			
Period 4	1049	146	170	1365			
Female n (%)	638 (52%)	76 (51%)	77 (45%)	791 (51%)	8.92*	119 (39%)	0.40
Urban n (%)	628 (52%)	148 (100%)	109 (63%)	885 (58%)	130.77***	123 (35%)	4.56*
Mean age (Std Dev)	37 (12)	35 (10)	40 (13)	37 (12)		41.1 (13.0)	
Black/African n (%)	1162 (95%)	145 (98%)	168 (98%)	1475 (96%)	4.13	212 (92%)	33.77***
Grade 8 and above n (%)	756 (62%)	125 (84%)	124 (72%)	1005 (65%)	34.20***	138 (61%)	6.72*
Married / Cohabitating n (%)	315 (26%)	48 (32%)	56 (33%)	419 (27%)	6.51	64 (23%)	0.14
Employed at interview n (%)	195 (16%)	75 (51%)	64 (37%)	334 (22%)	132.73***	82 (39%)	14.88***
Predicted SES quintile distribution[b] n (%)	Quintile 1: 33 (3%)	Quintile 1: 0 (0%)	Quintile 1: 3 (2%)	Quintile 1: 36 (2%)	123.58***	14 (6%)	4.57
	Quintile 2: 618 (51%)	Quintile 2: 23 (16%)	Quintile 2: 65 (38%)	Quintile 2: 706 (46%)		126 (46%)	
	Quintile 3: 440 (36%)	Quintile 3: 76 (51%)	Quintile 3: 68 (40%)	Quintile 3: 584 (38%)		83 (37%)	
	Quintile 4: 120 (10%)	Quintile 4: 49 (33%)	Quintile 4: 34 (20%)	Quintile 4: 203 (13%)		21 (11%)	
	Quintile 5: 8 (1%)	Quintile 5: 0 (0%)	Quintile 5: 2 (1%)	Quintile 5: 10 (%)		(0%)	
Coping strategies n (%)	Coping: 223 (18%)	Coping: 35 (24%)	Coping: 21 (12%)	Coping: 279 (18%)	9.31*		
	Took loans: 212 (17%)	Took loans: 32 (22%)	Took loans: 19 (11%)	Took loans: 263 (17%)	8.48*		
	Sold assets: 26 (2%)	Sold assets: 7 (5%)	Sold assets: 5 (3%)	Sold assets: 38 (2%)	4.82		

n number of observations; Std Dev Standard Deviation; SES socioeconomic [a] proportions weighted using survey weights to reflect the national average [b] Quintile based on predicted monthly household income from quantile regression: Quintile 1 < $135.60; Quintile 2 ≤ $288.93; Quintile 3 ≤ $587.38; Quintile 4 ≤ $1494.60; Quintile 5 > $1494.60 [17] *** p < 0.001; ** p < 0.01; * p < 0.05

Predicted Household Income Quintiles

Coefficients for the regression to estimate household income are listed in Supplementary Table 9-5. Coefficients for most covariates were significant, and tests after the quantile regression indicate that coefficients varied significantly across quantiles. However, the predictive power for the quantile regression approach as indicated by the Pseudo R2 was relatively low (0.18), and the Shapiro-Wilk test indicates that residuals for the regression deviate significantly from a normal distribution.

Predicted income values were adjusted using a Duan smear factor [36], and households assigned to SES quintiles based on the adjusted predicted income using upper-income thresholds from Statistics South Africa. Only two per cent of observations from the pooled dataset fell into the first quintile, while most predictions fell into the second and third income quintile (46% and 38% respectively). In comparison, it has been estimated nationally that 37% of those with TB fall into the first quintile [10].

Direct Costs and Time

Table 9-2 lists the total visits per month, costs per visit, and time spent per visit by provider type and time period for each of the datasets. Availability of data varied by dataset and period. Data on direct non-medical costs and time spent per visit were unavailable for providers other than the study clinic in the REACH dataset. Costs and time for the intensive phase of treatment (Period 3) were only available for one participant in the MERGE dataset; participants were interviewed using a 1-month recall period, and most were interviewed more than one month after the start of the continuation phase of treatment.

The majority of participants across all datasets accessed care primarily at the study clinic. However, the number of visits per month to the study clinic for the continuation phase of treatment varied significantly between datasets. Participants in the REACH study visited the study clinic an average of 8.3 times per month in the intensive phase of treatment and 8.9 times per month in the continuation phase of treatment; in comparison, participants in the MERGE trial attended the study clinic only 4.3 times per month and participants in the XTEND trial attended the study clinic less than once per month in the continuation phase of treatment. Participants in the REACH study also used other providers such as pharmacies and GPs significantly more than participants in the MERGE and XTEND trials. There was also wide variation in the direct costs encountered for other providers; the direct cost per visit for GPs and traditional healers were particularly high in the MERGE and XTEND datasets.

Table 9-2 Mean visits, costs, and time by dataset and period from the pooled primary data

	Period 3				Period 4			
	MERGE n = 1	REACH n = 102	XTEND n = 172	One-way ANOVA (F statistic)	MERGE n = 146	REACH n = 1021	XTEND n = 172	One-way ANOVA (F statistic)
Mean visits per month								
This clinic	2.0	8.3	6.3	1.99	4.3	8.9	0.8	74.39***
Pharmacy	0.0	0.2	0.0	4.03*	0.0	0.4	0.0	9.11***
General Practitioner	0.0	0.1	0.1	0.04	0.0	0.1	0.0	4.36*
Outpatient Hospital	0.0	0.0	0.1	0.60	0.0	0.0	0.0	0.48
Inpatient Hospital	0.0	0.1	0.1	0.01	0.0	0.1	0.0	1.52
Traditional Healer	0.0	0.0	0.0	1.17	0.0	0.1	0.0	2.92
Mean direct medical cost per visit								
This clinic	$0.00	$0.00	$0.00		$0.00	$0.00	$0.00	
Pharmacy		$2.42	$54.13	2.50	$0.22	$1.84	$7.13	5.02**
General Practitioner		$23.23	$110.46	0.62	$23.78	$17.38	$55.18	27.58***
Outpatient Hospital		$7.28	$40.05	0.11	$4.12	$2.87	$4.63	0.45
Inpatient Hospital		$0.00	$104.72	0.15	$18.69	$1.14	$13.46	4.00*
Traditional Healer			$90.37		$439.05	$20.58	$109.76	139.02***
Mean direct non-medical cost per visit								
This clinic	$0.00	$1.65	$0.66	8.27***	$1.00	$2.06	$1.14	1.39
Pharmacy			$3.42		$0.00		$3.29	
General Practitioner			$6.88		$26.56		$4.28	1.91
Outpatient Hospital			$12.66		$9.88		$5.39	0.76
Inpatient Hospital			$24.39		$17.57		$5.43	0.60
Traditional Healer			$14.63		$21.95		$0.00	0.06
Mean travel hours per visit								
This clinic	1.0	0.7	0.6	0.06	1.2	0.6	0.9	55.95***
Pharmacy			0.5		1.9		0.2	3.33
General Practitioner			0.9		1.7		1.1	0.40
Outpatient Hospital			0.2		2.0		1.5	0.30
Inpatient Hospital			1.0		2.7		0.6	5.46*
Traditional Healer			1.0		3.0		0.2	
Mean consult hours per visit								
This clinic	1.0	1.4	1.1	0.15	1.8	0.9	0.4	24.70***
Pharmacy			0.5		1.2		0.3	2.36
General Practitioner			1.1		1.5		0.9	1.97
Outpatient Hospital			2.7		5.3		2.6	7.85*
Inpatient Hospital			126.3		104.0		26.4	3.80
Traditional Healer			0.6		9.0		13.2	
Mean cost of 'special foods' or supplements								
Cost per period	27.44	4.21	15.60	7.80***	50.83	4.21	15.60	185.70***
Cost per month	2.0	8.3	6.3	1.99	4.3	8.9	0.8	74.39***

* p<0.05, ** p<0.01, *** p<0.001

Table 9-3 Mean costs and time by period; from study summary statistics

	MERGE			REACH			XTEND			One-way ANOVA
	n	Mean	Std Dev	n	Mean	Std Dev	n	Mean	Std Dev	(F statistic)
Period 3										
Direct medical costs										
Study clinic	1	0.00	0.00	102	0.00	0.00	172	0.00	0.00	
Other providers	1	0.00	0.00	104	4.01	16.94	165	30.24	191.11	0.98
Direct non-medical costs										
Study clinic	1	0.00	0.00	102	12.44	38.13	159	2.94	7.43	4.70**
Other providers	1	0.00	0.00	90	0.00	0.00	149	3.96	17.63	2.28
Total travel and consult time										
Study clinic	1	8.00	0.00	89	13.12	12.21	17	4.54	9.96	3.76*
Other providers	1	0.00	0.00	90	0.00	0.00	147	13.92	65.46	2.05
Cost of 'special foods' or supplements										
Cost per period	1	54.88	0.00	104	8.41	21.70	162	31.19	57.14	7.80***
Period 4										
Direct medical costs										
Study clinic	146	0.00	0.00	1021	0.00	0.00	172	0.00	0.00	
Other providers	143	5.35	38.94	1050	12.71	50.4	167	5.42	19.40	2.96
Direct non-medical costs										
Study clinic	146	14.49	33.52	1020	23.51	74.02	142	3.06	10.44	6.53**
Other providers	145	4.07	22.60	854	0.00	0.00	152	0.54	2.24	15.91***
Total travel and consult time										
Study clinic	145	42.88	33.53	898	25.97	29.23	29	1.16	2.55	32.55***
Other providers	144	7.79	34.70	854	0.00	0.00	153	0.67	3.35	24.79***
Cost of 'special foods' or supplements										
Cost per period	140	203.34	301.17	1050	14.32	39.12	170	96.32	150.99	185.70***

* p<0.05, ** p<0.01, *** p<0.001

Participants in the MERGE and XTEND datasets also encountered comparatively high direct costs for food supplements and special foods.

Model outputs

Meta-analysis approach

Supplementary Figures 9-1 through 9-5 show the adjusted mean estimates for direct medical costs, direct non-medical costs, food costs, and time respectively as identified in the meta-analysis. Table 9-4 and Figure 9-2 show the outputs from the model after 500 model runs for both approaches, by quintile. The median direct medical cost produced using parameters obtained through the meta-analysis approach was $34.25, varying from $80.66 in Quintile 1 to $6.64 in Quintile 4. Median direct non-medical costs were $65.23 (ranging from $94.92 in Q2 to $22.11 in Q4), and median costs of supplementary foods were $40.81 (ranging from $63.92 in Q2 to $20.04 in Q1). The median estimated hours spent seeking care (including travel and consultation time) was 82.8 hours (ranging from 32.9 hours in Q1 to 171.39 hours in Q2). Overall, model outcomes from the meta-analysis approach show the majority of the catastrophic cost burden falling on the first income quintile. The median prevalence of catastrophic costs in Quintile 1 is 28%, dropping to 2% for Quintile 2 and 0% in Quintiles 3 and 4. Overall, 11% of people with TB nationally are predicted to encounter catastrophic costs using the meta-analysis approach.

There was considerable uncertainty in adjusted mean estimates for some variables. A one-way analysis of variance (ANOVA) identified significant differences in mean time spent accessing the study clinic, and mean direct costs and time for spent accessing other providers in Period 4 (Table 9-3). This was likely partially due to small numbers of observations. To some extent however, this could also reflect true variances in total costs in the different settings. The extent to which TB and HIV services are integrated varies widely across South Africa; this could lead to a wide variety in the number of visits required for those with both TB and HIV in different places, for example. Similarly, the implementation of DOTS varies widely across participants in the pooled dataset, with the mean number of visits per month varying from 0.8 in the XTEND dataset to 8.9 in the REACH dataset as shown in Table 9-2.

As the sample sizes of each dataset are unequal, and the pooled dataset does not reflect the demographics or geography of the country, a simple adjusted mean across datasets will not appropriately reflect the national mean if uncertainty is driven by factors not

accounted for in the meta-analysis. It was unclear to what extent uncertainty in meta-analysis results was driven by demographic differences, and thus difficult to interpret meta-analysis findings. This provided motivation for a regression analysis, which allowed inclusion of other explanatory variables in estimation of costs and time associated with accessing care.

Regression approach

The total number of imputations for the regression approach are listed in Supplementary Table 9-2, and coefficients for the regression analysis to identify inputs into the model are listed in Supplementary Table 9-3. Several determinants were found to have a significant effect on cost, including HIV status, urbanicity, and employment status. Income quintile had no significant effect on costs; education level had a marginally significant only on costs for special foods in Period 4.

In our tests of the regression model on the raw un-imputed data separately for each dataset (Supplementary Table 9-3), some regression model coefficients were not consistent across datasets. For example, both positive HIV status and employment had a positive effect on costs in the MERGE and REACH datasets but a negative effect on costs for the XTEND dataset. Rural location had a positive effect on travel and consultation time in the REACH dataset, but a small (non-significant) negative effect on time in the XTEND dataset. There were no substantial differences observed in significant coefficients across datasets; where multiple datasets had significant coefficients for a given variable, coefficients were in the same direction and largely similar magnitudes.

The median direct medical costs produced using parameters obtained through the regression approach was $58.52, ranging from $21.06 in Q3 to $96.82 in Q1. Median direct non-medical costs were $35.00 (ranging from $30.90 in Q1 to $40.35 in Q1), and median costs of supplementary foods were $43.87 (ranging from $16.969 in Q4 to $75.50 in Q1). The median total estimated hours spent seeking care (including travel and consultation time) was 36.5 hours. The overall prevalence of catastrophic costs for the regression approach was 10%; again catastrophic costs were almost exclusively incurred by the lowest income quintile (median: 27%; 5th percentile: 19%; 95th percentile: 38%), falling to 1% at Quintile 2 and 0% at Quintiles 3 and above.

Results of the sensitivity analysis testing the impact of methods for valuing the time of unemployed people are shown in Supplementary Figure 9-6. Valuing costs for unemployed people using their full potential individual salary per hour slightly increased the prevalence

of catastrophic costs, but the overall impact of this increase was negligible. Estimating full costs in Periods 3 and 4 for those lost to follow-up increased cost estimates particularly for the regression approach. A combined sensitivity analysis with a full valuation of time for unemployed people and full costs for those lost to follow-up increased overall median catastrophic costs from 11% in baseline estimates to 17% for the meta-analysis approach, and from 10% in baseline estimates to 15% for the regression approach. The greatest impact of this change was observed in Quintile 1 - moving from a median 25% catastrophic to median 40% catastrophic for the meta-analysis approach and from median 10% catastrophic to median 39% catastrophic for the regression approach.

Figure 9-2 Prevalence of catastrophic cost by approach and quintile (baseline results from 500 model runs)

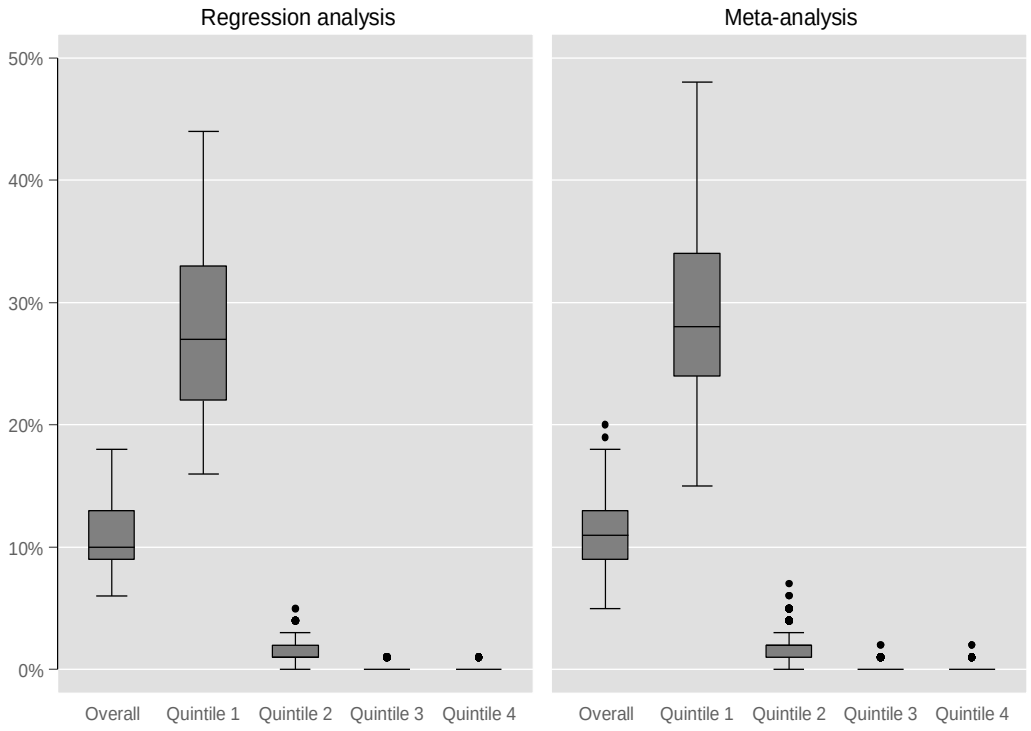


Table 9-4 Total Costs, Time, and Income by Quintile

	Direct medical costs (study clinic & other providers) Median (5^{th} – 95^{th} Pctile)	Direct non-medical costs (study clinic & other providers) Median (5^{th} – 95^{th} Pctile)	Direct non-medical costs (special foods) Median (5^{th} – 95^{th} Pctile)	Travel and consultation time (study clinic & other providers) Median (5^{th} – 95^{th} Pctile)	Total Indirect Costs Median (5^{th} – 95^{th} Pctile)	Annual Household Income Median (5^{th} – 95^{th} Pctile)	Prevalence of Catastrophic Costs Median (5^{th} – 95^{th} Pctile)
Meta-analysis approach							
Quintile 1	$80.66 ($51.97 - $121.39)	$72.04 ($50.76 - $107.19)	$20.04 ($19.04 - $21.16)	32.9 (23.5 - 46.0)	$2.05 ($1.07 - $3.99)	$1,313 ($1,227 - $1,400)	28% (21% - 41%)
Quintile 2	$7.48 ($5.08 - $10.86)	$94.92 ($67.54 - $135.09)	$63.92 ($59.35 - $68.01)	171.4 (123.1 - 242.9)	$48.68 ($26.98 - $79.71)	$4,158 ($4,036 - $4,291)	2% (0% - 4%)
Quintile 3	$7.21 ($4.94 - $10.14)	$43.67 ($24.54 - $69.14)	$56.28 ($45.90 - $68.24)	70.8 (49.6 - 99.1)	$50.23 ($26.07 - $84.66)	$8,391 ($8,118 - $8,670)	0% (0% - 1%)
Quintile 4	$6.64 ($3.20 - $15.88)	$22.11 ($12.01 - $48.48)	$29.80 ($18.01 - $45.94)	63.8 (40.0 - 90.4)	$163.34 ($76.24 - $345.58)	$27,291 ($23,158 - $36,017)	0% (0% - 1%)
Overall	$34.25 ($22.87 - $51.96)	$65.23 ($47.84 - $93.67)	$40.81 ($37.11 - $44.70)	82.8 (60.4 - 115.1)	$52.60 ($30.76 - $85.37)	$7,757 ($6,794 - $9,427)	11% (7% - 16%)
Regression approach							
Quintile 1	$71.09 ($44.86 - $106.74)	$41.94 ($31.71 - $58.80)	$75.41 ($71.20 - $80.39)	42.4 (31.5 - 59.3)	$3.52 ($1.98 - $5.68)	$1,315 ($1,249 - $1,374)	26% (19% - 37%)
Quintile 2	$21.77 ($16.15 - $31.69)	$25.62 ($19.29 - $36.32)	$35.46 ($32.10 - $39.32)	33.5 (25.1 - 47.6)	$11.29 ($7.12 - $16.89)	$4,156 ($4,071- $4,246)	0% (0% - 0%)
Quintile 3	$23.36 ($17.13 - $33.31)	$29.82 ($22.18 - $41.46)	$18.78 ($16.96 - $20.86)	25.2 (18.5 - 34.7)	$20.18 ($12.45 - $30.43)	$8,379 ($8,173 - $8,595)	0% (0% - 1%)
Quintile 4	$25.91 ($17.73 - $36.31)	$32.93 ($24.54 - $45.97)	$22.97 ($20.26 - $25.83)	23.3 (17.6 - 32.5)	$73.52 ($43.56 - $118.50)	$27,897 ($24,362 - $34,044)	0% (0% - 1%)
Overall	$40.96 ($28.81 - $59.40)	$33.39 ($25.95 - $47.08)	$45.11 ($42.60 - $47.75)	33.2 (25.6 - 46.7)	$20.55 ($13.61 - $30.45)	$7,883 ($7,094 - $8,969)	10% (7% - 14%)

DISCUSSION

This paper has presented estimates of the prevalence of catastrophic costs associated with TB, employing an individual-level cohort model using two approaches to parameterize direct and indirect cost estimates: a meta-analysis approach using summary statistics, and a regression approach using pooled primary data. Overall, the median prevalence of catastrophic costs encountered at the population level using both approaches was 10-11% of households. There was some uncertainty around these estimates using both approaches, ranging from 7-15% (5^{th}-95^{th} pctile) for the meta-analysis approach and 7-14% (5^{th} – 95^{th} pctile) using the regression approach.

Both estimation approaches showed that the majority of the burden of catastrophic cost falls on households in the first income quintile; the prevalence of catastrophic cost for the poorest quintile was estimated at 28% using the meta-analysis approach and 26% in the regression approach. Both approaches produced wide uncertainty around the prevalence of catastrophic costs for people falling in the first income quintile – ranging from 20-42% in the meta-analysis approach and 19-37% in the regression approach. This was largely due to uncertainty around costs encountered by the lowest quintile, particularly direct medical and direct non-medical costs associated with seeking care.

The similarity of estimates using these different approaches suggests that an individual-level analysis did not contribute any additional benefit over a study-level meta-analysis. There was no substantial reduction in uncertainty of cost estimates through the inclusion of additional determinants in the regression model.

This finding is counter-intuitive; in theory, individual data can contribute a great deal of value. The small difference observed in results between the two parameterization methods may have been a result of strong underlying uncertainty in the data. As demonstrated in the individual regression analyses run by study, trends in regression coefficients varied across datasets. This was likely partially a consequence of small sample sizes and varying demographics across datasets; where sample sizes for individual datasets were small the regression may not have effectively identified significant trends that were more easily observed in the larger pooled dataset.

However, the varying trends in coefficients across datasets could also be a reflection of differing models of care in different settings. As described in the Results chapter, models of care differed substantially across datasets. This could lead to differences not only in total

costs, but also in cost drivers. For example, variation in the availability of integrated TB/HIV care could lead to a substantial difference in the degree to which positive HIV status is a driver of costs. Differences in implementation of DOTS and frequency of visits could also lead to differences in cost drivers across datasets, for example increasing travel time for rural participants. Unfortunately, due to the structure of the available data it was not possible to control for these possible differences in models of care; our model therefore retained substantial uncertainty and was therefore limited in its ability to predict the national prevalence of catastrophic costs with any specificity.

The design of the model may also have contributed; representation of uncertainty in a cohort model is always conditional on its structural assumptions, and the structure of the modelling approach involves several assumptions that may have introduced bias into the estimates. The model was designed around determinants for which there was nationally-representative data available - notably SES quintile, employment status, and HIV status. As shown in the regression results, urbanicity is also an important determinant of patient costs, however it was not possible to build this into the model as no data exists on the current prevalence of TB amongst rural vs urban households in South Africa. It was also impossible to incorporate interactions in the model; for example, although there is evidence available on the comparative risk of TB infection across quintiles [15,41], there is no existing published evidence on the prevalence of TB/HIV coinfection or on the prevalence of TB on employed vs unemployed individuals.

A strength in using the cohort model as described is that it allowed adjustment for some demographics, and by time period. Demographics in the pooled data did not accurately reflect national demographics. One of the strongest potential benefits of pooling data is to improve the cultural and economic diversity of patient populations reflected in the data [13], theoretically making a pooled dataset more reflective of reality. However, pooling these particular data did not successfully eliminate sampling bias. Households in the pooled dataset on average fell into higher income quintiles than would be expected in South Africa, where 65% of TB cases are observed in households in the lowest two income quintiles. Use of the cohort model allowed us to adjust cases across income quintiles, matching the income distribution observed among TB patients in South Africa. The cohort model also allowed us to adjust for loss to follow-up along the patient pathway of care, more accurately capturing the costs of those in care. As more primary data on household costs of TB in South Africa becomes available, we may see socioeconomic diversity of the pooled primary data widens, which would reduce the need for this type of cohort model.

Another important caveat to this finding is that researchers must be sure that all variables are estimated in the same way before conducting a meta-analysis. This poses a particular concern where methods for estimating patient costs vary substantially across authors and institutions. This analysis required substantial effort in the recalculation of variables to reconcile cost estimation methods and time periods across studies before it was possible to conduct the meta-analysis. This analysis would not have been possible using only the summary statistics reported in the study papers. In order for meta-analysis to be a feasible alternative going forward, standardization of patient cost reporting is essential.

Methods for estimation and reporting of income data in patient cost surveys are currently inconsistent, with limited guidance on methods to collect income data that is high quality [37]. The wide variety of methods for estimating income across the three studies made income data collected by the individual studies included in this analysis unusable and required a separate regression analysis to predict household income for observations in the pooled dataset. The predictive power of the regression analysis given the demographic variables available was relatively low, weakening confidence in the predicted income estimates. These estimates may have been improved through the inclusion of other determinants (such as household size and dependency ratio; age, sex, and occupation of the head of the household; or information on land ownership and income source [38–40]). However, going forward, standardization of methods to estimate household income is critical for any future attempts to pool data for drawing national estimates. Better guidance from national governments and international bodies like the WHO as to which income measures to use and how these data should be collected would facilitate future efforts to estimate catastrophic costs. Guidance on the appropriate measures of ability to pay in the denominator (e.g. household income vs household expenditures) would also improve the theoretical validity of the metric.

Due to the above-mentioned limitations, the results from this model should be judged as indicative at best, and serve as inspiration for further analysis. A repeat of this analysis with additional primary data from South Africa added would test the validity of the main finding. Similar analyses conducted using data collected in different countries would also contribute to an understanding of the relative contribution of individual-level data on patient costs in a variety of settings.

It would also be good to test our results against other national estimates of catastrophic cost in South Africa. There is currently only one published paper that presents estimates of

the national prevalence of catastrophic cost for South Africa, to which we can compare results. Model results from this analysis were roughly equivalent to the lower bound of baseline estimates presented by Verguet et al. [10], who use a similar approach to the national model presented here, drawing on data from one of the datasets included in our pooled analysis [9]. Our estimates improve on estimates from Verguet et al. in that they use a systematic approach to test two different methods for pooling data from multiple studies. However, the results of this analysis should be considered highly conservative. As discussed above, we consider only the costs of treatment for DS-TB; we did not consider the potentially higher costs of MDR-TB nor did we consider costs encountered before the start of treatment. Furthermore, we assumed patients who were lost to follow-up did not encounter further costs. We did not include the indirect costs associated with reduced productivity due to illness due to a lack of data. As all data were collected at the health facility level, we were unable to include any cost estimates for people unable to access care. This ignores some of the most vulnerable households impacted by TB, and thus likely results in an underestimate of the economic burden of TB. Finally, we do not include funeral costs for TB-related deaths, as there is limited evidence on these costs.

The South African government is planning to conduct a nationally representative study to estimate catastrophic costs due to TB in the year 2019. The validity of our predictions should be tested against data from this nationally representative survey to support future estimation of the national prevalence of catastrophic cost using these approaches.

Our findings on significant determinants of catastrophic costs due to TB as identified in the regression approach are largely supported by the existing literature. We found that HIV co-infection was a significant determinant of some costs; this was also found in Nigeria [33]. We also found that employment was a significant determinant of costs in Period 3; this was also found in China [35] and South Africa [9]. Rural residence had a significant negative effect on direct costs and a positive effect on travel and consultation time; evidence is also mixed in previous studies - residence was found to be a significant determinant of catastrophic costs in Nigeria [33] Benin [34], and South Africa [9]. Several analyses also found that formal education increased the risk of catastrophic costs [33,34], while our analysis found no significant effect. We also found no significant effect of income quintile. Other potential determinants not included in our analysis which may be significant include delay in diagnosis [34], use of coping strategies [42], and smaller household size [30].

This analysis evaluates the ability to use existing data to estimate 'catastrophic total cost due to TB', following the definition of this metric in the WHO Handbook for TB Patient Cost Surveys [11]. This was in response to a direct request from the World Health Organization. We were unable to conduct a direct meta-analysis of catastrophic cost as only one existing paper presents primary data on the prevalence of catastrophic cost among TB patients [8]; this is likely similar to other countries. We find that in the absence of nationally representative data, both modelling and regression approaches provide alternatives for estimating catastrophic prevalence. However, to improve estimates from such cost-saving approaches, there is an urgent need for more standardized methods to collect cost and income data, and standardized reporting of cost estimates.

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CHAPTER 10. DISCUSSION

This thesis set out to improve the measurement of disease-specific catastrophic costs collected in the context of facility-level intervention-focused studies for different policy purposes, drawing on research from a number of projects and focusing specifically on the case study of TB in South Africa.

The thesis had five main objectives:

1. Estimate the prevalence of catastrophic costs among a cohort of people with TB using primary data, collected using conventional methods
2. Identify and critically review the methods used in measuring patient costs
3. Evaluate the impact of methodological variation in catastrophic cost estimation on study findings
4. Estimate nationally representative catastrophic costs due to TB in South Africa, using existing data
5. Identify the policy implications and next steps for research in this area

Through a series of analyses, the thesis has evaluated methods that are currently used, introduced frameworks to help researchers and policymakers recognize the impact of varying methodologies, and analysed the validity of current methods to address different policy questions. This last chapter summarises the findings of the thesis, its contributions to policy, the limitations inherent in the methods, and areas where further research is needed.

MAIN FINDINGS

Prevalence of catastrophic costs among a cohort of people with TB

The first objective was addressed in Chapter 5, which estimated the prevalence of catastrophic costs encountered by a cohort of people with TB and/or in South Africa. In Chapter 5, I apply the best practice costing methods as currently understood, and as summarized in Chapter 4. The patient questionnaire was adapted from the USAID Tool to Estimate Patient Costs, and a descriptive analysis presents the monthly costs of people with TB-only, HIV-only, and TB/HIV. At the time this paper was written, there was no comprehensive evidence on the economic impact of illness on people with both TB and HIV, despite the fact that this population group accounts for over 60% of those with TB.

Chapter 5 provides the first empirical evidence of the patient costs incurred by people living with both TB and HIV in South Africa. It provides a strong argument for action by the South African government to reduce the economic impact of TB/HIV co-infection on households. The paper found that people with TB/HIV in South Africa are at high risk of catastrophic costs. Over 45% of participants in the study experienced catastrophic costs even at thresholds as high as 25% of individual income. People with both TB and HIV on average faced higher levels of post-diagnosis catastrophic costs than those with TB-only or HIV-only, an effect that was stronger at higher threshold levels of catastrophic costs.

Evidence on disease-specific catastrophic costs can inform two distinct policy purposes: allocation of health expenditures, and the targeting of social protection. Chapter 5 notes several areas where changes in the way TB/HIV services are delivered could reduce the impact of catastrophic costs. Integration of TB/HIV services reduced the number of standalone TB/HIV service visits to the health facility and could reduce costs. The paper also noted that the frequent use of a 'treatment buddy' for people with HIV to support adherence often results in increased costs to the household; community-based approaches to HIV treatment supervision may alleviate this burden. Finally, the paper found that supplementary foods, often including foods outside of the typical South African diet, are an important cost driver and that further nutritional education may be needed to help households meet additional dietary needs within their household budgets.

However, the extent of the impact on poverty found in the paper means that it is unlikely that catastrophic cost can be averted by service integration alone; other types of intervention are also needed by the government of South Africa to reduce the burden of catastrophic cost. Social and income protection policies are currently not effectively implemented in large part in South Africa, and the paper found that many of those with TB/HIV co-infection who should qualify for social protection were unable to access it. The paper also identifies potential avenues for better targeting of social protection, including unconditional immediate cash for TB patients, and subsidization of food supplements or travel costs. This chapter provides a powerful example of the potential for high-quality health economics research to inform policy. The insights from this chapter give the South African government several potential policy tools to reduce the burden of catastrophic costs on some of the most vulnerable households in society.

However, this chapter also provides the first example in this PhD of practical challenges of measuring the impact of ill-health on costs incurred by households, and poverty. Although

Chapter 5 illustrates the application of the prevailing methods, implementation of 'gold standard' methods was not possible in some areas and in other areas there was no clear 'gold standard' to implement. The sample size for the paper was small, due to recruitment constraints and because the patient cost questionnaire was time-consuming, risking patient and interviewer fatigue. A relatively long recall period of 3 to 5 months was used; this posed some risk of recall bias, which was weighed against the potential to miss costs. Following inconsistency in the literature regarding methods to estimate indirect costs [1–4], reported income loss was used as the primary measure of indirect cost in order to avoid double-counting and possible bias against people with zero income. Individual income was used in the denominator of the 'catastrophic costs' estimate, as the survey did not include an estimate of household income.

These decisions and their potential implications are described in the limitations section of the paper and set the frame for the remaining chapters of the PhD. The remainder of the PhD examines these and other constraints faced by researchers working in low- and middle-income settings, and systematically identifies opportunities for the research community to take action to improve the quality and reliability of patient cost data going forward.

Methods used in measuring patient costs

Chapters 6 and 7 address the second objective of this thesis: to identify and critically review the methods used in measuring patient costs.

Chapter 6 builds on the lessons learned in the writing of Chapter 5, using various case studies to explore and reflect on the methodological challenges faced by researchers collecting patient costs in pragmatic intervention-based settings such as the one presented in Chapter 5. The paper finds that practical challenges resulted in different methodological approaches to data collection, including: comprehensiveness of survey design; time frame and recall; sample size and representativeness; data sources and survey administration.

The paper concludes that it is inevitable that some degree of variation in methods will occur across studies where context and data availability vary, particularly where data collection is linked to intervention study design. In Chapter 6, I argue that economists first and foremost have a responsibility to communicate data requirements in the study design phase, advocate for the collection of patient cost data as an essential part of the economic evaluation, and highlight the key aspects that need to be reported. However, it is also important to recognize that research funding for health economic research is often limited,

and even the most well-funded trials often face some budget or practical limitations. A framework is therefore presented to enable researchers to think more systematically about trade-offs in collection of patient cost data under practical constraints.

This framework does not provide easy solutions or 'best practice' methods for researchers faced with logistical limitations, but instead encourages consideration of potential biases in cost data collection and advocates for robust reporting of data collection methods. This necessarily includes detailed reporting of the methods used to facilitate standardization of methods and growth of the field, but also includes reflection of potential biases introduced by the methods to help policymakers understand and interpret findings.

This paper was written with the purpose of estimating catastrophic costs to be included in economic evaluation in mind. Some elements of the discussion of the trade-offs and research options available may be limited to the economic evaluation setting; for example, the discussion of challenges in survey timing focuses on situations when data collection is structured around outcome measurement for an economic evaluation. These same limitations will likely not be present when conducting a national survey, although there may be different challenges. However, many of the methodological points are also relevant for researchers seeking to estimate the national prevalence of catastrophic costs, as they address more general points to help researchers consider the impact of methodological decisions on quality of data, and any potential for bias introduced by these choices.

Chapter 6 concludes with the message that transparency in data collection for economic evaluation is critical, and presentation of cost data should be accompanied with a full, detailed description of how the data were estimated to prevent misuse or misapplication of the data for other purposes. It is essential that methodological choices are made with full understanding of the 'gold standard' approach, and how the chosen approach might introduce bias into cost estimates.

Chapter 7 presents a bibliometric review of the literature to examine the extent to which existing guidance on estimating patient costs enables researchers to make informed choices on study design, considering their context and practical limitations. The aim of this paper was to understand which, if any, methodological resources are available and accessible to researchers estimating disease-specific patient costs in LMIC settings, to what extent the evolution of costing methods has involved the LMIC context, and to what degree the available guidance has been used in collecting disease-specific patient cost data in LMIC settings with specific reference to TB.

Overall, I found that although guidance on data collection for estimation of patient costs is available, it is mostly not accessible or relevant for researchers working in low- and middle-income country contexts. Furthermore, I found that the ideas of researchers working in low- and middle-income country context have largely not contributed to the development of methods for patient costing; there was a lack of discussion between authors working at the 'cutting edge' of methods development, and those making costing accessible to practitioners working in LMIC settings. This has resulted in over-reliance on institutional knowledge, driving differences in methods undertaken by researchers from different institutions.

Impact of methodological variation on study findings

The current lack of clarity around methods for patient costing identified in Chapters 6 and 7 has potential ramifications for efforts to estimate catastrophic costs; both to estimate national progress towards global WHO targets, and to include in economic evaluations. Economic evaluations, even if conducted within a defined setting, often aim to inform national resource allocation and need to be generalised within countries; where different methods lead to different results, this can result in limited generalizability. The risk of limited generalizability is somewhat reduced where countries are using the same standardized methods identified in the WHO Handbook to estimate catastrophic costs due to TB [5]. However, there remain some methods in the WHO Handbook which are not clearly specified. For example, the WHO Handbook is currently unclear as to how countries should measure household income; several different options are listed, and no clear guidance on the relative advantages or disadvantages of different approaches is provided.

Chapter 8 presents the results of an analysis to address one of the key concerns in addition to patient cost measurement, the measurement of household income. Chapter 8 finds that different methods to estimate income result in substantially different estimates of catastrophic cost prevalence. Self-reported mean annual income was significantly lower than permanent income estimated using an asset linking approach, or income estimated using the national average. It further shows that income estimation methods can introduce substantial bias into studies. Self-reported income was unavailable for of 33 out of 99 participants, a number of whom had to sell assets or take out loans to meet the costs of TB.

The results of Chapter 8 are meaningful for efforts to estimate disease-specific catastrophic costs both in the context of economic evaluation and in estimating the national prevalence of catastrophic cost. The wide variation in frequency of catastrophic costs encountered by

the same study population, when estimated using different methods, confirms the importance of transparency and communication in reporting patient cost estimates. When this transparency and communication is not present in economic evaluations, policymakers cannot understand the implications of findings or compare across studies to inform policy decisions.

Different methods for estimating income across individual studies also make a national estimation of catastrophic costs difficult. Pooling study data together to come to a national estimate will not be possible where income has been estimated in such different ways. The ability for organizations such as the WHO to use the indicator of catastrophic cost prevalence as a tracking mechanism is also diminished where national studies use different estimation approaches. At best, data from multiple countries will be incomparable. At worst, the potential for differing methods to lead to different findings introduces the possibility of gaming, or choosing a particular method to minimize the frequency of catastrophic costs in order to meet international targets or curry favour among donors.

As with other chapters, Chapter 8 ends with a call to researchers to be more systematic in their data collection approaches, to be more transparent in their reporting, and to communicate more across institutions to further develop the field.

National prevalence of catastrophic costs due to TB in South Africa

Finally, Chapter 9 presents an evaluation of methods to combine data to estimate the national prevalence of catastrophic costs due to TB in South Africa, addressing objective #4. This analysis was conducted following a request from the Global TB Program at the World Health Organization to investigate the potential to use existing data to estimate the national prevalence of catastrophic costs; but also has implications for researchers conducting economic evaluations from a societal perspective. The paper evaluates to what degree the above-discussed limitations in the current data can be overcome with further analysis relying on modelling, exploring the extent to which cost data collected as part of trial-based economic evaluations can be used to estimate the national prevalence of catastrophic costs.

This analysis identifies some limitations and some promising indications for going forward. First, I identified some limitations of data availability during the process of data pooling. There is not currently sufficient data to estimate costs encountered by households before the start of treatment. I was also unable to access data for people with MDR TB, or for people not receiving care at a public health facility. Finally, the pooled dataset contained

several missing variables due to variations across studies in time periods and provider types for which cost data collected. This lack of data availability introduced some complexity into the analysis and likely resulted in a substantial underestimate of the prevalence of catastrophic costs due to TB in the model.

I also encountered limitations associated with compatibility of data across datasets – particularly in terms of differences in income estimation approaches, supporting findings from Chapter 8 that this area is vital. Current studies evaluate patient and household income in many different ways, making this data incomparable and impossible to use. The paper presents a potential solution for this issue in the regression analysis to predict household income, however this approach was imperfect. The regression results indicated a low predictive power and non-normally distributed residuals. For national estimates to be valid for tracking against international targets, methods for estimating income must be improved going forward.

A promising aspect of the findings of Chapter 9 is that when cost and income estimates are standardized, an individual-level regression analysis did not result in any substantial reduction in uncertainty of estimates of the national prevalence of catastrophic cost. This would suggest that it may not be necessary to obtain individual-level data to produce national estimates, where a meta-analysis is a reasonable alternative approach. Although the quality of the data included in this analysis was somewhat artificial, as I obtained primary data and recalculated several variables before conducting the meta-analysis in order to standardize estimates, this is encouraging for future efforts.

The results of Chapter 9 will be best interpreted in the context of findings from a national survey of TB-related catastrophic costs in South Africa, using methods articulated in the WHO Handbook. This study is currently being planned and is expected to be completed in 2019. Once this nationally representative data is available, I hope to compare results against estimates from Chapter 9 in order to determine whether any systematic bias is introduced by using pooled study data.

Chapter 9 shows that it is possible to use study-level data to estimate the national prevalence of catastrophic cost, if reporting of findings and methods for cost data estimation can be made more standardized and transparent. This finding could be vitally important for countries seeking to maintain surveillance on the prevalence of catastrophic cost within the country, without needing to conduct costly nationally representative surveys every couple of years.

OVERALL CONTRIBUTIONS OF THE THESIS

This thesis has made substantial contributions to understanding of the economic challenges faced by households affected by TB in South Africa. These empirical findings can be used by policy makers in South Africa to improve TB care and social support for those affected by TB. It has also made contributions in terms of advancing methods for estimating disease-specific patient and household costs. These lessons can be used by users and producers of patient cost data to improve the quality and use of cost data going forward. The contributions of this thesis are described below.

Catastrophic costs for TB in South Africa

The research presented in this thesis has confirmed that people in South Africa continue to encounter catastrophic costs due to TB and has provided some indications of potential areas where investment from the South African government can reduce this burden.

The thesis contains three chapters presenting estimates of catastrophic costs incurred by people with TB in South Africa: Chapter 5, Chapter 8, and Chapter 9. The results of Chapter 5 should be taken as specific to the MERGE study population. While some policy lessons can be drawn from these results on the economic impact of TB/HIV coinfection, they should not be taken as indicative of the national experience. Although catastrophic costs are estimated in Chapter 8, the results from this chapter should not be taken to be representative of the study population or the South African population due to the small sample size and high numbers of data loss. This paper, therefore, does not draw any policy lessons from these findings, but rather draws methodological lessons. The estimates presented in Chapter 9 can be taken as an estimate of the national prevalence of catastrophic cost, and therefore provide the most applicable policy lessons for South Africa.

First, some lessons can be drawn about potential improvements the South African government can make to the way that health care is provided. All data presented in Chapter 9 consistently indicates that direct medical costs at the facility where people receive their primary treatment are zero. The findings from this paper also support previously published evidence that the use of private alternative providers is common in South Africa, and can introduce a substantial economic burden on the household [6–9]. Improved coordination of care across providers, and the introduction of risk pooling schemes for those seeking care at private or alternative providers, could reduce this burden.

Chapter 9 shows that people with TB lose a great deal of time due to TB-related travel and consultation time. The results of Chapter 5 indicate that these costs are highest for people with both TB and HIV. Chapter 5 was unable to directly estimate the potential of integrating TB/HIV services to reduce these costs, however in principle integration has the potential to reduce the overall number of visits. This chapter suggests that efforts to ensure 'integrated' visits are delivered by the same provider or within the same room, reducing waiting periods between multiple visits in a day, may reduce the burden of catastrophic costs due to TB.

Chapters 5 and 9 also show that supplementary foods are important drivers of costs for TB patients in South Africa. This finding has also been reported by other costing studies from South Africa [10–12]. Previous studies have indicated that patients may perceive that TB and HIV drugs must be supplemented with higher food intake, often including foods outside of the typical South African diet including eggs, fruit, soft drinks, and meat. Improved nutritional education for people with TB in South Africa may help households meet dietary needs within their spending capabilities.

The results presented in this thesis also provide some lessons to inform targeting of social protection in South Africa. As shown in Chapter 9, the national prevalence of catastrophic costs is 7-14%; this burden falls almost exclusively on those in the lowest income quintile. Currently, the South African government offers a temporary grant for patients who at the discretion of a doctor are deemed unfit to undertake remunerative work. However, across study populations from Chapters 5 and 9, access to these grants was consistently low. Better targeting of social protection is urgently needed to reduce the prevalence of catastrophic costs. As noted above, expenditures on special foods and food supplements were high across all patients in Chapter 9. Targeted social support in the form of food packages or vouchers may also be an important pathway to reduce the economic burden of TB on households.

Implications for policy in South Africa

Several of the above-listed contributions are directly applicable for policy makers in South Africa, including those working in the National TB Programme, the National Department of Health, and the Department of Social Development (among others). The evidence generated in this PhD supports several policies already included in the South African National Strategic Plan on HIV, TB and STIs 2017-2022. For example, this thesis shows that people with both TB and HIV experience a disproportionate economic burden; this supports the effective integration of HIV, TB and STI services and interventions is critical to

the success of NSP goals. This thesis also notes that social support (e.g. in the form of disability grants) is currently difficult for TB patients to access; this is also acknowledged in the NSP, with plans laid out to improve multi-sector engagement to address social and structural determinants of HIV, TB and STIs.

Some additional findings from the thesis may also inform future approaches by the above-listed agencies to reduce the economic burden of TB on households. For example, the finding that the use of private alternative providers can introduce a substantial economic burden on the household makes a strong argument that improved risk pooling for these providers is needed to protect households from catastrophic costs. This could inform design of the National Health Insurance Scheme, currently in the second phase of implementation. This thesis further shows that supplementary foods are important drivers of costs for TB patients in South Africa. This could inform the Department of Social Development how best to to target efforts to reduce the economic impact of TB; nutritional support and education are strongly needed alongside income support for TB patients and their households.

Methods to estimate disease-specific catastrophic cost in LMIC settings

The above-described findings underline the importance of disease-specific catastrophic cost as a tool for decision-making. Information on disease-specific catastrophic costs can inform economic evaluation of new interventions and targeting of social protection, and help with program evaluation. These purposes cannot currently be addressed with more general estimates of catastrophic total health expenditures. However, this thesis identifies several limitations in the current implementation of methods to estimate disease-specific catastrophic costs, largely resulting from a lack of definitive guidance on best practice and study reporting.

Chapters 6 and 7 have shown that the current quality of patient cost estimates is highly variable, due to often unavoidable practical limitations and limited accessibility, relevance, and use of guidance on how to estimate costs. This variability leads to substantially different estimates of the prevalence of catastrophic cost, as demonstrated in Chapter 8. Chapter 9 shows when methods for estimating patient costs across studies can be reconciled, they could be useful for national estimates of the prevalence of catastrophic cost.

The results of this thesis make a strong argument in favour of a reference case on estimating disease-specific patient, household, and catastrophic costs. Reference cases

have been used to improve comparability of cost and cost-effectiveness analyses globally, most commonly from the provider perspective. Most recently, the GHCC has developed and promoted a Reference Case for Estimating the Costs of Global Health Services and Interventions from the provider perspective [13]. This signals an interest from economists globally to improve data collection methods, and recognition by global institutions that standardization of reporting on methods for data collection is needed.

The World Health Organization has developed a handbook for national surveys to estimate catastrophic costs associated with TB [5]. This is a valuable resource however it is not an appropriate substitute for a reference case on patient cost data collection more widely. As discussed throughout this thesis, methods for estimating patient costs in the context of economic evaluations may differ from methods for nationally representative surveys on catastrophic cost. Data needs are often different, and researchers who estimate patient costs in the context of an economic evaluation may face some practical limitations that are not applicable to those conducting a nationally representative survey. Furthermore, in areas where no current 'gold standard' exists we would not wish to limit researchers testing different approaches in order to improve methods. However, transparency in reporting methods for data collection and analysis remain essential – not only so that the results of economic evaluations can be appropriately interpreted by policymakers but also so that cost data estimated in the context of economic evaluation can serve other purposes.

This thesis has identified a number of priority areas where improved methods guidance and standardized reporting are particularly necessary. First, as discussed in Chapter 7, researchers working in LMIC settings need access to guidance clearly defining the 'gold standard' for patient cost data collection where this exists – particularly in the fields of estimation of resource use, and cost valuation where much work has been done to identify 'gold standard' methods. Where this guidance does exist, it is mostly not currently accessible or relevant to researchers working in LMIC settings.

Second, researchers need guidance to help them identify the likely impact of methodological compromises taken due to practical limitations. Practical concerns can introduce limitations in several aspects of study design, including: comprehensiveness of survey design, time frame and recall, sample size and representativeness, and data sources and survey administration. This can substantially influence data quality, as discussed in Chapter 6. As discussed in Chapter 7, there is not currently suitable guidance to help

researchers understand the impact of these decisions. Making this guidance available would help researchers to more accurately communicate the implications and limitations of their findings, resulting in a more informed policy.

In some cases, no clear 'gold standard' exists, or the 'gold standard' is impossible to implement in LMIC settings. For example, Chapter 8 describes several possible methods to estimate individual and household income, all of which are problematic in some way. In cases like these, clear reporting of methods and improved communication across research groups is necessary to facilitate comparative analysis, until further research can help to identify a better solution.

Finally, as discussed in Chapter 9, there is also a need for standardization of reporting for patient costs – specifically with relevance to time periods, cost types, and provider types. Gaining group consensus on standardized 'outputs' for a patient costing study would facilitate the use of this data for different purposes going forward. I learned how best to facilitate this type of discussion during my involvement in drafting the GHCC Reference Case for Estimating the Costs of Global Health Services and Interventions, which has identified these outputs from the provider perspective, facilitating the use of these costs in modelling estimates going forward. The same is possible for patient-perspective costs, which would facilitate the use of this data in national estimates of catastrophic cost.

This thesis has made some preliminary progress toward providing guidance in all these areas. The framework presented in Chapter 6 provides a resource for helping researchers to think through the impact of methodological choices where practical limitations are encountered. The database compiled for the bibliometric review in Chapter 7 will be posted on the GHCC website and should help improve the accessibility of guidance for researchers working in LMIC settings. Chapter 8 contains a substantial theoretical discussion on differences behind different concepts of capacity to pay for health and provided a discussion of the economic theory behind the choice of permanent vs current income for estimation of catastrophic cost. The supplemental material for the paper also contains a detailed glossary defining these terms and clarifying concepts.

Implications for users and producers of patient cost data

The above-listed contributions all benefit users and producers of cost data. For researchers looking to collect this type of data, this PhD has provided resources to facilitate the process of designing a study whilst limiting bias as much as possible. In some cases, I have described a 'gold-standard' approach for best practice. For example, the gold standard for

estimating household expenditure for the denominator of the 'catastrophic costs' equation is through an expenditures module. Two approaches are considered to be 'gold standard' for collecting information on resource use whilst seeking health care; including a review of administrative records and a diary approach.

Unfortunately, in many cases the state of the literature is not sufficient to enable conclusive recommendations as to best practice where the gold standard is not implementable. For example, the empirical evidence on suitability of recall to estimate resource use in the place of records review is mixed; 32% of references found in Chapter 7 that self-reported data was unreliable, while 26% of studies state that self-reported data is reliable. There is no existing research comparing the validity of different measures of household 'capacity to pay' for health care in the absence of a consumption module.

Finally, in some cases a 'gold standard' does not exist. There is no published research on methods for sampling when estimating disease-specific household costs. Nor is there any agreement in the literature as to the most appropriate method to value indirect costs as a result of time spent seeking health care (ie. through the 'human capital' or 'outputs' methods). Finally, although generally a shorter recall period is considered to be better when interviewing patients about their resource use, the ideal length of recall has not been evaluated and depends substantially on context and the time frame for the disease in question.

Implications for researchers

on all of these points, there remains a need for group consensus on required reporting and further empirical research to confirm 'best practice'. In looking towards my future career post-PhD, I would be motivated to take an active role in facilitating this type of discussion across research groups and conducting some further empirical research. There are two particular analyses which could be done in the near future thanks to the efforts of the WHO-TB programme in coordinating and supporting national patient costing surveys. First, several country surveys have collected income data using a variety of methods in a similar fashion to the data presented in Chapter 8, but also including an expenditure module. I am currently in negotiations to obtain access to this data, in order to conduct an analysis to validate the findings of Chapter 8 and test the appropriateness of an expenditure module to estimate household income. Second, as mentioned in Chapter 9, the South African government is planning to conduct a nationally representative study of catastrophic costs

due to TB in the coming year. Once this study has completed, I plan to negotiate access to this data in order to test the findings presented in Chapter 9.

LIMITATIONS AND AREAS FOR FURTHER RESEARCH

Somewhat fitting for a thesis about the practical limitations of cost data collection, this thesis has a number of limitations – often due to practical restrictions. First, as this was a staff PhD, it was reliant on data that had already been collected. This limited study design, often preventing implementation of a 'gold standard' against which I could compare estimates.

For example, it would have been ideal to estimate household consumption expenditure for Chapter 8, in order to facilitate a direct comparison of commonly used estimates against the 'gold standard'. This was not included in the original study design and was therefore not possible. Further research to develop and implement a short-form consumption expenditure module for use in low- and middle-income settings would greatly facilitate the estimation of catastrophic costs.

Chapter 7 presents the results of a bibliometric review on availability, accessibility, and use of guidance. Double extraction is usually recommended for systematic reviews in order to minimize potential bias or errors in results. This was not possible as this exercise was done solely for the purposes of the PhD. Some further verification or checking of extraction by a second person will be necessary for this analysis to be publishable in future.

As mentioned above, due to data limitations all of the papers included in this PhD focus only on the costs of people accessing care at public facilities, and only for drug-sensitive TB. I do not include any findings or methodological lessons on estimating the cost of care for those unable to access care, those with MDR-TB, or those receiving care exclusively from private or alternative providers. These people are often the most vulnerable, and methods need to be developed to help researchers estimate their costs.

As shown in Chapters 5 and 9, households with TB often employ coping strategies in an attempt to smooth the impact of TB-related costs *ex-post*. This can involve selling assets, taking loans (sometimes at very high interest rates), or reducing consumption. Data on the use of coping strategies is relatively easily collected for all households, unlike some quantitative measures explored. Coping strategies may also be a better indication of long-term financial hardship than the quantitative indicator of catastrophic costs. This thesis did not evaluate the long-term impact of coping strategies or appropriateness of their use as

an indicator for financial hardship, however this should be a priority area of research going forward.

CONCLUSIONS

This thesis has demonstrated the need for improved discussion and consensus for patient costing methods. Changes in the international policy environment in the last five years have created an opportunity for evidence on disease-specific catastrophic costs to have a greater impact than ever before. There is international motivation to reduce the prevalence of catastrophic costs due to TB, and a growing interest in incorporating estimates of catastrophic cost in economic evaluation. However, as noted by Graves et al., "No amount of statistical analysis can compensate for inadequate costing methods" [14]. There are currently gaps in data collection methods that prevent full realisation of the opportunities available. Researchers should be challenged to take this opportunity to address methodological gaps and come together as a community to strengthen data collection methods.

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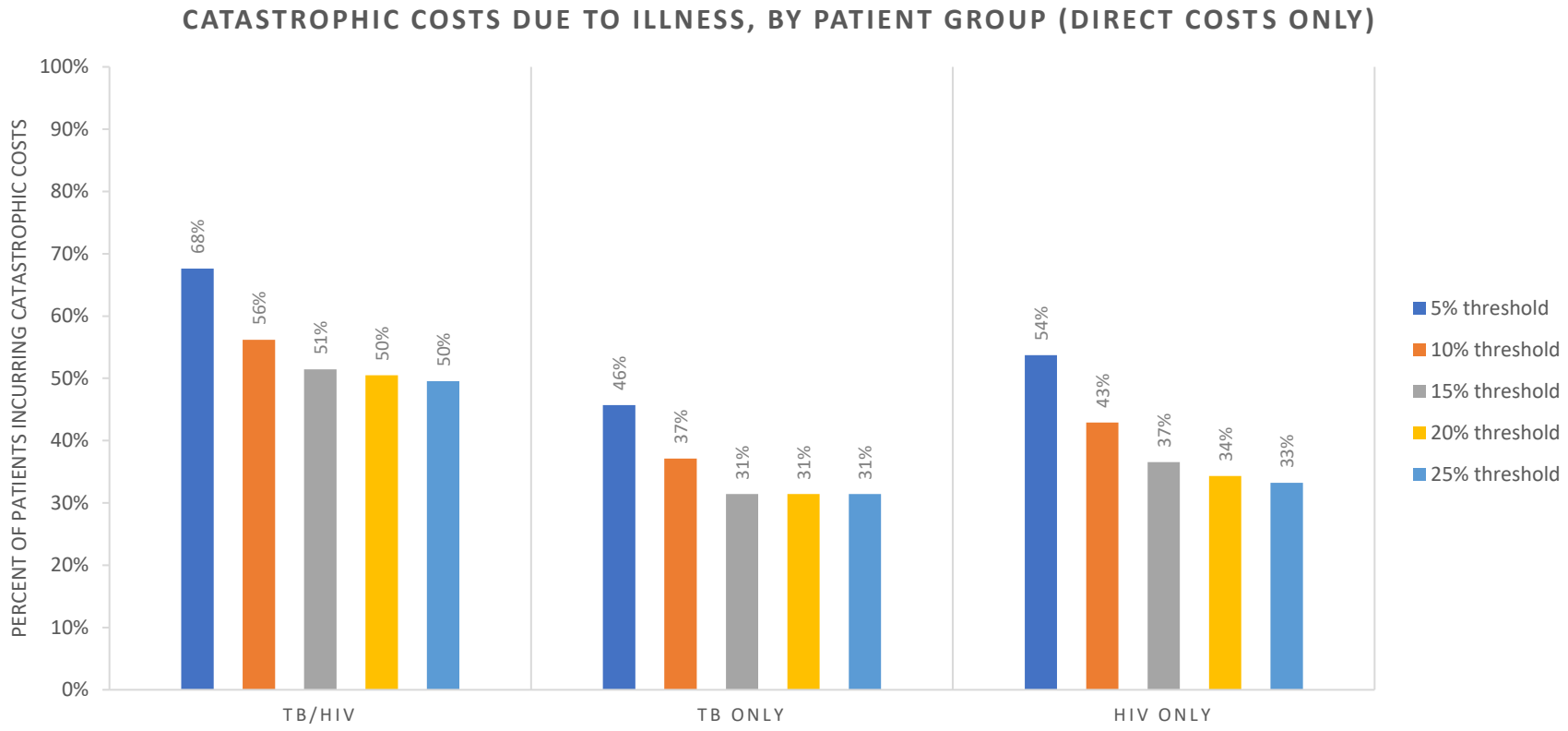
SUPPLEMENTARY FILES

SUPPLEMENTARY FILES FOR CHAPTER 5

Supplementary Figure 5-1 Catastrophic costs due to illness, by patient group (direct costs only)



Supplementary Table 5-1 Number of health facility visits, by patient group, provider type and visit type

	Number of participants visiting facility type			Mean number of visits in post-diagnosis period among those participants visiting facility type		
Participant group	**TB/HIV (n = 116)**	**TB only (n = 40)**	**HIV only (n = 298)**	**TB/HIV (n = 116)**	**TB only (n = 40)**	**HIV only (n = 298)**
Study Clinic						
TB/HIV visits	91	27	0	6.4	1.1	
TB visits	95	39	0	13.3	14.9	
HIV visits	52	2	298	4.4	1.0	4.6
Other Clinic						
TB visits	6	5	0	1.3	4.4	
HIV visits	2	2	7	1.5	1.0	1.6
Pharmacy						
TB visits	2	0	0	1.5		
HIV visits	2	0	10	1.5		1.2
General Practitioner						
TB visits	4	1	0	1.8	1.0	
HIV visits	3	0	20	3.3		1.6
Hospital (inpatient)						
TB visits	10	0	0	1.2		
HIV visits	3	0	2	1.0		1.0
Hospital (outpatient)						
TB visits	3	0	0	2.0		
HIV visits	5	0	0	1.2		
Traditional Healer						
TB visits	1	0	0	1.0		
HIV visits	0	0	9			1.7

Supplementary Table 5-2 Detailed costs for all facility types, by participant group

				TB/HIV (n=116)		TB only (n=40)		HIV only (n=298)	
				mean	**(SD)**	**Mean**	**(SD)**	**mean**	**(SD)**
Direct costs	Medical	Study clinic		0.00	0.00	0.00	0.00	0.00	0.00
		Other clinic		0.00	0.00	0.00	0.00	0.00	0.00
		Pharmacy		0.00	0.01	0.07	0.42	0.00	0.00
		General practitioner		0.30	2.72	0.00	0.00	0.82	4.13
		Hospital-outpatient		0.11	0.70	0.00	0.00	0.00	0.00
		Hospital-inpatient		0.32	2.28	0.00	0.00	0.01	0.14
		Traditional healer		1.00	9.67	0.00	0.00	0.05	0.44
	Travel	Patient	Study clinic	4.12	8.91	1.69	3.31	1.25	3.07
			Other clinic	0.02	0.12	0.05	0.20	0.02	0.15
			Pharmacy	0.00	0.00	0.00	0.00	0.04	0.35
			General practitioner	0.30	2.70	0.00	0.00	0.13	1.10
			Hospital-outpatient	0.21	0.93	0.00	0.00	0.00	0.00
			Hospital-inpatient	0.06	0.43	0.00	0.00	0.03	0.60
			Traditional healer	0.04	0.48	0.00	0.00	0.01	0.13
		Guardian	Study clinic	0.43	2.37	0.00	0.00	0.27	2.78
			Other clinic	0.00	0.00	0.00	0.00	0.01	0.08
			Pharmacy	0.00	0.00	0.00	0.00	0.01	0.18
			General practitioner	0.25	2.65	0.00	0.00	0.05	0.81
			Hospital-outpatient	0.12	0.83	0.00	0.00	0.00	0.00
			Hospital-inpatient	0.14	1.45	0.00	0.00	0.10	1.28
			Traditional healer	0.00	0.00	0.00	0.00	0.01	0.09
	Food	Hospital		0.26	1.31	0.00	0.00	0.04	0.47
		Special foods		13.14	17.33	8.06	11.05	9.76	14.91
	Loan interest			0.93	9.78	0.00	0.00	5.68	89.11
	Total direct			**21.72**	**29%[1]**	**9.86**	**14%**	**18.28**	**45%[1]**
Indirect Costs	Patient Income Loss	Job loss income loss		15.40	126.17	17.78	76.69	2.99	24.30
		Care-seeking income loss		30.45	105.56	34.60	98.99	13.81	59.03
	Opportunity Costs of Time	Guardian	Study clinic	1.13	4.58	0.23	1.00	3.92	3.35
			Other clinic	0.00	0.00	0.03	0.17	0.03	0.36
			Pharmacy	0.00	0.00	0.01	0.06	0.00	0.04
			General practitioner	0.03	0.32	0.00	0.00	0.04	0.41
			Hospital-outpatient	0.05	0.65	0.00	0.00	0.00	0.00
			Hospital-inpatient	0.88	6.19	0.00	0.00	0.13	1.11
			Traditional healer	0.00	0.00	0.00	0.00	0.01	0.16
		Carer		4.42	11.35	5.81	13.52	1.19	5.77
	Total indirect			**52.34**	**71%[1]**	**58.47**	**86%**	**22.13**	**55%[1]**
Grand total				**74.07**		**68.33**		**40.41**	

[1] percentage of the overall total

SUPPLEMENTARY FILES FOR CHAPTER 7

Appendix 1: Full Search Strategy

Search Round 1

Website / Database	Search terms
Web of Science	TITLE: (("costing" or (cost NEAR collect*) or (cost NEAR estimat*) or (cost NEAR measur*) or (cost NEAR valu*) or (cost NEAR calculat*) or (cost NEAR analys*))) *AND* TITLE: ((method$ or methodology or valid* or generalizab* or compar* or approach* or standard$ or guideline$ or recommendation$ or accura* or bias)) *AND* TOPIC: ((HIV or "human immunodeficiency virus" or AIDS or "acquired immune deficiency syndrome" or TB or tuberculosis or malaria or immuniz* or vaccinat* or disease* or ill* or health* or treat* or care or medic*))
Embase	(("costing" or "cost collection" or "cost estimation" or "cost measurement") adj (method$ or methodology or valid* or generalizab* or compar* or approach* or standard$ or guideline$ or recommendation$ or accura* or bias)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
IBSS	((ti("costing") or (ti(cost) NEAR/3 ti(collect*)) or (ti(cost) NEAR/3 ti(estimat*)) or (ti(cost) NEAR/3 ti(measur*))) NEAR/3 (ti(method$) or ti(methodology) or ti(valid*) or ti(generalizab*) or ti(compar*) or ti(approach*) or ti(standard$) or ti(guideline$) or ti(recommendation$) or ti(accura*) or ti(bias))) AND (all(HIV) or all("human immunodeficiency virus") or all(AIDS) or all("acquired immune deficiency syndrome") or all(TB) or all(tuberculosis) or all(malaria) or all(immuniz*) or all(vaccinat*) or all(disease*) or all(ill*) or all(health*) or all(treat*) or all(care) or all(medic*))
Pubmed	search: "costing"[Title/Abstract] OR "cost collection"[Title/Abstract] or "cost estimation"[Title/Abstract]) AND (method$ or methodology OR validity OR generalizability OR comparison OR approach OR standard$ OR guideline$ OR recommendation$)
Econlit	1 ("costing" or (cost adj collect*) or (cost adj estimat*) or (cost adj measur*) or (cost adj valu*) or (cost adj calculat*) or (cost adj analys*)).mp. [mp=heading words, abstract, title, country as subject] 2 (method$ or methodology or valid* or generalizab* or compar* or approach* or standard$ or guideline$ or recommendation$ or accura* or bias).mp. [mp=heading words, abstract, title, country as subject] 3 (HIV or "human immunodeficiency virus" or AIDS or "acquired immune deficiency syndrome" or TB or tuberculosis or malaria or immuniz* or vaccinat* or disease* or ill* or health* or treat* or care or medic*).mp. [mp=heading words, abstract, title, country as subject] 4 1 and 2 and 3
Global Health	1 ("costing" or (cost adj collect*) or (cost adj estimat*) or (cost adj measur*) or (cost adj valu*) or (cost adj calculat*) or (cost adj analys*)).mp. [mp=heading words, abstract, title, country as subject] 2 (method$ or methodology or valid* or generalizab* or compar* or approach* or standard$ or guideline$ or recommendation$ or accura* or bias).mp. [mp=heading words, abstract, title, country as subject] 3 1 and 2
World Bank website (Google search)	(cost OR "costing" OR "cost collection" OR "cost estimation" OR "cost measurement") AROUND (method OR methodology OR valid OR

	generalizable OR compare OR approach OR standards OR guidelines OR recommendations OR accuracy OR bias) site:worldbank.org
WHO website (Google search)	(cost OR "costing" OR "cost collection" OR "cost estimation" OR "cost measurement") AROUND (method OR methodology OR valid OR generalizable OR compare OR approach OR standards OR guidelines OR recommendations OR accuracy OR bias) site:who.int
UNAIDS website (Google search)	(cost OR "costing" OR "cost collection" OR "cost estimation" OR "cost measurement") AROUND (method OR methodology OR valid OR generalizable OR compare OR approach OR standards OR guidelines OR recommendations OR accuracy OR bias) site:unaids.org

Search Round 2

Website / Database	Search terms
Web of Science	((productivity OR indirect OR opportunity OR patient OR direct OR out-of-pocket)) *AND* TITLE: ((cost OR loss burden OR expenditure OR spend OR economic OR catastrophic OR impoverishing)) *AND* TITLE: ((measure OR collect OR value OR calculate OR method OR analyse OR estimate))OR method OR analyse OR estimate)
Embase	1 (productiv* or indirect or opportunity or patient or direct or "out of pocket" or "out-of-pocket") title 2 cost* or loss or burden or expenditure* or spend* or economic title 3 1 AND 2 4 (catastroph* or impoverish*) title 5 3 OR 4 6 (measur* or collect* or valu* or calculat* or method* or analys* or estimat*) title 7 5 AND 6
IBSS	((ti((productiv* OR indirect OR opportunity OR patient OR direct OR "out of pocket" OR "out-of-pocket")) AND ti(cost* OR loss OR burden OR expenditure* OR spend* OR economic)) OR ti((catastroph* OR impoverish*))) AND (ti(measur*) or ti(collect*) or ti(valu*) or ti(calculat*) or ti(method*) or ti(analys*) or ti(estimat*))
Pubmed	((measur*[Title] OR collect*[Title] OR valu*[Title] OR calculat*[Title] OR method*[Title] OR analy*[Title] OR estimat*[Title])) AND ((((((productiv*[Title] OR indirect[Title] OR opportunity[Title] OR patient[Title] OR direct[Title] OR "out of pocket"[Title] OR "out-of-pocket"[Title] OR OOP[Title]))) AND ((cost$[Title] OR loss[Title] OR burden[Title] OR expenditure$[Title] OR spending[Title] OR economic[Title])))) OR ((catastrophic[Title] OR impoverishing[Title] OR impoverishment[Title] OR catastrophe[Title])))
Econlit	1 (productiv* or indirect or opportunity or patient or direct or "out of pocket" or "out-of-pocket") title 2 cost* or loss or burden or expenditure* or spend* or economic title 3 1 AND 2 4 (catastroph* or impoverish*) title 5 3 OR 4 6 (measur* or collect* or valu* or calculat* or method* or analys* or estimat*) title 7 5 AND 6
Global Health	1 (productiv* or indirect or opportunity or patientor direct or "out of pocket" or "out-of-pocket") title 2 cost* or loss or burden or expenditure* or spend* or economic title 3 1 AND 2

	4 (catastroph* or impoverish*) title 5 3 OR 4 6 (measur* or collect* or valu* or calculat* or method* or analys* or estimat*) title 7 5 AND 6
World Bank website (Google search)	(productivity OR indirect OR opportunity OR patient OR direct OR out-of-pocket) AND (cost OR loss burden OR expenditure OR spend OR economic OR catastrophic OR impoverishing) AND (measure OR collect OR value OR calculate OR method OR analyse OR estimate) site:worldbank.org
WHO website (Google search)	(productivity OR indirect OR opportunity OR patient OR direct OR out-of-pocket) AND (cost OR loss burden OR expenditure OR spend OR economic OR catastrophic OR impoverishing) AND (measure OR collect OR value OR calculate OR method OR analyse OR estimate) site:who.int
UNAIDS website (Google search)	(productivity OR indirect OR opportunity OR patient OR direct OR out-of-pocket) AND (cost OR loss burden OR expenditure OR spend OR economic OR catastrophic OR impoverishing) AND (measure OR collect OR value OR calculate OR method OR analyse OR estimate) site:unaids.org

Appendix 2: Topic-specific study details

Supplementary Table 7-3 Broad costing guidance

	General			Disease- or intervention-specific		
	Number of references	Mean methodological citations per year	Mean total citations per year	Number of references	Mean methodological citations per year	Mean total citations per year
What kind of guidance exists?						
Methodological papers on one aspect of costing				2	0.07	1.04
Purpose-written costing guidelines or costing tool	11	0.06	9.82	15	0.02	2.64
Costing results with methodological commentary				1	0.11	1.33
Does any analysis underlie guidance?						
Empirical comparison / validation				1	0.11	1.33
Literature review				1	0.07	0.93
No analysis (theory-based)	11	0.06	9.82	16	0.02	2.57
What setting is guidance relevant to?						
All income levels (not country specific)	5	0.00	14.32	7	0.00	1.21
High income settings	4	0.15	7.59	5	0.10	1.69
LMIC settings	2	0.00	3.06	6	0.00	3.54
Is guidance targeted towards a costing purpose?						
Economic evaluation / priority setting	11	0.06	9.82	14	0.04	2.75
Equity and poverty analyses				2	0.00	0.43
Financial planning / management				2	0.00	0.81
Is guidance widely accessible?						
Not open access	9	0.08	11.56	8	0.05	1.81
Open access or grey literature	2	0.00	2.02	10	0.02	2.69

Supplementary Table 7-4 Study design

	Number of references	Mean methodological citations per year	Mean total citations per year
What kind of guidance exists?			
Methodological papers on one aspect of costing	2	0.05	4.83
Does any analysis underlie guidance?			
Literature review	2	0.05	4.83
What setting is guidance relevant to?			
High income	2	0.05	4.83
Is guidance targeted towards a specific costing purpose?			
Economic evaluation / priority setting	2	0.05	4.83
Is guidance widely accessible?			
Not open access	2	0.05	4.83

Supplementary Table 7-5 Estimating resource use

	General			Disease- or intervention-specific		
	Number of references	Mean methodological citations per year	Mean total citations per year	Number of references	Mean methodological citations per year	Mean total citations per year
What kind of guidance exists?						
Methodological papers on one aspect of costing	38	0.29	6.70	40	0.12	2.73
Cost results with some methodological commentary	1	0.08	4.92	6	0.04	2.99
Reviews of cost methods	1	0.00	0.06	1	0.00	1.00
Does any analysis underlie guidance?						
Case study / worked example	2	0.21	11.11	4	0.03	2.64
Empirical comparison / validation	36	0.30	6.41	42	0.11	2.77
Expert consultation	1	0.00	6.50			
Literature review	1	0.00	0.06	1	0.00	1.00
What setting is guidance relevant to?						
All income levels (not country specific)	1	0.00	0.06			
High income	39	0.29	6.65	47	0.10	2.72
Is guidance targeted towards a specific costing purpose?						
Economic evaluation / priority setting	15	0.28	8.61	24	0.13	3.35
Purpose not specified / multiple purposes	25	0.28	5.22	23	0.07	2.07
Is guidance widely accessible?						
Not open access	38	0.30	6.67	42	0.11	2.75
Open access or grey literature	2	0.00	3.03	5	0.06	2.49

Supplementary Table 7-6 Valuation of direct costs

	General			Disease- or intervention-specific		
	Number of references	Mean methodological citations per year	Mean total citations per year	Number of references	Mean methodological citations per year	Mean total citations per year
What kind of guidance exists?						
Methodological papers on one aspect of costing	12	0.05	4.37	3	0.03	1.54
Reviews of cost methods	1	0.00	7.25			
Does any analysis underlie guidance?						
Empirical comparison / validation	6	0.08	5.00	2	0.05	0.95
Expert consultation	2	0.00	4.91			
Literature review	1	0.00	7.25			
No analysis (theory-based)	4	0.02	2.84	1	0.00	2.71
What setting is guidance relevant to?						
All income levels (not country specific)	5	0.05	4.64			
High income settings	3	0.02	0.25	3	0.03	1.54
LMIC settings	5	0.06	6.36			
Is guidance targeted towards a specific costing purpose?						
Economic evaluation / priority setting	2	2.00	4.87	1	1.00	1.09
Equity and poverty analyses	8	10.00	4.95			
Financial planning / management	1	1.00	1.14			
Purpose not specified / multiple purposes	2	2.00	4.03	2	2.00	1.77
Is guidance widely accessible?						
Not open access	12	0.05	4.81	3	0.03	1.54
Open access or grey literature	1	0.00	1.14			

Supplementary Table 7-7 Valuation of indirect costs

	General			Disease- or intervention-specific		
	Number of references	**Mean methodological citations per year**	**Mean total citations per year**	**Number of references**	**Mean methodological citations per year**	**Mean total citations per year**
What kind of guidance exists?						
Methodological papers on one aspect of costing	30	0.14	7.02	10	0.12	6.00
Cost results with some methodological commentary				3	0.00	2.48
Reviews of cost methods	1	0.08	9.00	1	0.00	6.00
Does any analysis underlie guidance?						
Case study / worked example	3	0.60	18.34	2	0.16	6.66
Empirical comparison / validation	13	0.19	5.81	11	0.10	4.92
Expert consultation	1	0.07	7.73			
Literature review	1	0.08	9.00	1	0.00	6.00
No analysis (theory-based)	13	0.18	5.57			
What setting is guidance relevant to?						
All income levels (not country specific)	3	0.00	1.00			
High income settings	27	0.23	7.96	14	0.10	5.24
LMIC settings	1	0.00	1.80			
Is guidance targeted towards a specific costing purpose?						
Economic evaluation / priority setting	30	0.21	7.14	14	0.10	5.24
Purpose not specified / multiple purposes	1	0.00	5.59			
Is guidance widely accessible?						
Not open access	31	0.14	7.09	13	0.09	5.19
Open access or grey literature				1	0.00	6.00

Supplementary Table 7-8 Reporting

	Number of references	General Mean methodological citations per year	Mean total citations per year
What kind of guidance exists?			
Methodological papers on one aspect of costing	2	0.03	3.26
Does any analysis underlie guidance?			
Literature review	2	0.03	3.26
What setting is guidance relevant to?			
All income levels (not country specific)	1	0.07	4.27
High income	1	0.00	2.25
Is guidance targeted towards a specific costing purpose?			
Economic evaluation / priority setting	2	0.03	3.26
Is guidance widely accessible?			
Not open access	2	0.03	3.26

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SUPPLEMENTARY FILES FOR CHAPTER 8

Supplementary File 1: Glossary

Current income:

The amount earned by a person or household at any one given time. This can include: cash and non-cash earnings from productive activities; rental income from the supply of land, capital, or other assets; businesses; current transfers from government or non-government agencies or other households, and/or investments (O'Donnell and Wagstaff, 2008; Wai-Poi et al., 2008). Current income tends to be lumpy and can be seasonal or dependent on the local labour market. Current income does not reflect important assets (such as savings) that can be drawn upon to finance health care without affecting economic wellbeing within the household (Flores et al., 2008; O'Donnell and Wagstaff, 2008).

Permanent income:

The long-term average income expectations of a person and/or household (Friedman, 1957; Hall, 1978; Meghir, 2004). According to the permanent income hypothesis, households 'smooth' their income by spending less in times of high income and borrowing or drawing on savings in times of low income.

Consumption:

The resources actually consumed by a household, including: food items; non-food items; consumer durables; and housing. Consumption includes purchased items and items produced at home (e.g. food that is grown at home) (Deaton and Grosh, 1999; O'Donnell et al., 2007).

Consumption expenditure:

Money spent on goods and services consumed by the household (Howe et al., 2012). According to the permanent income hypothesis, consumption expenditure is a more accurate reflection of household living standards than current income (Friedman, 1957), as consumption stays relatively constant according to one's socio-economic status (Garvy, 1948).

Coping strategies:

A form of consumption smoothing, which allows households to manage the costs of financial shocks. For example, when faced with a minor illness, a household will typically cope by drawing upon its available resources to smooth the financial shock of illness,

reducing the impact on non-health spending and avoiding impoverishment (Wagstaff, 2008). There are a variety of methods that households can employ to cope with health shocks, either by generating cash to meet out of pocket payments, or through rearranging human or social capital to cope with indirect costs. Common coping strategies include: mobilizing savings, deferring expenditure, selling assets, taking loans, income diversification, taking on additional labour, or relying on gifts/mutual support networks (Bharadwaj, 2014; Goldman and Smith, 2001; Sauerborn et al., 1996). In addition, in many subsistence-based economies family members will fill in for a sick person during the planting season in agriculture (Su et al., 2007). Coping strategies can help households manage transitory shocks (Wagstaff, 2008), however consumption smoothing or other risk management mechanisms can break down under repeated shocks or long-term shocks (Alderman, 1996; Dercon, 2002). When households are unable to manage shocks through coping strategies, they might take more desperate adaptive measures - such as depleting productive assets, removing children from school, reducing consumption, sex work, begging, and crime - which can lead to an increased cycle of vulnerability (Alwang et al., 2001; Ilboudo et al., 2013; Sauerborn et al., 1996).

Direct costs:

Direct costs include any direct expenditures associated with illness, or with accessing care (Cooper and Rice, 1976; McIntyre et al., 2006; Rice, 1967). This includes direct medical costs (for example money paid for medicines, diagnostics, consultation fees, or informal payments made to health workers) and direct non-medical costs (for example transport costs to attend a health facility, accommodation costs whilst seeking care, costs of any special foods or supplements taken as a result of illness, or costs of childcare).

Indirect costs:

Indirect costs refer both to the opportunity costs of time spent by the patient and household members in seeking care (e.g. travel time, waiting time, and time in consultations), time spent by household members who provide informal care for the patient, and time spent unproductive as a result of illness (McIntyre et al., 2006).

Productivity costs:

Productivity costs are a subset of indirect costs, and refer to the time spent unproductive as a result of illness. Productivity costs are incurred in the form of absenteeism and presenteeism

Wealth:

The aggregate value of all household assets and holdings (Wai-Poi et al., 2008). Households use a variety of assets as wealth stores, and can invest in or draw on these investments in order to mitigate income shocks (Alwang et al., 2001; Scoones, 1998; Sen, 1981). The specific assets available to a household have been classified in the literature differently depending on the framework (Bebbington, 1999; Moser, 1998; Scoones, 1998; Wallman and Baker, 1996), but often include: human capital (skills, good health and ability to labour, ability to pursue livelihoods), natural capital (land, water, environmental resources), physical capital (basic infrastructure of housing, water, transport, electricity), financial capital (savings, credit, pensions etc. which produce livelihood options), and social capital (networks, associations, institutions on which people can draw) (Scoones, 1998). Households can store, accumulate, exchange, deplete, or put these assets to work in their day to day management of risk and generation of income (Rakodi, 1999).

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Supplementary File 2: Data Collection Questionnaire

Data collection questionnaires are available freely online here:

https://www.sciencedirect.com/science/article/pii/S0277953618304738#mmc2

Supplementary File 3: Detailed costs for included and excluded participants

Supplementary Table 8-9 Total costs for patients included and excluded from analysis

	Participants included in analysis (n = 66)			Participants excluded due to missing income data (n = 33)		
	Average Number Visits	Average Direct Medical Cost	Average Direct Non-Medical Cost	Average Number Visits	Average Direct Medical Cost	Average Direct Non-Medical Cost
Study clinic	12.98	$0.00	$27.32	14.15	$0.00	$35.64
Other clinic	0.12	$0.00	$0.31	0.24	$0.00	$0.97
Pharmacy	1.44	$4.60	$0.86	0.55	$1.49	$0.92
General practitioner	0.35	$7.56	$0.86	0.18	$2.51	$0.92
Hospital-inpatient	0.12	$0.80	$4.49	0.18	$5.94	$2.56
Traditional healer	0.21	$8.95	$0.69	0.33	$35.54	$0.78
Specialist	0.57	$0.57	$1.19	0.25	$0.25	$0.39
Radiologist	0.00	$0.00	$0.88	0.00	$0.00	$1.16
DOTS	0.00	$0.00	$0.00	0.00	$0.00	$0.00
Total	**15.80**	**$22.48**	**$36.60**	**15.89**	**$45.73**	**$43.33**

Supplementary file 4: MCA Results

Supplementary Table 8-10 MCA Results

	TBFT Dataset Frequency	NIDS Dataset Frequency	Dimension 1 Coordinates	Contribution
Assets				
Stove				
Owns a stove	86%	16%	1.05	1.1%
Does not own a stove	14%	84%	-0.20	0.2%
Satellite television				
Owns a satellite television	38%	30%	1.75	5.9%
Does not own a satellite television	62%	70%	-0.77	2.6%
DVD player				
Owns a DVD player	71%	36%	1.19	3.2%
Does not own a DVD player	29%	64%	-0.66	1.7%
Motor car				
Owns a motor car	18%	18%	2.11	5.0%
Does not own a motor car	82%	82%	-0.46	1.1%
Radio				
Owns a radio	77%	63%	0.44	0.7%
Does not own a radio	23%	37%	-0.74	1.3%
Television				
Owns a television	87%	80%	0.54	1.5%
Does not own a television	13%	20%	-2.24	6.1%
Computer				
Owns a computer	17%	16%	2.20	4.9%
Does not own a computer	83%	84%	-0.43	1.0%
Refrigerator				
Owns a refrigerator	82%	76%	0.64	2.0%
Does not own a refrigerator	18%	24%	-2.08	6.3%
Cell phone				
Owns a cell phone	97%	89%	0.20	0.2%
Does not own a cell phone	3%	11%	-1.63	1.8%
Bicycle				
Owns a bicycle	11%	8%	1.76	1.5%
Does not own a bicycle	89%	92%	-0.15	0.1%
Washing machine				
Owns a washing machine	36%	33%	1.83	6.9%
Does not own a washing machine	64%	67%	-0.91	3.5%
Toilet type				
Flush toilet with onsite disposal (septic tank / soak-away)	54%	28%	1.31	2.9%
Flush toilet with offsite disposal	3%	23%	1.03	1.5%
Chemical toilet	0%	2%	-1.38	0.3%

Pit latrine with ventilation pipe (VIP)	16%	16%	-1.26	1.6%
Pit latrine without ventilation pipe	25%	25%	-0.93	1.3%
Bucket toilet	0%	3%	-1.54	0.5%
None	1%	3%	-2.67	1.4%
Other	0%	0%	-1.53	0.0%
Main Walls Material				
Mud	0%	4%	-2.89	1.9%
Mud / cement	6%	7%	-2.77	3.2%
Corrugated iron / zinc	17%	9%	-1.22	0.8%
Prefab / wood	0%	1%	-0.50	0.0%
Bare	14%	77%	0.54	1.4%
Plaster / finished	60%	1%	0.19	0.0%
Other	2%	1%	-1.10	0.1%
Main Floors Material				
Natural floor (earth / sand / dung)	8%	9%	-2.35	3.2%
Rudimentary floor (bare wood planks)	0%	39%	-0.68	1.1%
Finished floor (parquet / polished / tiles / cement / carpet)	92%	52%	0.91	2.7%
Dwelling Type				
Dwelling/house on a separate stand or yard or on farm	73%	72%	0.53	1.3%
Traditional dwelling / hut made of traditional materials	1%	12%	-2.44	4.3%
Flat or apartment in a block of flats	1%	2%	0.67	0.1%
Town / cluster / semi-detached house (simplex, duplex)	0%	1%	1.20	0.1%
Dwelling / house / flat / room in backyard	6%	3%	0.33	0.0%
Informal dwelling / shack in backyard	14%	4%	-1.14	0.3%
Informal dwelling / shack in informal/ squatter settlement	4%	5%	-1.62	0.8%
Room/flat let	2%	1%	-0.55	0.0%
Caravan/tent	0%	0%	0.03	0.0%
Other (specify)	0%	0%	-0.65	0.0%
Source of water				
Piped inside dwelling	37%	39%	1.40	4.8%
Piped inside yard	44%	30%	-0.15	0.0%
Piped inside community stand	14%	17%	-1.53	2.5%
No access to piped water	1%	3%	-1.74	0.5%
Borehole	2%	2%	-0.69	0.1%
Open source	2%	7%	-2.32	2.3%
Other	0%	1%	-1.55	0.2%

Supplementary Table 8-11 Quintile results from MCA

NIDS quintile	Number Households (TBFT Dataset)	Number Households (NIDS Dataset)	Mean annual permanent income per household	Standard Error	95% Confidence Interval
Quintile 1	9	5,007	$193.30	3.89	$185.68 - $200.93
Quintile 2	9	4,869	$263.30	4.42	$254.63 - $271.96
Quintile 3	35	4,674	$339.23	4.84	$329.75 - $348.72
Quintile 4	24	4,272	$501.82	14.58	$473.25 - $530.4
Quintile 5	22	4,418	$1,109.88	17.46	$1,075.66 - $1,144.11

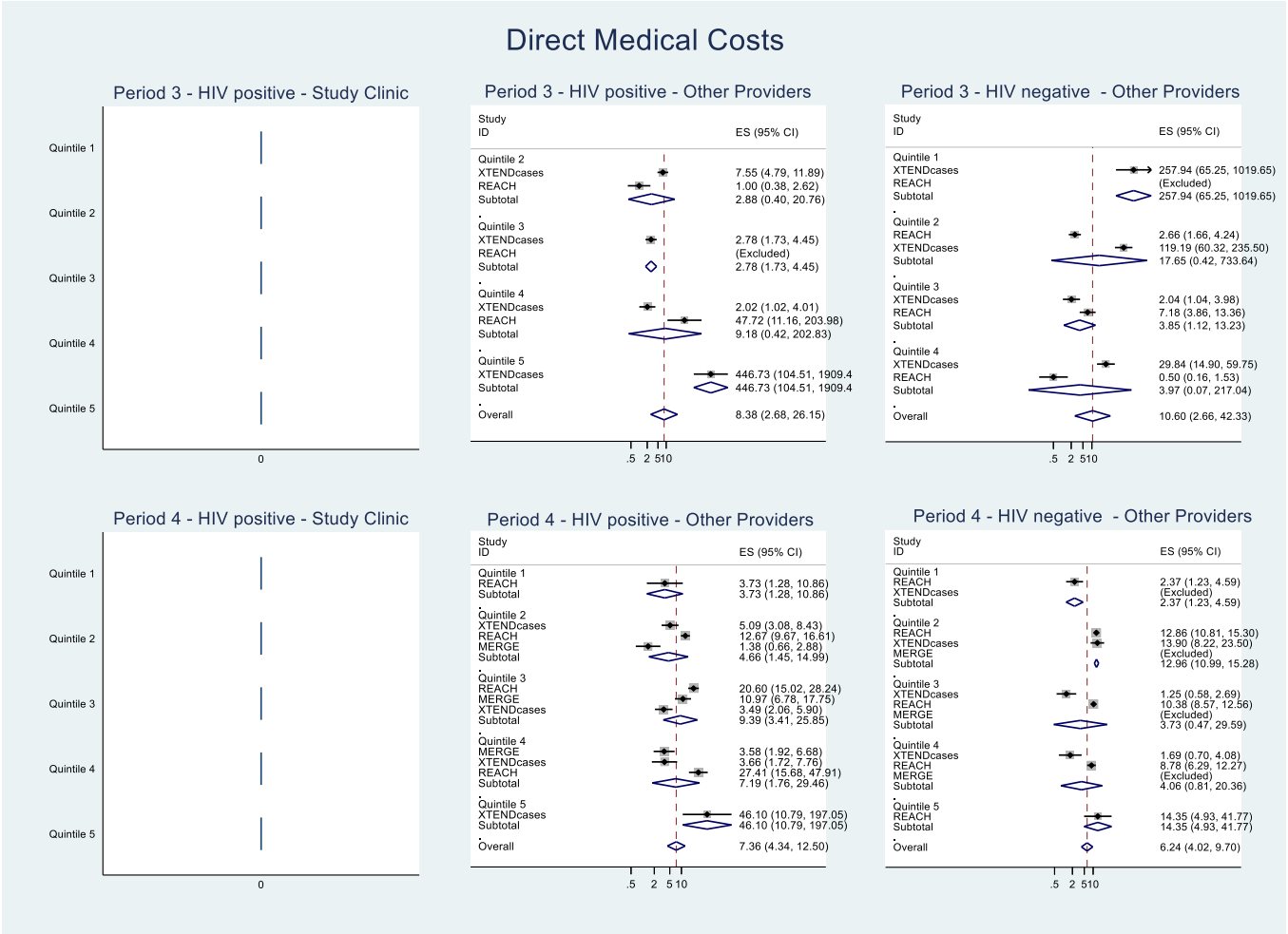
SUPPLEMENTARY FILES FOR CHAPTER 9

Appendix 1: Supplementary Tables and Figures

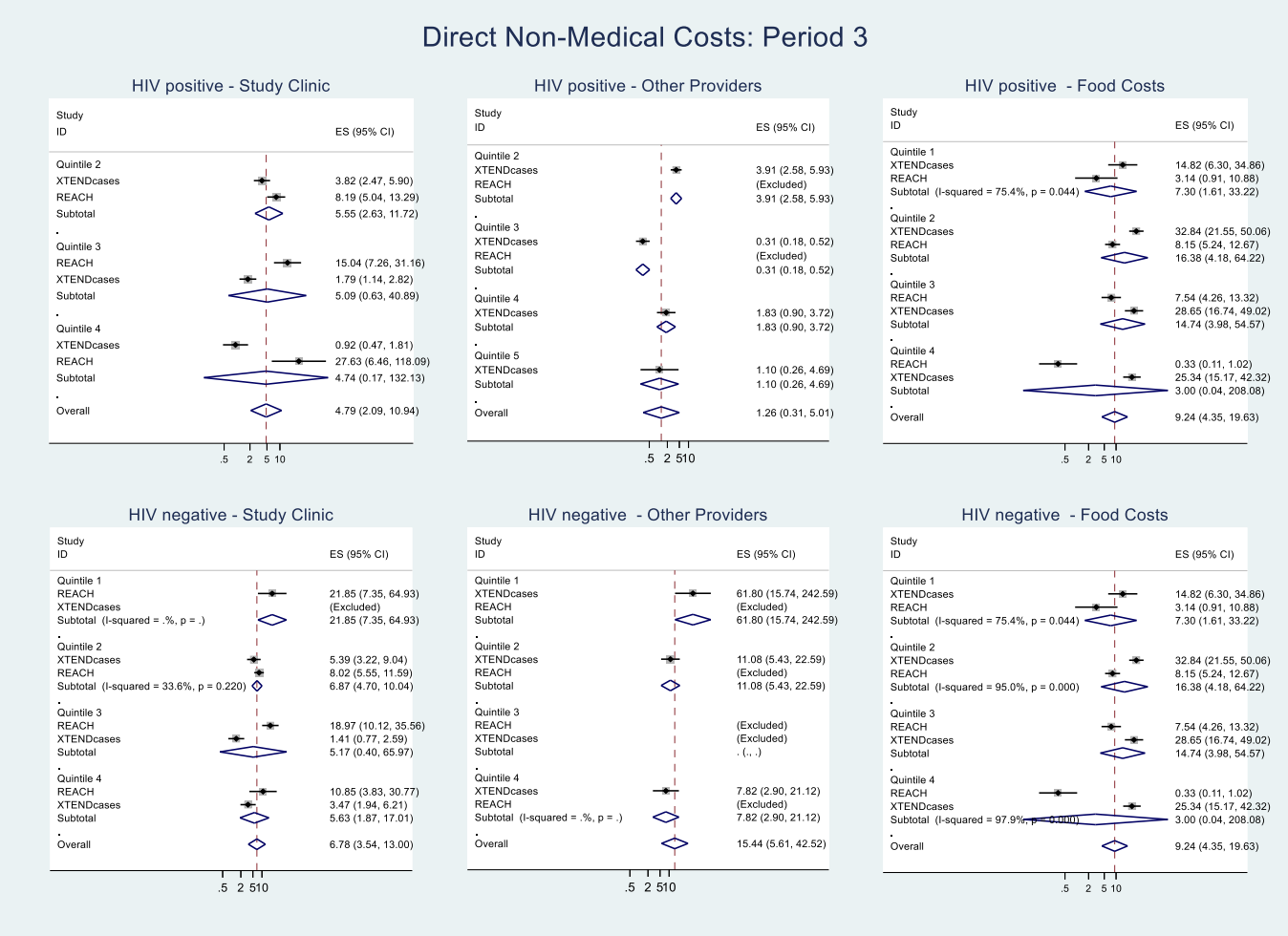
Supplementary Table 9-1 Details of studies identified as relevant for analysis

Study	Study Name	Provinces	Number MDR-TB patients	Number DS TB patients	Included in analysis?
Fairall (2010)		Free State	0	1,999	No
Van Rie (2013)		Johannesburg	0	199	No
Du Toit (2015)		Cape Town	153	0	No
Ramma (2015)		Cape Town	134	0	No
Chimbindi (2015)	REACH	KwaZulu-Natal, Gauteng, Mpumalanga	0	1,219	Yes
Foster (2015)	XTEND	Gauteng, Mpumalanga, Eastern Cape, Free State	0	171 (cases); 35 (suspects)	Yes
Mudzengi (2016)	MERGE	Gauteng	0	148	Yes

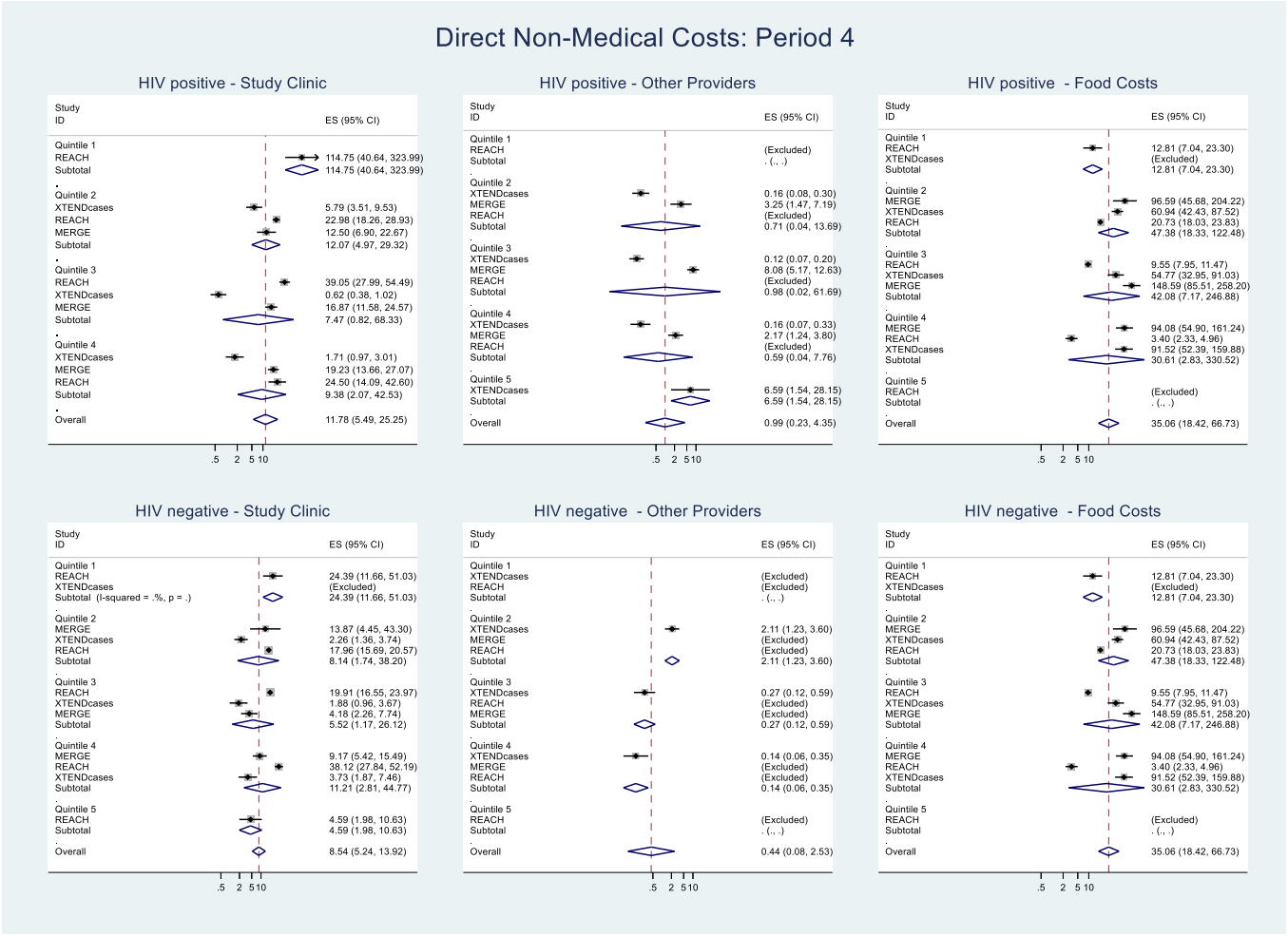
Supplementary Figure 9-2 Meta-analysis results: direct medical costs (Periods 3 and 4)



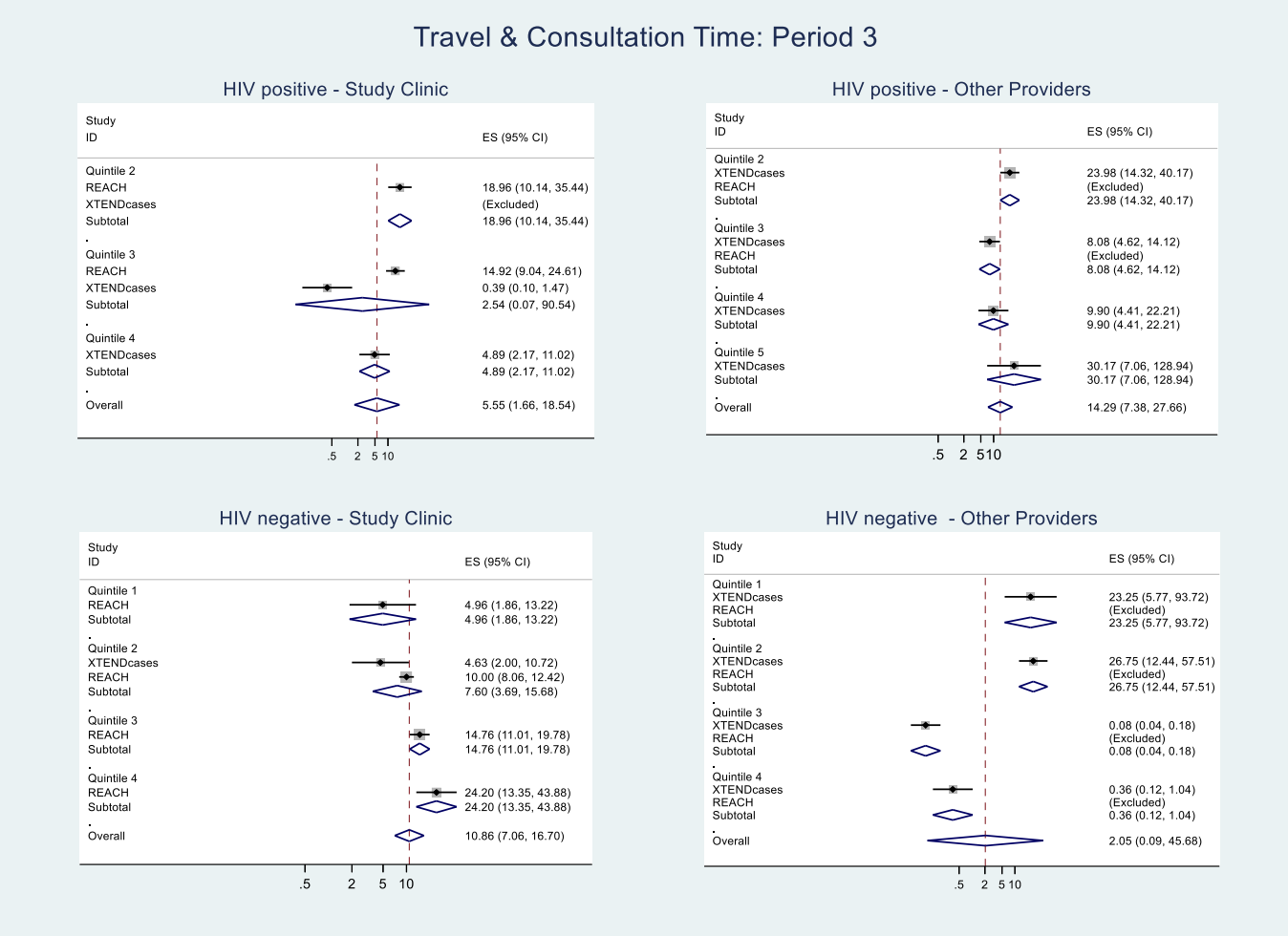
Supplementary Figure 9-3 Meta-analysis results: direct non-medical costs (Period 3)



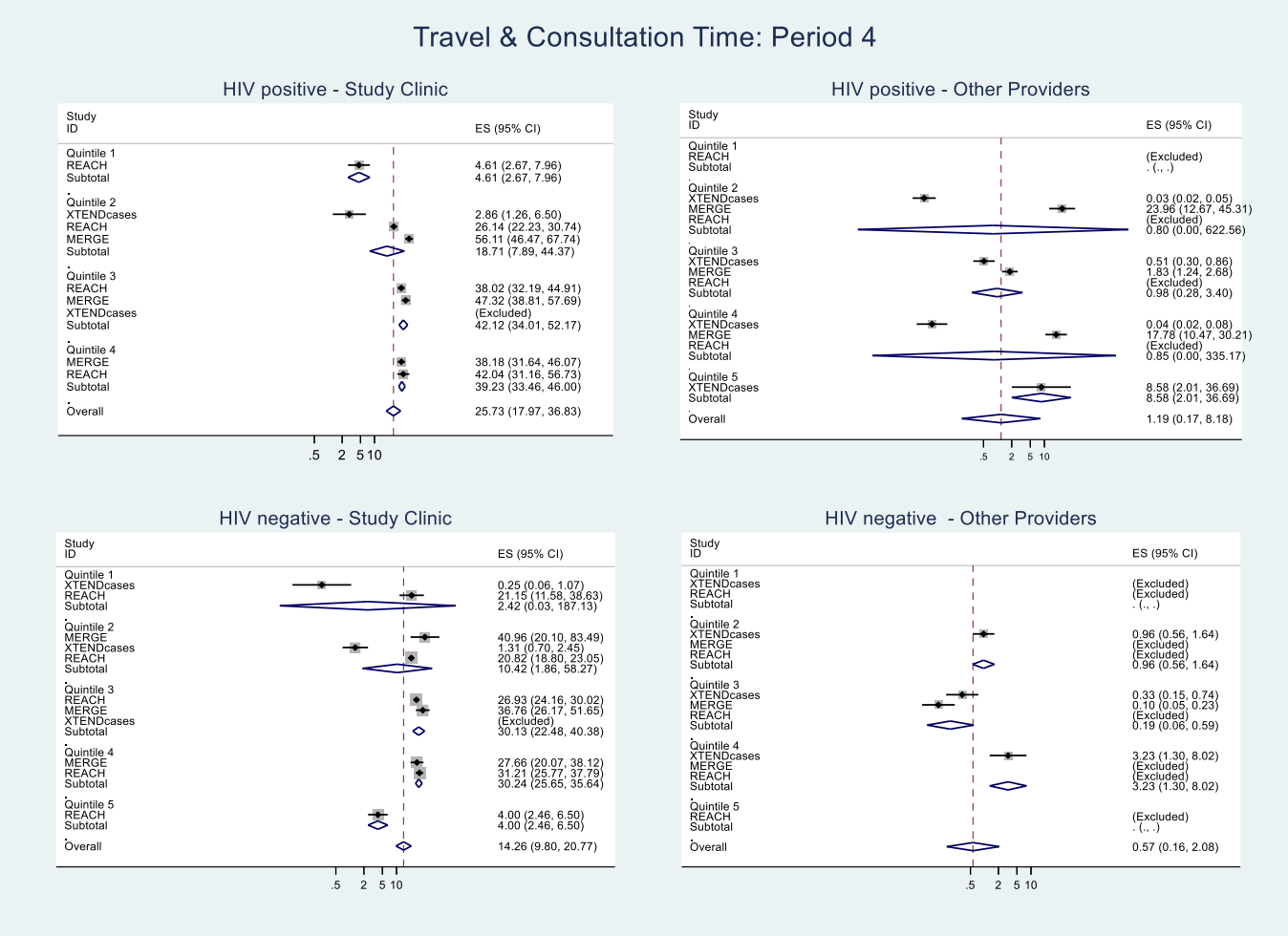
Supplementary Figure 9-4 Meta-analysis results: direct non-medical costs (Period 4)



Supplementary Figure 9-5 Meta-analysis results: travel and consultation time (Period 3)



Supplementary Figure 9-6 Meta-analysis results: travel and consultation time (Period 4)



Supplementary Table 9-2 Unimputed regression results by dataset

	Total travel and consultation time (study clinic & other providers)				Direct medical costs (study clinic & other providers)			
	MERGE	**XTEND**	**REACH**	**Pooled dataset**	**MERGE**	**XTEND**	**REACH**	**Pooled dataset**
Constant	3.660*** (0.27)	-0.57 (1.52)	2.732*** (0.25)	2.622*** (0.25)	-10.97 ((.))	-4.04 (4.04)	0.87 (0.79)	0.82 (0.80)
HIV Positive	0.557** (0.17)	-0.18 (0.49)	0.17 (0.09)	0.171* (0.08)	26.41 (2096.90)	-6.47 (19.84)	0.42 (0.28)	0.22 (0.24)
Rural		-0.61 (0.51)	1.118*** (0.09)	1.189*** (0.09)		-7.32 (19.74)	-0.916** (0.30)	-1.071*** (0.29)
Grade > 8	0.10 (0.22)	0.47 (0.47)	-0.210* (0.08)	-0.165* (0.08)	-17.82 (2096.90)	12.61 (39.50)	0.22 (0.27)	0.17 (0.25)
Employed	0.28 (0.17)	-0.78 (0.45)	0.05 (0.11)	0.08 (0.09)	20.37 (2096.90)	-0.29 (0.99)	0.08 (0.35)	0.01 (0.29)
Quintile								
Quintile 2		2.26 (1.57)	-0.17 (0.26)	-0.16 (0.26)		5.74 (3.82)	1.636* (0.82)	1.728* (0.83)
Quintile 3	-0.39 (0.23)	1.67 (1.59)	-0.37 (0.28)	-0.39 (0.27)	-15.18 (2096.90)	6.15 (3.71)	2.051* (0.87)	2.198* (0.87)
Quintile 4	-0.572* (0.28)	1.95 (1.74)	-0.33 (0.30)	-0.40 (0.29)	-16.83 (2096.90)	-0.64 (20.13)	2.011* (0.93)	1.877* (0.90)
Quintile 5		3.82 (2.48)	-2.304*** (0.56)	-2.170*** (0.53)		9.34 ((.))	2.41 (1.77)	3.03 (1.67)
N	146	172	1050	1368	146	172	1050	1368
AIC	1447.1	679.3	8399.1	11006.3	1473.8	599.7	7234.2	8992.6

Standard errors in parentheses; * p<0.05, ** p<0.01, *** p<0.001

Supplementary Table 9-2 Unimputed regression results by dataset (continued)

	Direct non-medical costs (study clinic & other providers)				Direct non-medical costs (special foods)			
	MERGE	**XTEND**	**REACH**	**Pooled dataset**	**MERGE**	**XTEND**	**REACH**	**Pooled dataset**
Constant	1.749** (0.58)	2.886* (1.43)	3.680*** (0.60)	3.745*** (0.61)	4.505*** (0.46)	3.616*** (0.79)	2.224** (0.75)	2.511*** (0.61)
HIV Positive	1.084** (0.42)	-0.02 (0.42)	0.38 (0.21)	0.14 (0.19)	0.630* (0.30)	0.796** (0.25)	-0.16 (0.31)	1.408*** (0.20)
Rural		-1.955*** (0.48)	0.10 (0.21)	0.07 (0.21)		-1.013*** (0.27)	-2.829*** (0.32)	-0.900*** (0.23)
Grade > 8	-0.24 (0.60)	0.26 (0.43)	0.13 (0.21)	0.08 (0.20)	0.06 (0.39)	-0.06 (0.28)	0.781* (0.30)	0.515* (0.21)
Employed	1.035** (0.37)	-0.52 (0.46)	0.25 (0.26)	0.10 (0.22)	0.02 (0.27)	0.23 (0.24)	0.20 (0.38)	0.728** (0.22)
Quintile								
Quintile 2		-0.95 (1.45)	-0.97 (0.62)	-1.01 (0.63)		0.60 (0.84)	0.80 (0.79)	0.31 (0.64)
Quintile 3	-0.24 (0.63)	-1.69 (1.54)	-0.90 (0.66)	-0.97 (0.67)	0.15 (0.42)	0.92 (0.90)	0.93 (0.85)	0.41 (0.68)
Quintile 4	-0.18 (0.68)	-0.48 (1.60)	-0.50 (0.72)	-0.79 (0.71)	0.43 (0.46)	1.41 (0.93)	0.00 (0.91)	0.97 (0.72)
Quintile 5		1.24 (2.35)	-2.633* (1.33)	-2.42 (1.27)		1.13 (1.37)	-68.32 ((.))	-1.07 (1.30)
N	146	172	1050	1368	140	170	1050	1360
AIC	1093.2	542.1	8582.4	10871.8	1766	1860.2	5864.8	12066.7

Standard errors in parentheses; * p<0.05, ** p<0.01, *** p<0.001

Supplementary Table 9-3 Data points imputed

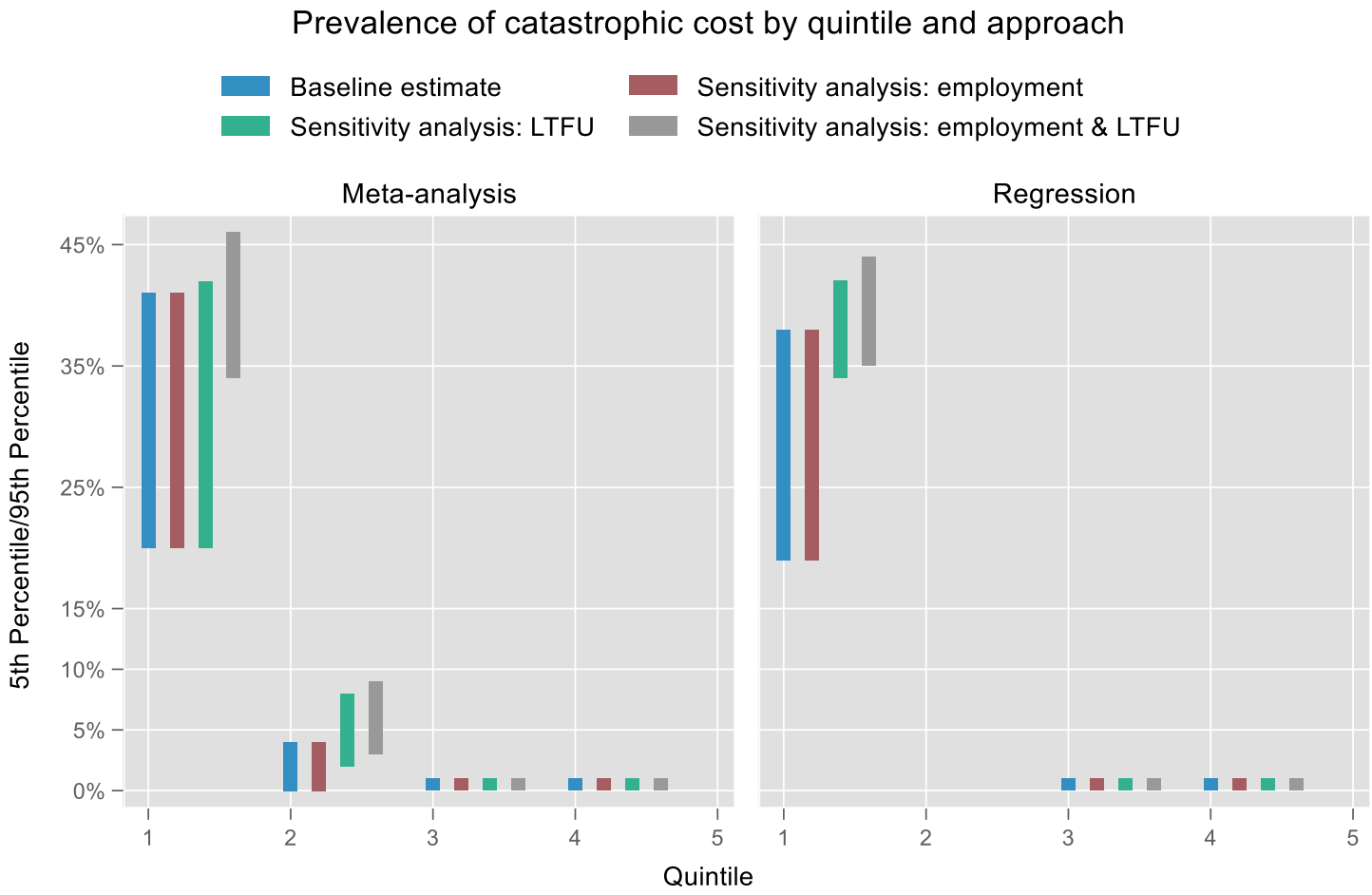
		Period 3			Period 4		
Provider	**Variable**	**Number Imputed (%)**	**Observed Mean (95% Conf Interval)**	**Imputed Mean (95% Conf Interval)**	**Number Imputed (%)**	**Observed Mean (95% Conf Interval)**	**Imputed Mean (95% Conf Interval)**
Study Clinic	direct medical cost	0 (0%)	0.00 (0.00 - 0.00)	0.00 (. - .)	0 (0%)	0.00 (0.00 - 0.00)	0.00 (. - .)
	direct non-medical cost	1277 (83%)	6.63 (0.00 - 353.64)	7.19 (5.07 - 9.31)	231 (15%)	20.29 (0.00 - 1237.76)	20.18 (16.61 - 23.76)
	travel hours	1273 (83%)	3.26 (0.00 - 44.00)	3.46 (2.93 - 3.99)	307 (20%)	13.10 (0.00 - 234.67)	12.80 (11.69 - 13.91)
	consult hours	1427 (93%)	6.50 (0.00 - 33.00)	6.39 (5.57 - 7.22)	424 (28%)	13.02 (0.00 - 186.00)	12.37 (11.51 - 13.23)
Pharmacy	direct medical cost	1266 (82%)	1.67 (0.00 - 241.48)	2.02 (0.61 - 3.43)	175 (11%)	1.88 (0.00 - 241.12)	1.87 (1.23 - 2.51)
	direct non-medical cost	1274 (83%)	0.17 (0.00 - 8.78)	0.34 (0.21 - 0.46)	252 (16%)	0.01 (0.00 - 3.29)	0.09 (0.06 - 0.13)
	travel hours	1274 (83%)	0.02 (0.00 - 1.00)	0.04 (0.03 - 0.06)	249 (16%)	0.02 (0.00 - 4.22)	0.05 (0.03 - 0.07)
	consult hours	1274 (83%)	0.03 (0.00 - 2.00)	0.06 (0.03 - 0.08)	249 (16%)	0.02 (0.00 - 2.56)	0.04 (0.03 - 0.06)
GP	direct medical cost	1262 (82%)	7.45 (0.00 - 878.09)	8.12 (2.99 - 13.24)	173 (11%)	5.11 (0.00 - 502.34)	5.36 (3.87 - 6.85)
	direct non-medical cost	1272 (83%)	0.63 (0.00 - 32.93)	0.51 (0.31 - 0.72)	247 (16%)	0.98 (0.00 - 241.48)	6.47 (4.18 - 8.77)
	travel hours	1274 (83%)	0.07 (0.00 - 3.00)	0.07 (0.05 - 0.09)	247 (16%)	0.09 (0.00 - 12.00)	0.33 (0.06 - 0.59)
	consult hours	1272 (83%)	0.11 (0.00 - 3.00)	0.12 (0.08 - 0.16)	247 (16%)	0.07 (0.00 - 6.00)	0.25 (0.14 - 0.36)
Inpatient Hospital	direct medical cost	1262 (82%)	6.35 (0.00 - 790.28)	5.81 (-1.77 - 13.38)	171 (11%)	0.44 (0.00 - 100.56)	0.43 (0.19 - 0.67)
	direct non-medical cost	1271 (83%)	1.93 (0.00 - 155.86)	1.18 (0.01 - 2.34)	214 (14%)	0.81 (0.00 - 93.30)	1.01 (0.69 - 1.32)
	travel hours	1268 (82%)	0.09 (0.00 - 5.00)	0.04 (0.01 - 0.07)	215 (14%)	0.09 (0.00 - 5.00)	0.11 (0.07 - 0.14)
	consult hours	1267 (82%)	13.11 (0.00 - 480.00)	7.76 (2.26 - 13.26)	211 (14%)	4.94 (0.00 - 224.00)	5.01 (3.36 - 6.65)
Outpatient Hospital	direct medical cost	1262 (82%)	2.35 (0.00 - 351.24)	2.40 (0.41 - 4.39)	171 (11%)	0.31 (0.00 - 50.23)	0.31 (0.13 - 0.48)
	direct non-medical cost	1270 (83%)	0.95 (0.00 - 65.86)	0.59 (0.18 - 1.01)	204 (13%)	0.37 (0.00 - 58.54)	0.91 (0.55 - 1.27)
	travel hours	1263 (82%)	0.02 (0.00 - 1.33)	0.01 (0.00 - 0.02)	205 (13%)	0.08 (0.00 - 8.00)	0.15 (0.10 - 0.21)
	consult hours	1268 (82%)	0.27 (0.00 - 7.00)	0.16 (0.08 - 0.24)	205 (13%)	0.19 (0.00 - 17.33)	0.33 (0.22 - 0.45)
Traditional Healer	direct medical cost	1265 (82%)	2.16 (0.00 - 439.05)	1.04 (-0.19 - 2.27)	173 (11%)	3.31 (0.00 - 502.34)	3.39 (1.77 - 5.00)
	direct non-medical cost	1266 (82%)	0.52 (0.00 - 65.86)	0.14 (-0.11 - 0.39)	210 (14%)	0.07 (0.00 - 21.95)	0.31 (0.12 - 0.51)
	travel hours	1266 (82%)	0.01 (0.00 - 1.00)	0.01 (0.00 - 0.02)	210 (14%)	0.01 (0.00 - 3.00)	0.04 (0.02 - 0.07)
	consult hours	1266 (82%)	0.02 (0.00 - 1.00)	0.01 (0.00 - 0.02)	210 (14%)	0.07 (0.00 - 13.17)	0.30 (0.20 - 0.40)
Food Supplements		1272 (83%)	22.41 (0.00 - 548.81)	19.85 (16.36 - 23.34)	1272 (83%)	44.03 (0.00 - 1756.19)	43.24 (36.51 - 49.97)

Supplementary Table 9-4 Regression coefficients for cost estimates (regression approach)

	Direct medical costs (study clinic & other providers)		Direct non-medical costs (study clinic & other providers)		Direct non-medical costs (special foods)		Total travel and consultation time (study clinic & other providers)	
	Period 3 Coeff (Std Err)	Period 4 Coeff (Std Err)	Period 3 Coeff (Std Err)	Period 4 Coeff (Std Err)	Period 3 Coeff (Std Err)	Period 4 Coeff (Std Err)	Period 3 Coeff (Std Err)	Period 4 Coeff (Std Err)
Constant	3.88*** (1.01)	1.04 (0.81)	3.11*** (0.54)	3.70*** (0.49)	2.30*** (0.57)	2.48*** (0.58)	2.69** (0.83)	2.69*** (0.28)
HIV positive	-0.44 (0.64)	0.21 (0.23)	-0.22 (0.29)	0.10 (0.16)	0.92** (0.28)	1.37*** (0.20)	0.41 (0.24)	0.28** (0.09)
Rural	-0.70 (0.61)	-1.05*** (0.28)	-0.64* (0.26)	-0.10 (0.17)	-1.43*** (0.33)	-0.88*** (0.23)	0.74** (0.24)	0.89*** (0.10)
Grade ≥ 8	-0.19 (0.61)	0.18 (0.24)	-0.53 (0.31)	0.11 (0.17)	-0.21 (0.23)	0.47* (0.20)	0.04 (0.21)	-0.06 (0.09)
Employed	1.88** (0.59)	0.02 (0.28)	0.66* (0.30)	0.02 (0.19)	0.86** (0.26)	0.74** (0.22)	0.46 (0.34)	0.03 (0.11)
Quintile *(ref: Q1)*								
Quintile 2	-1.54 (1.17)	1.52 (0.83)	-0.41 (0.59)	-0.51 (0.51)	0.48 (0.63)	0.37 (0.61)	-0.40 (0.84)	0.21 (0.30)
Quintile 3	-2.04 (1.23)	1.98* (0.87)	-0.29 (0.62)	-0.39 (0.55)	0.95 (0.73)	0.48 (0.65)	-0.97 (0.84)	0.02 (0.33)
Quintile 4	-1.83 (1.61)	1.65 (0.90)	-0.32 (0.76)	-0.28 (0.57)	1.44 (0.82)	1.03 (0.69)	-1.20 (0.88)	0.00 (0.35)
Quintile 5	0.78 (2.43)	2.82 (1.60)	0.21 (1.42)	0.33 (1.09)	1.76 (1.47)	-1.01 (1.24)	-1.17 (1.46)	-1.14 (0.60)
N	1,539	1,539	1,539	1,539	1,539	1,539	1,539	1,539
F statistic	2.52*	2.36*	2.42*	0.45	5.37***	10.35***	2.30*	14.67***

* $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

Supplementary Figure 9-7 Model sensitivity analysis results



Appendix 2: Methods for estimating income

This supplementary appendix describes in further detail methods for the regression used to predict income for the analysis presented in Chapter 9.

Constructing the Asset Index

We first constructed an asset index using information on housing quality and ownership of durable assets (1). The asset index was designed to reflect the relative socio-economic standing of households within South Africa as a whole, rather than the relative SES of households within the pooled dataset alone. We therefore used the South African National Income Dynamics Survey (NIDS) to draw weights for an asset index (2).

Vyas and Kumaranayake (3) recommend a principal components analysis (PCA) approach to estimate a wealth index, however, PCA was designed for use with continuous, normally-distributed variables and therefore its application to the categorical variables in a wealth index is considered by some to be inappropriate (4,5). MCA is analogous to PCA but is designed for use with discrete data and was more appropriate to the type of asset data available in the dataset.

Inclusion of variables for the MCA model was tested before model finalization. The final model for the MCA included indicator variables for dwelling type, source of water, toilet type, main wall materials, and ownership of a number of durable assets including: a DVD player, a car, a radio, a television, a refrigerator, a cell phone, and a bicycle. Exploration with the MCA model indicated that inclusion of indicators of ownership of livestock and donkeys reduced the quality of the model rather than improved it; these were therefore left out of the final model. The MCA was conducted separately for rural and urban households, as asset ownership and inequality tend to be different in rural and urban areas (6).

The first dimension from the MCA explained 62.5% of variation in the dataset for rural households, and 73.4% of variation for urban households. Dimension weights were predicted using the Stata 'predict' command; dimension weights are listed in Table 1. Weights were largely positive for ownership of durable goods and indicators of high-quality housing (e.g. flush to sewage toilet, piped water inside dwelling), and negative for indicators of poor housing (e.g. no access to piped water, bucket toilet). Households in the NIDS dataset were classified into five socio-economic groups through splitting the dimension weight into five quintiles.

Coding for asset variables from the pooled dataset was then mapped to coding for the same questions from the NIDS, and weights from the MCA were applied to asset data in the pooled dataset. Using MCA weights, the position of households from the pooled dataset in the country-level SES quintiles were interpolated to reflect nationally-representative socio-economic quintile. The total number of households per quintile for each dataset is detailed in Table 9-1 in the main paper.

Regression to predict income

We then used data from the NIDS dataset to predict coefficients for a number of demographic factors on household income and individual income.

Both household and individual income data were heavily right-skewed. In planning the regression we tested two regression approaches which have been recommended as appropriate for non-normally distributed data: a generalized linear model (GLM) with a gamma distribution and log link, and a quantile regression model (7).

Both regression models for household income were fit on covariates that are commonly included as determinants of income: urbanicity (1 = rural), gender (1 = female), education level (1 = educated to grade 8 and above), marital status (1 = married or cohabitating), employment status (1 = employed); asset quintile (quintiles 1-5, as described above), age group (1 = age 15-29; 2 = age 30-45; 3 = age > 45) and province. Following evidence that the burden of TB falls overwhelmingly on those with lower socioeconomic status (8,9), TB status (1 = current TB) was also included as a covariate in both regression models and the quantile regression model was fit on the log of household income at the 25^{th} quantile. Both regression models incorporated survey weights from the NIDS study calibrated to the corresponding population totals as given in the mid-year population estimates released in 2015 (10).

Robust standard errors were estimated in the quantile regression models to account for skewed data. Normality of residuals for both quantile regression and GLM models were tested using the Shapiro-Wilk normality test. The goodness of fit for a GLM is generally tested using the Akaike information criterion (AIC) and no R^2 is reported for a GLM; direct comparison of the predictive power between the two models is therefore difficult. We report the pseudo R^2 for the quantile regression model and AIC for the GLM.

Regression coefficients for both regression approaches (quintile and GLM) to estimate individual and household income are listed in Supplementary Table 9-5. Coefficients for

most covariates were significant, and there was little difference in coefficients across the two approaches. Tests after the quantile regression indicate that coefficients varied significantly across quantiles, suggesting that the quantile regression approach was more appropriate than the GLM approach. Supplementary Figure 9-7 shows the predicted coefficients for each covariate across quintiles. However, the predictive power for the quantile regression approach as indicated by the Pseudo R2 was relatively low (0.18), and the Shapiro-Wilk test indicates that residuals for both approaches deviate significantly from a normal distribution.

Coefficients from both regression analyses were used to predict the income for patients in the pooled dataset, and correlation of predicted income and self-reported income variables were tested. Each dataset contained different self-reported income variables; correlation coefficients for predicted income and income data collected in each dataset is listed in Supplmentary Table 9-6. All correlation coefficients are relatively low; this is partly due to poor predictive power of the model, but also because most self-reported income variables were individual, whilst both regression approaches predicted household income. Most correlation coefficients were significant. There was relatively little difference in the size or significance of correlation coefficients between the quantile regression approach and the GLM approach.

The quantile regression approach was chosen as the best model, and income predictions using this model were used to classify households in the pooled analysis into nationally representative income quintiles.

Supplementary Table 9-12 MCA results

	Frequency by Dataset				Urban		Rural	
	AHRI	MERGE	XTEND	NIDS	Dimension 1 Coordinates	Contribution	Dimension 1 Coordinates	Contribution
Stove								
owns a Stove	36%	91%	82%	16%	0.72	0.01	1.18	0.02
does not own a Stove	64%	9%	18%	84%	-0.12	0.00	-0.20	0.00
DVD player								
owns a DVD player	45%	74%	63%	37%	0.92	0.03	1.54	0.05
does not own a DVD player	55%	26%	37%	63%	-0.62	0.02	-0.57	0.02
Motor car								
owns a Motor car	12%	19%	19%	19%	1.64	0.05	2.36	0.06
does not own a Motor car	88%	81%	81%	81%	-0.44	0.01	-0.32	0.01
Radio								
owns a Radio	75%	77%	80%	63%	0.49	0.01	0.53	0.02
does not own a Radio	25%	23%	20%	37%	-0.77	0.02	-0.86	0.02
Television								
owns a Television	69%	86%	84%	81%	0.49	0.02	0.84	0.04
does not own a Television	31%	14%	16%	19%	-2.37	0.08	-2.14	0.11
Refrigerator								
owns a Refrigerator	65%	69%	69%	77%	0.64	0.03	0.93	0.05
does not own a Refrigerator	35%	31%	31%	23%	-2.26	0.09	-1.91	0.10
Cell phone								
owns a cell phone	83%	99%	96%	90%	0.19	0.00	0.27	0.01
does not own a cell phone	17%	1%	4%	10%	-1.64	0.02	-1.82	0.04
Bicycle								
owns a Bicycle	9%	4%	8%	8%	1.65	1.65	1.65	1.65
does not own a Bicycle	91%	96%	92%	92%	-0.13	-0.13	-0.13	-0.13
Toilet type								
Flush to sewage	45%	70%	53%	29%	0.68	0.02	2.26	0.04
Flush to septic tank	2%	16%	1%	24%	0.28	0.00	1.72	0.02
Chemical	1%	3%	2%	2%	-2.99	0.01	-0.58	0.00
VIP	12%	3%	11%	15%	-1.79	0.01	-0.29	0.00
Pit without ventilation	27%	5%	31%	24%	-2.65	0.03	-0.07	0.00
Bucket	5%	1%	0%	3%	-3.21	0.02	-1.13	0.00
None	9%	1%	1%	3%	-4.04	0.03	-2.59	0.03
Other	0%	0%	1%	0%	-4.11	0.00	-0.44	0.00
Main Walls Material								
Mud	5%	1%	3%	3%	-3.65	0.01	-2.60	0.04
Mud/cement	6%	20%	6%	6%	-3.26	0.01	-2.32	0.05
Corrugated iron/zinc	15%	18%	10%	10%	-2.74	0.10	-1.13	0.01
Prefab/wood	6%	1%	1%	1%	-1.68	0.01	-1.25	0.00
Bare brick/cement blocks	25%	22%	78%	78%	0.71	0.03	0.76	0.04
Plaster/finished	42%	37%	1%	1%	0.61	0.00	-1.48	0.00
Other	1%	0%	1%	1%	-1.56	0.00	-1.74	0.00
Dwelling Type								

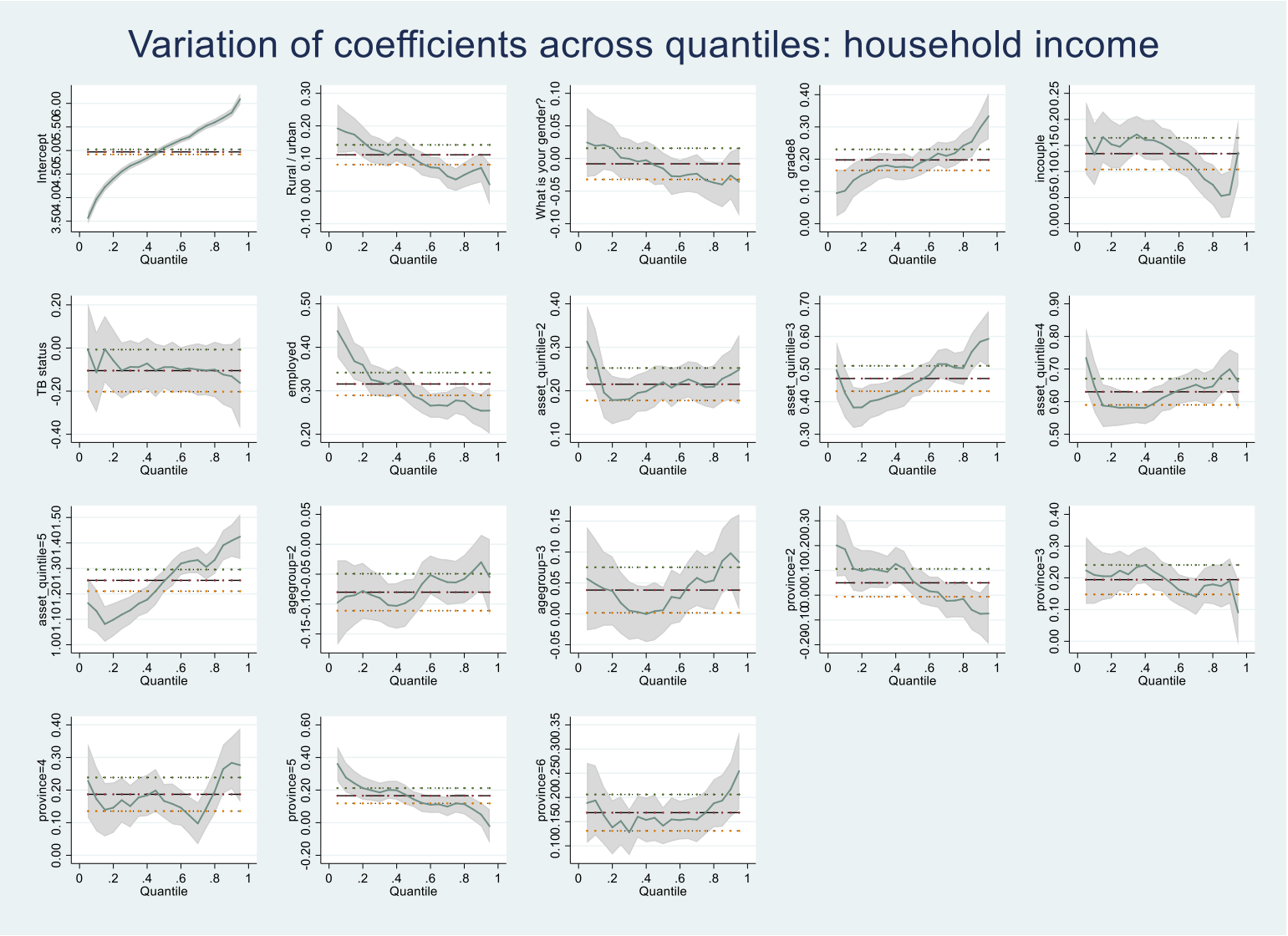
House/concrete block	51%	33%	61%	72%	0.77	0.03	0.73	0.03
Traditional	5%	0%	15%	11%	-1.46	0.00	-2.14	0.08
Flat	17%	3%	1%	2%	0.41	0.00	-0.25	0.00
Cluster house	1%	5%	0%	1%	0.82	0.00	0.23	0.00
backyard dwelling	6%	31%	2%	4%	0.07	0.00	0.15	0.00
Informal	10%	12%	14%	4%	-2.21	0.03	-1.72	0.01
Informal squatter	10%	10%	6%	6%	-3.39	0.09	-1.66	0.01
Room on property	0%	5%	2%	1%	-0.44	0.00	0.24	0.00
Caravan/tent	0%	1%	0%	0%	-0.49	0.00	-2.33	0.00
Other	0%	0%	0%	0%	-1.40	0.00	0.14	0.00
Source of water								
Piped inside dwelling	36%	30%	28%	41%	0.91	0.04	1.80	0.05
Piped inside yard	31%	55%	44%	31%	-0.58	0.01	0.55	0.01
Piped community stand	18%	14%	21%	16%	-3.70	0.09	-0.64	0.01
No access to piped water	1%	1%	2%	3%	-3.78	0.01	-0.87	0.00
Borehole	1%	0%	1%	2%	-3.97	0.00	0.29	0.00
Open source	7%	0%	3%	6%	-2.50	0.00	-1.94	0.04
Other	5%	0%	1%	1%	-4.03	0.01	-0.67	0.00

Supplementary Table 9-13 Regression coefficients for income prediction

	Quantile Regression (25^{th} quantile; Log)	GLM regression (gamma log)
Constant	4.26*** (0.06)	5.24*** (0.08)
Urban	0.15*** (0.04)	-0.01* (0.04)
Female	0.07* (0.03)	0.04* (0.03)
Educated ≥ grade 8	0.27*** (0.04)	0.31*** (0.04)
Married / cohabitating	0.21*** (0.04)	0.20*** (0.04)
Has TB	-0.28*** (0.04)	-0.27** (0.10)
Employed	0.33*** (0.03)	0.33*** (0.04)
Asset quintile (ref Q1)		
Quintile 2	0.20*** (0.04)	0.25*** (0.03)
Quintile 3	0.48*** (0.05)	0.57*** (0.04)
Quintile 4	0.73*** (0.04)	0.73*** (0.04)
Quintile 5	1.37*** (0.05)	1.66*** (0.06)
Age group (ref age 15-29)		
30-44	-0.09** (0.04)	-0.19*** (0.03)
45 and over	0.10* (0.05)	0.10* (0.05)
Province (ref: Eastern Cape)		
Free State	0.04* (0.07)	-0.19* (0.13)
Gauteng	0.26*** (0.05)	-0.09* (0.13)
Mpumalanga	0.13* (0.06)	0.13* (0.11)
Western Cape	0.26*** (0.05)	-0.08* (0.14)
KwaZulu-Natal	0.24*** (0.04)	0.10* (0.10)
N	16,396	16,396
Pseudo R2	0.18	
AIC		24947.96
Shapiro-Wilk test for normality of residuals	1.00***	0.97***

*** p < 0.001; ** p < 0.01; * p < 0.05

Supplementary Figure 9-8 Variation of regression coefficients across quantiles



Supplementary Table 9-14 Correlation coefficients for predicted and self-reported income

	Quantile Regression	GLM Regression
Self-reported individual income: symptom onset (collected in MERGE dataset)	0.42***	0.33***
Self-reported individual income: diagnosis (collected in MERGE dataset)	0.39***	0.29***
Self-reported individual income: intensive phase (collected in XTEND dataset)	0.24**	0.25***
Self-reported individual income: continuation phase (collected in XTEND dataset)	0.21**	0.23**
Self-reported household expenditure (collected in REACH dataset)	0.33***	0.34***

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

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