Bozzani, FM; (2021) Incorporating feasibility in priority setting: a case study of tuberculosis control in South Africa. PhD (research paper style) thesis, London School of Hygiene & Tropical Medicine. DOI: https://doi.org/10.17037/PUBS.04662736

DOI: https://doi.org/10.17037/PUBS.04662736

INCORPORATING FEASIBILITY IN PRIORITY SETTING: A CASE STUDY OF TUBERCULOSIS CONTROL IN SOUTH AFRICA

Fiammetta Maria Bozzani

Thesis submitted in accordance with the requirements for the degree of
Doctor of Philosophy of the University of London

JUNE 2021

Department of Global Health and Development

Faculty of Public Health and Policy

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

Funded by the Bill and Melinda Gates Foundation and Bloomsbury SET

DECLARATION OF ORIGINALITY

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

Signed: [redacted] Date: 1st June 2021

ABSTRACT

Priority setting for infectious disease control has evolved beyond simple descriptions of costs and consequences of single interventions. Applications of economic evaluation alongside disease transmission modelling now include user-friendly models, which account for setting-specific variations in input prices and epidemiological characteristics, as well as optimisation routines. These developments allow the straightforward assessment of the local cost-effectiveness of new health technologies and rankings of multiple intervention options.

At the same time, priority setting increasingly recognises that policymakers may be fulfilling multiple objectives alongside efficient resource allocation, such as pursuing equity in health outcomes, access to health care and financial protection, and that they are faced with a range of health system constraints in any given settings. These constraints may encompass physical input shortages on the supply side (e.g. lack of skilled human resources or disruptions in procuring supplies) and lack of uptake on the demand side (e.g. financial or other barriers such as hesitancy or stigma). Failure to take these into account can result in unfeasible health interventions being recommended and, ultimately, in economic evaluation evidence being disregarded.

Different methods for incorporating constraints in priority setting have been put forward, both within the traditional cost-effectiveness analysis framework and alongside it. All these methods present strengths and weaknesses in terms of how they deal with different types of constraints and priority setting contexts, as well as in the extent to which decisions are arrived at algorithmically or through a more deliberative process.

My PhD thesis was conceived during two years spent on a project advising the South African National Department of Health on tuberculosis (TB) control policy and implementation. In 2015, the South African Deputy President announced plans for a comprehensive TB screening programme to tackle one of the world’s worst TB epidemics driven by HIV. A key question was how to implement such a complex and costly intervention as intensified TB case-finding (ICF) at full scale in an over-stretched health system.

The aim of my thesis was therefore to explore and develop the methods for incorporating feasibility concerns, and specifically health systems constraints, in priority setting models both internally and externally to the traditional cost-effectiveness analysis framework, using priority setting around TB prevention and control in South Africa as a case study.

The first step was to carry out a systematic review of the literature on the possible ways to restrict disease transmission model outputs to account for health system constraints that affect the achievable coverage and outputs of disease control interventions. I then carried out an incremental micro-costing exercise of the TB control interventions that the South African Department of Health was considering for inclusion in the latest National TB Plan. The costing covered all the resources needed to deliver the intervention at scale, including the costs of the extra resources needed to relax health system constraints, such as hiring additional clinical staff and budgeting for additional diagnostic equipment. These constraints were identified in consultation with experts on the South African TB Think Tank.

Intervention costs were then attached to disease transmission model outputs to generate incremental cost-effectiveness ratios under three different scenarios: (1) without considering the constraints to implementation; (2) considering the constrains; and (3) including the costs of 'relaxing' the constraints to achieve unconstrained coverage. This exercise showed that the cost-effectiveness ranking of interventions is substantially affected by considering health system constraints. It also provided valuable information for policymakers on the practical feasibility of the proposed interventions.

Lastly, the use of group model building, a qualitative system dynamics modelling technique, was explored to elicit information on the health system constraints that apply to a given setting and set of interventions. This approach was found to be superior to the unstructured expert elicitation usually employed to generate unit cost and quantities assumptions in economic evaluation, as it takes into account the dynamic interactions between the intervention and the health system. The approach was also more likely to identify high level health system constraints that are difficult to incorporate in quantitative analyses. Information on these constraints might be best presented to decisionmakers either alongside, but externally to cost-effectiveness analysis results; or in the form of disease transmission model 'exemplary' scenarios where intervention effects (but not costs) are restricted.

ACKNOWLEDGMENTS

I owe an enormous debt of gratitude to several people, without whom this work would not have been possible.

Firstly, I am thankful to my supervisors Anna Vassall and Gabriela Gomez for being an endless source of support and inspiration. Thank you for the opportunity to undertake this PhD, for all the encouragement, insights and knowledge you shared with me over the years and for committing your time and energy to this project. I have learned so much from you both and it is a privilege to be a part of your research group.

I would also like to thank my colleagues at LSHTM and beyond, who have variously supported me, helped me get my ideas together and given valuable advice, making me feel part of our research community even at a distance: Karin Diaconu, Giulia Ferrari, Yoko Laurence, Don Mudzengi, Debora Pedrazzoli, Catherine Pitt, Sergio Torres-Rueda and many other lovely people I have crossed professional paths with and learned from over the years. A special thank you to Ulla Griffiths, my mentor at the start of this journey; to the TB Modelling Group at LSHTM, who have been excellent collaborators and have provided invaluable support to my work; and the *Umoya omuhle* study team at LSHTM and AHRI, whose data and expertise have informed this work.

Finally, I would like to express my deepest gratitude to my family and friends. To my parents, for always encouraging me to explore. To my husband Angelo and our daughters, Angelica and Amelia, for letting me see the world through their eyes and holding my hand along the way.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACRONYMS AND ABBREVIATIONS

A4R	Accountability for Reasonableness framework
AIM	AIDS Impact Model
ART	Antiretroviral Therapy
CCMDD	Central Chronic Medicines Dispensing and Distribution
CEA	Cost-Effectiveness Analysis
DALYs	Disability-Adjusted Life-Years
DOTS	Directly Observed Treatment, Short-course
DHIS	District Health Information System
DS-TB	Drug-Susceptible TB
FTE	Full Time Equivalent
GDP	Gross Domestic Product
GMB	Group Model Building
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Human Resource
HSS	Health Systems Strengthening
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICF	Intensified TB Case-finding
ILTFU	Initial Loss to Follow-Up
INH	Isoniazid
IPC	Infection Prevention and Control
IPT	Isoniazid Preventive Therapy
LiST	Lives Saved Tool
LMICs	Low- and Middle-Income Countries
MCDA	Multi-Criteria Decision Analysis
MDR-TB	Multi-Drug Resistant TB
M&E	Monitoring and Evaluation

MeSH	Medical Subject Headings terms
Mtb	*Mycobacterium tuberculosis*
NTP	National TB Plan
NDoH	National Department of Health
OPD	Out-Patient Department
PHC	Primary Health Care
QALYs	Quality-Adjusted Life-Years
SANC	South African Nursing Council
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDGs	Sustainable Development Goals
SDM	Systems Dynamics Modelling
TasP	Treatment as Prevention
TB	Tuberculosis
TB-MAC	TB Modelling and Analysis Consortium
UHC	Universal Health Coverage
UNAIDS	Joint United Nations Programme on HIV/AIDS
UVGI	Ultra Violet Germicidal Irradiation
WHO	World Health Organisation
WTP	Willingness-To-Pay

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND AND RATIONALE

Priority setting for investments in infectious disease programmes is evolving and receiving increased attention. Traditionally, investment decisions in health care are supported by economic evaluations comparing the value for money of a contained choice set of alternative intervention options, with the aim of maximising health gains by optimising the use of scarce resources (Drummond et al., 2015, Sloan and Hsieh, 2012). However, priority setting currently goes beyond simple descriptions of costs and consequences of single interventions: it now allows for the ranking and optimisation of multiple intervention options (Drummond et al., 2015). Moreover, it is being increasingly recognised that priority setting in health may be aimed at fulfilling multiple objectives and that policy makers may need to consider a range of constraints in any given setting (Vassall et al., 2016). A literature review on 'real-world' priority setting using explicit decision criteria found that programme effectiveness, equity, affordability, cost-effectiveness and the number of beneficiaries are the most frequently used in health care (Cromwell et al., 2015). The authors conclude that "health care decisions are made based on criteria related both to the health need of the population and the organisational context of the decision" (Cromwell et al., 2015).

For this reason, alongside information on the efficiency and cost-effectiveness of investments in health care, increasing attention is being placed on generating evidence around other local health system characteristics that determine the viability of interventions. For analytical purposes, these characteristics can be grouped into:

a) **Policy objectives,** which encompass the prevailing norms and values that determine policy priorities as well as the structure of the health system and institutions. Resource allocation in health can be guided by welfarist (allocative efficiency) or extra-welfarist (maximising population health or achieving equitable outcomes) objectives and the extent of the balance between them depends on the political and social environment. For example, the launch of the Sustainable Development Goals (SDGs) on health care, with their emphasis on Universal Health Coverage, has brought particular attention to the impact of health interventions on equity and social protection (United Nations, 2016). In line with the SDGs, disease programmes such as tuberculosis (TB) control now have an explicit objective to reduce catastrophic expenditures for patients (WHO, 2014). The reference case for economic evaluation by the International Decision Support Initiative (iDSI) aims to improve the quality of evidence informing policy decisions and recommends that economic evaluations should from now on explore the equity impact of health interventions (principle 11) (Wilkinson et al., 2016).

b) **Demand and supply constraints.** Priority setting has traditionally seen the budgetary constraint as the only limitation to resource allocation. However, it is being increasingly recognised that a range of non-financial constraints around the *feasibility of implementation,* both on the supply (health system) and demand (patient) side, must be considered when selecting interventions. These constraints may limit the pace of intervention scale-up (e.g. human resources scarcity in the short run); or may be insurmountable even with increased resourcing (e.g. an ethical obligation to provide treatment to all those in need); or again may incur costs that are not observable when interventions are tested in research settings.

Failure to account for such setting- and intervention-specific influences on the priority setting process itself and on the implementation of the resulting recommendations can result in unfeasible health interventions being recommended and, ultimately, in evidence being disregarded by decision-makers (Hauck et al., 2016, Mikkelsen et al., 2017).

Yet, despite the recent emphasis on the importance of taking these objectives and constraints into account, methods and applications of economic evaluations or priority setting exercises incorporating multiple decision criteria remain limited (Hauck et al., 2019, Hontelez et al., 2016, Langley et al., 2014a, van Baal et al., 2018). Currently, user-friendly models are being developed to assist decision-makers in low- and middle-income countries (LMICs) to assess the local cost-effectiveness of new health technologies by accounting for setting-specific variations in factors such as input prices and epidemiological characteristics (Houben et al., 2016b, Lubell et al., 2008, Stegmuller et al., 2017). However, these tools do not typically take into account the country- and intervention-specific characteristics that affect priority setting described above, such as existing constraints on the demand and supply of health services, power relationships and political processes within the health system (Hauck et al., 2016, Mikkelsen et al., 2017, Vassall et al., 2016). Going forward, a key challenge to be addressed is how to incorporate this additional complexity in priority setting in a way that: (a) provides accurate information; (b) retains transparency and ownership by decision-makers; and (c) retains a notion of the trade-offs (opportunity costs) between investment choices.

The focus of this thesis is to add to these efforts by examining the way constraints, and specifically those related to the *feasibility of implementation*, can be best incorporated in priority setting.

1.2 CASE STUDY: TUBERCULOSIS CONTROL IN SOUTH AFRICA

To explore the incorporation of constraints and, more generally, feasibility concerns in priority setting, I focussed on tuberculosis (TB) control as a case study. The World Health Organisation (WHO) set ambitious global targets towards TB elimination in its End TB strategy (WHO, 2014). The targets call for reductions in TB deaths and incidence rate of 95% and 90%, respectively, compared to 2015 levels by 2035 and zero TB-affected households facing catastrophic costs due to TB (WHO, 2014). Although progress in TB control has been made over the past two decades, an effective TB response has been hampered by weak health systems, poverty and sub-optimal medical technologies (Vassall, 2014). To address these challenges, the End TB strategy rests on three pillars:

1. *Integrated, patient-centred care and prevention*, focussed on early diagnosis, scaling up treatment, and prevention;
2. *Bold policies and supportive systems*, calling for political commitment with adequate resourcing, community engagement and universal health coverage to guarantee social protection and alleviation of poverty and other social determinants of TB;
3. *Intensified research and innovation*, emphasising the development of new tools and interventions, and research to optimise implementation.

The End TB strategy thus recognises the complexity of the TB response, which spans across multiple dimensions and levels of the health system. It also recognises that resource scarcity and constraints to implementation play a role in hampering the response and must be overcome. For these reasons, as well as for the characteristics of TB epidemiology that determine the landscape of available interventions, TB control makes for an ideal case study for exploring feasibility in priority setting.

1.2.1 Clinical characteristics and epidemiology of TB

Tuberculosis is one of the oldest recorded diseases in humans and it remains one of the major killers among infectious diseases. Skeletons with apparent tubercular deformities were unearthed in ancient Egypt as well as in Neolithic sites in Italy, Denmark and the Middle-East, suggesting that TB was found throughout the world up to 4,000 years ago (Smith, 2003). The disease is caused by *Mycobacterium tuberculosis*, a pathogen that is transmitted when a patient with pulmonary TB expels droplet nuclei into the air that are then inhaled by a susceptible person (Talbot and Raffa, 2015). Transmission occurs more efficiently indoors, where dilution of infectious droplets in air is limited and occupants are concentrated (Nardell, 2015). This is one of the reasons why TB is considered a disease of poverty, that disproportionately affects people living in conditions of poor housing and overcrowding (Sulis et al., 2014).

If the *M. tuberculosis* infection is not immediately eradicated by the host's immune system, it may still be kept under control in a dormant state called latent TB infection (LTBI), which is asymptomatic and estimated to affect around one-fourth of the world's population (Cohen et al., 2019). Progress to active TB occurs in approximately 10% of people with LTBI and persons with an impaired immune response, for example from acquired immunodeficiency syndrome (AIDS), have a much higher risk of progression (Gray and Cohn, 2013). Pulmonary TB manifests by chronic, usually productive coughing, sometimes with blood in the sputum in the presence of invasive disease (Talbot and Raffa, 2015). Other common symptoms used in screening checklists for TB include fever, night sweats, unintended weight loss and fatigue.

A characteristic of mycobacteria is that they are slow growing, with a generation time in vitro of approximately 18-24 hours against an average of 20 minutes for most bacteria. This considerably lengthens the time to diagnosis with culture-based methods. For this reason, TB diagnosis in high-burden settings has traditionally relied on sputum smear microscopy, which takes advantage of acid-fastness, a property of mycobacteria that resist de-staining, but has low sensitivity particularly among patients with human immunodeficiency virus (HIV) co-infection (Steingart et al., 2006). In 2010, WHO endorsed a new rapid molecular test called Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), which is highly sensitive and specific for pulmonary TB diagnosis even in the presence of HIV co-infection and can detect resistance to rifampicin, the most powerful first-line TB drug, but is costlier than microscopy (Pantoja et al., 2013).

Rapid case detection, linkage and adherence to treatment are of vital importance for infection control and, in particular, for preventing the spread of drug-resistant TB (DR-TB). Drug-resistant TB strains are more difficult to treat than drug-susceptible ones due to longer regimens and more frequent and serious potential side-effects, and thus present a major challenge for both patients and the health care service (WHO, 2020). The combination of TB control strategies that is optimal for any given setting is thus dependent on the extent to which the epidemic is driven by HIV and/or presents a high burden of DR-TB, as well as on the characteristics of the health care system and socio-demographic characteristics of the population.

1.2.2 Priority setting models in tuberculosis control

The substantial uncertainty around the mix of interventions that can achieve the post-2015 TB Targets in different high-burden settings, given the varying characteristics of the TB epidemic across geographical areas coupled with widespread resource scarcity, call for an extensive use of priority setting models in TB control.

There have been several previous attempts to incorporate constraints in TB priority setting and economic evaluation models. For example, Lin, Langley and colleagues applied dynamic transmission models linked to operational models describing in detail the roll-out of new diagnostic technologies within the Tanzanian health system to analyse their potential impact not only on TB epidemiology but also on health system processes (Langley et al., 2014a, Lin et al., 2011). This integrated modelling approach suggested that full roll-out of Xpert MTB/RIF has the potential to significantly reduce the burden of TB in Tanzania and is a cost-effective diagnostic option, although a considerable increase in TB funding is required to translate this strategy into clinical practice (Langley et al., 2014b).

Similarly, findings from a recent exercise combining results from nine transmission models found that aggressive scale-up of TB control interventions in India, China and South Africa could be highly cost-effective, with intensified case-finding (ICF, improved facility-based case detection) being the single most cost-effective intervention for reaching the post-2015 TB Targets (Menzies et al., 2016). However, ICF was also the costliest intervention available and its combination with improved diagnosis using Xpert MTB/RIF and expanded access to care more than doubled the current TB budget in all three study countries (Menzies et al., 2016). This analysis did not consider other health system constraints to services scale-up besides affordability, but did conclude that these might be substantial and that an optimal scenario might allow for a mix of the interventions considered at different coverage levels.

A subsequent real-world analysis of Xpert MTB/RIF roll-out in South Africa by Vassall and colleagues subverted these findings on the cost-effectiveness of the new diagnostic, concluding that roll-out did not greatly impact the costs of TB diagnosis as it brought about savings elsewhere in the TB case cascade (Vassall et al., 2017). Cost-neutrality, however, was not accompanied by mortality reductions, possibly because clinicians relied less on empirical treatment in the presence of a new diagnostic and therefore scale-up of Xpert MTB/RIF did not prove to be a cost-effective intervention in the South African context. Similar findings on the lack of effect of Xpert on drug-susceptible TB (DS-TB) incidence and mortality were obtained from a study applying an agent-based simulation model to the TB epidemic in India (Kasaie et al., 2017). The study concluded that any recommendations on the optimal and most cost-effective strategy for Xpert scale-up in the country is dependent on further analysis considering the demands placed by the new technology on the health system as well as issues around its affordability.

1.2.3 Priority setting for TB in South Africa

This thesis was conceived during two years spent working with the South African National Department of Health on setting up the South African TB Think Tank, a network of policy-makers, researchers and other stakeholders tasked with advising on TB control policy and implementation for achieving the nationally agreed targets for TB.

TB control is a major concern for the South African health system, which faces one of the world's worst TB epidemics driven by HIV (Churchyard et al., 2014). In 2015, the South African Deputy President announced plans for a comprehensive TB screening programme, one component of which involves using ICF to screen all the people attending health facilities for any reason. Prior to that, TB case detection relied on passive case-finding, whereby only patients reporting any symptoms suggestive of TB as the cause of their clinic visit were screened. One study in the Eastern Cape estimated that approximately 70% of people with TB attending primary care clinics for TB-related symptoms, and more than 90% of those attending clinics for any other reasons were not diagnosed with TB during their visit (Kweza et al., 2018). This suggests that the prevalence of untreated, infectious TB in clinic attendees may be higher than in the general population, highlighting the importance of nosocomial TB infection prevention and control (IPC) measures as well as effective screening.

National level scale-up of both these interventions, however, presents challenges in the context of an over-stretched health system. Guidelines for airborne IPC in health facilities are widely available (National Department of Health, 2015, World Health Organisation, 2009), but recommended measures remain poorly implemented by health workers (Claassens et al., 2013, Farley et al., 2012, Malangu and Mngomezulu, 2015, World Health Organisation, 2014). Clinic design, climatic conditions, work practices and the organization of care, risk perceptions, competing priorities, organizational culture, and concern about stigma may contribute to the poor implementation of IPC measures. Recommendations to improve adherence to guidelines tend to focus on training and supportive resources to encourage individual behaviours, such as mask wearing and opening of windows to allow ventilation, but little attention has been paid to the complex contextual features of the wider health system that underpin successful implementation (Kielmann et al., 2020). Understanding these constraints and identifying possible health system investments to overcome them is therefore vital to decrease transmission.

Intensifying symptoms screening of facility attendees is also estimated to be very effective at reducing transmission, both within health facilities and in the general population (Houben et al., 2016a). However, ICF is extremely costly to scale up as it increases resource requirements for diagnosis and treatment further along the TB care cascade (Menzies et al., 2016). Efficient allocation of scarce resources across interventions that place different demands on constrained inputs is thus a critical question in this case, as the modality of implementation and approaches to addressing feasibility concerns will in part determine both the providers' and patients' costs of screening and overall cost-effectiveness.

1.3 AIMS AND OBJECTIVES

This thesis aims to explore and develop the methods for incorporating feasibility concerns, and specifically health system constraints, in priority setting models both internally and externally to the traditional cost-effectiveness analysis framework. This will be done using the case study of priority setting around TB control in South Africa.

Specific objectives are:

1. To explore how *feasibility* is characterised and built into priority setting models in LMICs, in terms of both existing constraints to intervention implementation and of the political considerations affecting the priority setting process itself;
2. To apply a pragmatic approach to characterising and empirically quantifying selected health system constraints to the implementation of TB case-finding strategies in South Africa;
3. To measure the costs and cost-effectiveness of different TB case-finding strategies in South Africa using a resource allocation model both with and without incorporating constraints and investments needed to relax those constraints;
4. To explore group model building, a deliberative process involving local managers, practitioners and policy-makers, as a systematic method for generating information on the health system constraints for use in economic analyses.

1.4 OVERVIEW OF THESIS STRUCTURE

At the core of this thesis are four academic papers that constitute separate chapters (Chapters 3 to 6). The papers are preceded by an overview of the frameworks and theories underpinning the methods used (Chapter 2). The papers presented in Chapters 3, 4 and 5, are published. The paper in Chapter 6 is currently under review. A discussion chapter (Chapter 7) follows the last paper.

The present chapter (Chapter 1) presents the experience and rationale motivating my research question (how to best include information on the feasibility of intervention implementation in priority setting for infectious disease control?) and the choice of analysing TB control in South Africa as a case study. Chapter 2 then details the theoretical frameworks (cost-effectiveness analysis decision rules, multi-criteria decision analysis and deliberative processes, system dynamics modelling and group model building) underpinning the methods and defines key concepts (feasibility, health system constraints, health systems strengthening).

The first of the core papers (Chapter 3) reports the results of a systematic literature review exploring how the concepts of feasibility and health system constraints are characterised and incorporated in mathematical models of infectious disease transmission. This review was carried out to achieve **objective 1**. Based on the findings of the systematic review, the second research paper (Chapter 4) develops a 'proof of concept' method to empirically estimate a sample set of health system constraints for inclusion in transmission model-based economic evaluations of TB control interventions. This addresses **objective 2** of the thesis. The third core paper (Chapter 5) then incorporates these constraints, estimated using routine health system data, into an economic model and carries out a cost-utility analysis of the different TB case-finding strategies under consideration by the South African National TB Programme. The economic model generates two separate rankings of the case-finding strategies, with or without including the additional resources needed to relax the constraints in the incremental cost-effectiveness ratios, thus addressing **objective 3**. The last research paper (Chapter 6) explores group model building, a participatory technique that involves facility managers, health practitioners and other relevant stakeholders, as a potentially comprehensive and systematic method for eliciting information on the constraints around infection control interventions and on the available measures to relax the constraints. This information is then used in a costing exercise of TB IPC interventions that produces an alternative estimation of their full opportunity cost for use in priority setting models, thus addressing **objective 4** of the thesis.

Lastly, the discussion (Chapter 7) reflects on the data generated qualitatively using the deliberative group model building process and makes recommendations on which elements might be amenable for inclusion in priority settings within, as opposed to alongside, cost-effectiveness analysis.

1.5 ROLE OF THE CANDIDATE

The idea for this PhD research was conceived during the course of my work alongside the South African TB Think Tank. The work builds on my supervisors' extensive experience with conducting TB and HIV research and providing technical assistance for health resource allocation in South Africa. Based on their insights and indication of existing research gaps, I set out to develop a framework to assist policymakers with priority setting for TB that expands on the standard cost-effectiveness decision rules, and to field test this framework within the policy timeframe.

Access to data and policymakers was secured through two existing projects I was a named investigator on. The first project aimed to carry out transmission and economic modelling to inform the preparation of South Africa's latest National TB Plan, under the umbrella of the TB Think Tank. The second project aimed to identify and evaluate 'whole-system' TB IPC interventions to prevent the spread of DR-TB in South African primary care clinics, using a multidisciplinary approach including anthropology, policy analysis, system dynamics, transmission and economic modelling. The two projects were pulled together pragmatically for this work, as they offered the opportunity to collect quantitative and qualitative data on a coherent set of TB control interventions and they fit the timeframe of this research.

I designed the studies presented in the core papers in collaboration with my supervisors, developed the research questions and sought ethical approval. For each paper, I led on all economic data generation processes, including building the cost and cost-effectiveness models and designing and populating all data collection and analysis tools. All economic analyses were conceptualised with input from my supervisors and I was responsible for generating, interpreting and writing up results and for submitting all core papers for publication as the first author.

1.6 FUNDING

This thesis draws from work supported under three different grants. The literature review presented in Chapter 3 was supported by a grant from the Bill & Melinda Gates Foundation to the Tuberculosis Modelling and Analysis Consortium (TB-MAC). The papers presented in

Chapters 4 and 5 were prepared with support from a Bill & Melinda Gates Foundation grant to set up the South African TB Think Tank. Lastly, the paper presented in Chapter 6 was supported by a UKRI grant under the Bloomsbury SET initiative to conduct research on antimicrobial resistance. The grant supported the addition of a health systems dynamics modelling component to the *Umoya Omuhle* project, a multidisciplinary study on the transmission of drug-resistant TB in South African clinics.

REFERENCES

CHURCHYARD, G. J., MAMETJA, L. D., MVUSI, L., NDJEKA, N., HESSELING, A. C., REID, A., BABATUNDE, S. & PILLAY, Y. 2014. Tuberculosis control in South Africa: Successes, challenges and recommendations. *S Afr Med J,* 104**,** 244-248.

CLAASSENS, M. M., VAN SCHALKWYK, C., DU TOIT, E., ROEST, E., LOMBARD, C. J., ENARSON, D. A. & ET AL. 2013. Tuberculosis in Healthcare Workers and Infection Control Measures at Primary Healthcare Facilities in South Africa. *PLoS One,* 8. doi: 10.1371/journal.pone.0076272.

COHEN, A., MATHIASEN, V. D., SCHON, T. & WEJSE, C. 2019. The global prevalence of latent tuberculosis: a systematic review and meta-analysis. *Eur Respir J,* 54. 10.1183/13993003.00655-2019.

CROMWELL, I., PEACOCK, S. J. & MITTON, C. 2015. 'Real-world' health care priority setting using explicit decision criteria: a systematic review of the literature. *BMC Health Serv Res,* 15.

DRUMMOND, M. F., SCULPHER, M., CLAXTON, K., STODDART, G. & TORRANCE, G. 2015. *Methods for the economic evaluation of health care programmes*, Oxford University Press.

FARLEY, J. E., TUDOR, C., MPHAHLELE, M., FRANZ, K., PERRIN, N. A., DORMAN, S. & VAN DER WALT, M. 2012. A national infection control evaluation of drug-resistant tuberculosis hospitals in South Africa. *Int J Tuberc Lung Dis,* 16**,** 82-9. 10.5588/ijtld.10.0791.

GRAY, J. M. & COHN, D. L. 2013. Tuberculosis and HIV coinfection. *Semin Respir Crit Care Med,* 34**,** 32-43. 10.1055/s-0032-1333469.

HAUCK, K., MORTON, A., CHALKIDOU, K., CHI, Y. L., CULYER, A., LEVIN, C., MEACOCK, R., OVER, M., THOMAS, R., VASSALL, A., VERGUET, S. & SMITH, P. C. 2019. How can we evaluate the cost-effectiveness of health system strengthening? A typology and illustrations. *Soc Sci Med,* 220**,** 141-149.

HAUCK, K., THOMAS, R. & SMITH, P. C. 2016. Departures from cost-effectiveness recommendations: The impact of health system constraints on priority setting. *Health Systems & Reform,* 2**,** 61-70.

HONTELEZ, J. A. C., CHANGE, A. Y., OGBUOJI, O., DE VLAS, S. J., BARNIGHAUSEN, T. & ATUN, R. 2016. Changing HIV treatment eligibility under health system constraints in sub-Saharan Africa: investment needs, population health gains, and cost-effectiveness. *AIDS,* 30**,** 2341-2350.

HOUBEN, R., MENZIES, N. A., SUMNER, T., HUYNH, G. H., ARINAMINAPATHY, N., GOLDHABER-FIEBERT, J. D., LIN, H., WU, C., MANDAL, S., PANDEY, S., SUEN, S., BENDAVID, E., AZMAN, A. S., DOWDY, D. W., BACAËR, N., RHINES, A. S., FELDMAN, M. W., HANDEL, A., WHALEN, C. C., CHANG, S. T., WAGNER, B. G., ECKHOFF, P. A., TRAUER, J. M., DENHOLM, J. T., MCBRYDE, E. S., COHEN, T., SALOMON, J., PRETORIUS, C., LALLI, M., EATON, J. W., BOCCIA, D., HOSSEINI, M., GOMEZ, G. B., SAHU, S., DANIELS, C., DITIU, L., CHIN, D. P., WANG, L., CHADHA, V. K., RADE, K., DEWAN, P., HIPPNER, P., CHARALAMBOUS, S., GRANT, A. D., CHURCHYARD, G., PILLAY, Y., MAMETJA, L. D., KIMERLING, M. E., VASSALL, A. & WHITE, R. G. 2016a. Feasibility of achieving the 2025 WHO global tuberculosis targets in South Africa, China, and India: a combined analysis of 11 mathematical models. *Lancet Glob Health,* 4**,** e806-e815.

HOUBEN, R. M. G. J., LALLI, M., SUMNER, T., HAMILTON, M., PEDRAZZOLI, D., BONSU, F., HIPPNER, P., PILLAY, Y., KIMERLING, M., AHMEDOV, S., PRETORIUS, C. & WHITE, R. G. 2016b. TIME Impact – a new user-friendly tuberculosis (TB) model to inform TB policy decisions. *BMC Medicine,* 14**,** 1-10. 10.1186/s12916-016-0608-4.

KASAIE, P., SOHN, H., KENDALL, E., DOWDY, D., GOMEZ, G. B., VASSALL, A. & PAI, M. Exploring the epidemiological impact of universal access to rapid tuberculosis diagnosis using agent-based simulation. *In:* CHAN, W. K. V., D'AMBROGIO, A., ZACHAREWICZ, G., MUSTAFEE, N., WAINER, G. & PAGE, E., eds. Winter simulation conference, 2017.

KIELMANN, K., KARAT, A. S., ZWAMA, G., COLVIN, C., SWARTZ, A., VOCE, A. S., YATES, T. A., MACGREGOR, H., MCCREESH, N., KALLON, I., VASSALL, A., GOVENDER, I., SEELEY, J. & GRANT, A. D. 2020. Tuberculosis infection prevention and control: why we need a whole systems approach. *Infect Dis Poverty,* 9. https://doi.org/10.1186/s40249-020-00667-6.

KWEZA, P. F., VAN SCHALKWYK, C., ABRAHAM, N., UYS, M., CLAASSENS, M. M. & MEDINA-MARINO, A. 2018. Estimating the magnitude of pulmonary tuberculosis patients missed by primary health care clinics in South Africa. *Int J Tuberc Lung Dis,* 22**,** 264-272. 10.5588/ijtld.17.0491.

LANGLEY, I., ADAMS, E., DOULLA, B. & SQUIRE, S. B. 2014a. Operational modelling to guide implementation and scale-up of diagnostic tests within the health system: Exploring opportunities for parasitic disease diagnostics based on example application for tuberculosis. *Parasitology,* 141**,** 1795-1802. 10.1017/S0031182014000985.

LANGLEY, I., LIN, H., EGWAGA, S., DOULLA, B., KU, C., MURRAY, M., COHEN, T. & SQUIRE, S. B. 2014b. Assessment of the patient, health system, and population effects of Xpert MTB/RIF and alternative diagnostics for tuberculosis in Tanzania: an integrated modelling approach. *Lancet Glob Health,* 2**,** e581-91.

LIN, H. H., LANGLEY, I., MWENDA, R., DOULLA, B., EGWAGA, S., MILLINGTON, K. A., MANN, G. H., MURRAY, M., SQUIRE, S. B. & COHEN, T. 2011. A modelling framework to support the selection and implementation of new tuberculosis diagnostic tools. *Int J Tuberc Lung Dis,* 15**,** 996-1004. 10.5588/ijtld.11.0062.

LUBELL, Y., HOPKINS H., WHITTY, C. J., STAEDKE, S. G. & MILLS, A. 2008. An interactive model for the assessment of the economic costs and benefits of different rapid diagnostic tests for malaria. *Malaria J,* 7**,** 21.

MALANGU, M. & MNGOMEZULU, M. 2015. Evaluation of tuberculosis infection control measures implemented at primary health care facilities in KwaZulu-Natal province of South Africa. *BMC Infect Dis,* 15**,** 117. 10.1186/s12879-015-0773-7.

MENZIES, N. A., GOMEZ, G. B., BOZZANI, F., CHATTERJEE, S., FOSTER, N., GARCIA BAENA, I., LAURENCE, Y. & ET AL. 2016. Cost-effectiveness and resource implications of aggressive TB control in China, India and South Africa: a combined analysis of nine models. *Lancet Glob Health,* 4**,** e816–e826.

MIKKELSEN, E., HONTELEZ, J. A. C., JANSEN, M. P. M., BÄRNIGHAUSEN, T., HAUCK, K., JOHANSSON, K. A., MEYER-RATH G., OVER, M., DE VLAS, S. J., VAN DER WILT, G. J., TROMP, N., BIJLMAKERS, L. & BALTUSSEN, R. M. P. M. 2017. Evidence for scaling up HIV treatment in sub-Saharan Africa: A call for incorporating health systems constraints. *PLoS Med,* 14**,** e1002240.

NARDELL, E. A. 2015. Transmission and Institutional Infection Control of Tuberculosis. *Cold Spring Harb Perspect Med,* 6**,** a018192. 10.1101/cshperspect.a018192.

NATIONAL DEPARTMENT OF HEALTH 2015. National Infection Prevention and Control Guidelines for TB, MDR-TB and XDR-TB. Pretoria, South Africa.

PANTOJA, A., FITZPATRICK, C., VASSALL, A., WEYER, K. & FLOYD, K. 2013. Xpert MTB/RIF for diagnosis of tuberculosis and drug-resistant tuberculosis: a cost and affordability analysis. *Eur Respir J,* 42**,** 708-20. 10.1183/09031936.00147912.

SLOAN, F. A. & HSIEH, C. 2012. *Health Economics*, MIT Press.

SMITH, I. 2003. Mycobacterium tuberculosis pathogenesis and molecular determinants of virulence. *Clin Microbiol Rev,* 16**,** 463-96. 10.1128/cmr.16.3.463-496.2003.

STEGMULLER, A. R., SELF, A., LITVIN, K. & ROBERTON, T. 2017. How is the Lives Saved Tool (LiST) used in the global health community? Results of a mixed-methods LiST user study. *BMC Public Health,* 17**,** 773.

STEINGART, K. R., NG, V., HENRY, M., HOPEWELL, P. C., RAMSAY, A., CUNNINGHAM, J., URBANCZIK, R., PERKINS, M. D., AZIZ, M. A. & PAI, M. 2006. Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis,* 6**,** 664-74. 10.1016/S1473-3099(06)70602-8.

SULIS, G., ROGGI, A., MATTEELLI, A. & RAVIGLIONE, M. C. 2014. Tuberculosis: epidemiology and control. *Mediterr J Hematol Infect Dis,* 6**,** e2014070. 10.4084/MJHID.2014.070.

TALBOT, E. A. & RAFFA, B. J. 2015. Mycobacterium tuberculosis. *Molecular Medical Microbiology.* Second ed.: Academic Press.

UNITED NATIONS. 2016. *Sustainable development goals. Goals 3: Ensure healthy lives and promote well-being for all at all ages* [Online]. Available: http://www.un.org/sustainabledevelopment/health/. [Accessed 22 December 2020].

VAN BAAL, P., MORTON, A. & SEVERENS, J. L. 2018. Health care input constraints and cost effectiveness analysis decision rules. *Soc Sci Med,* 200**,** 59-64. 10.1016/j.socscimed.2018.01.026.

VASSALL, A. 2014. Benefits and costs of the tuberculosis targets for the post-2015 development agenda. Copenhagen Consensus Center.

VASSALL, A., MANGHAM-JEFFERIES, L., GOMEZ, G. B., PITT, C. & FOSTER, N. 2016. Incorporating demand and supply constraints into economic evaluation in low-income and middle-income countries. *Health Econ,* 25**,** 95-115. 10.1002/hec.3306.

VASSALL, A., SIAPKA, M., FOSTER, N., CUNNAMA, L., RAMMA, L., FIELDING, K., MCCARTHY, K., CHURCHYARD, G., GRANT, A. & SINANOVIC, E. 2017. Cost-effectiveness of Xpert MTB/RIF for tuberculosis diagnosis in South Africa: a real-world cost analysis and economic evaluation. *Lancet Glob Health,* 5**,** e710-19.

WHO. 2014. *The End TB Strategy. Global strategy and targets fro tuberculosis prevention, care and control after 2015* [Online]. Available: http://who.int/tb/post2015_TBstrategy.pdf?ua=1 [Accessed].

WHO 2020. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug resistant tuberculosis treatment. Geneva: World Health Organisation.

WILKINSON, T., SCULPHER, M., CLAXTON, K., REVILL, P., BRIGGS, A., CAIRNS, J. A., TEERAWATTANANON, Y., ASFAW, E., LOPERT, R., CULYER, A. J. & WALKER, D. G. 2016. The International Decision Support Initiative Reference Case for Economic Evaluation: An aid to thought. *Value in Health,* 19**,** 921-28.

WORLD HEALTH ORGANISATION 2009. WHO infection prevention and control in health care facilities, congregate settings and households. Geneva, Switzerland.

WORLD HEALTH ORGANISATION 2014. Infection prevention and control of epidemic-and pandemic-prone acute respiratory infections in health care. Geneva: World Health Organisation.

CHAPTER 2: METHODOLOGY AND DEFINITIONS

This chapter outlines the theoretical frameworks that the thesis seeks to expand. The focus of this work are complex interventions that place demands on a variety of health system inputs, have knock-on effects along the TB treatment and care cascade and are, in turn, affected by a number of health system constraints operating at different levels of the health system. Given the level of complexity, this chapter seeks to delimit and clarify the scope of the work and to present the operational definitions of key concepts adopted throughout. Secondly, as this research draws on empirical approaches rooted in health system research to expand the standard cost-effectiveness decision rules, this chapter provides an overview of these frameworks and approaches. Part of the material in this chapter was adapted and published in a methods review to which I collaborated while conducting research for this thesis (Vassall et al., 2019).

2.1 OVERVIEW OF KEY CONCEPTS AND TECHNICAL TERMS

2.1.1 Feasibility and health system constraints

The incorporation of constraints in priority setting requires a clear understanding of their definition and characteristics. In the context of LMIC health systems, *feasibility* is a term often used to justify investment decisions (or lack of investment) in specific health interventions and technologies on the basis of intervention and/or contextual characteristics. The concept of feasibility and its influence on priority setting have been ill-defined and may encompass a range of aspects such as intervention affordability, physical health system constraints that directly restrict access to services or technologies (human resources scarcity, barriers to use and uptake etc.), and arbitrary beliefs held by policy-makers and the wider environment that influence the priority setting process (Guindo et al., 2012, Kim et al., 2006, Sendi and Briggs, 2001, van Baal et al., 2018). Anderson and Hardwick urge analysts to view interventions not just as ‘treatment’ but as “the assumptions, perspectives, hunches and hopes in the policymaker’s head” that often do not get articulated (Anderson and Hardwick, 2016). Since standard (’black box’) evaluations “make no attempt to uncover or elucidate the causal connection between the inputs and tangible components of an intervention and its expected outcomes”, the authors call for theory- driven evaluations using a realist approach to identify the causal processes that determine feasibility (Anderson and Hardwick, 2016). Anderson and Hardwick, however, do not use the term feasibility explicitly and they do not provide guidance on which aspects of the health system and intervention matter. Also, importantly, they do not discuss how theory-driven approaches can be incorporated prospectively in economic evaluation studies, rather than retrospectively in reviews (Anderson and Hardwick, 2016). Thus, while the importance of feasibility as a decision criterion is widely recognised (Mikkelsen et al., 2017, Vassall et al., 2016), there is no consensus around its definition and little guidance on how it can be characterised in practice in different contexts or how to best address it in priority setting processes (Baltussen et al., 2013, Tromp and Baltussen, 2012).

In the literature on priority setting for infectious diseases, the term *feasibility* has been used by Baltussen and colleagues to refer to the set of “constraints at the personal and health system level that may impede the implementation” of programmes (Baltussen et al., 2013). Restricting the analysis to the supply of health services only, Hanson and colleagues relate feasibility to a scarcity of resources that limits the pursuit of desired health system goals (Hanson et al., 2003). In their framework, which aims to guide resource allocation among priority interventions in LMICs, health system constraints are seen as obstacles that “might affect the feasibility and returns from rapid expansion of health services” (Hanson et al., 2003). Both these ways of addressing feasibility have in common that they acknowledge it as (1) a product of health system constraints that (2) have an influence on priority setting decisions and that (3) are not limited to financial resources. In fact, the Hanson framework for intervention scale-up explicitly acknowledges that not all constraints can be relaxed by injecting new funds in the health sector (Hanson et al., 2003).

Another similarity in the Baltussen and Hanson definitions, which is in line with the theories of realist evaluators, is that they all consider feasibility as the dynamic product of the characteristics of the health system and of the intervention. This interaction of intrinsic and extrinsic intervention characteristics as the determinants of feasibility is further acknowledged in the ‘intervention complexity’ framework put forward by Gericke and colleagues to inform priority setting in LMICs (Gericke et al., 2005). According to this framework, the feasibility of an intervention is determined by:

- Local institutional capacity; and
- The degree of technical complexity of the intervention.

Feasibility is thus the “match between technical complexity and capacity”, and intervention complexity is defined as the “quality and quantity of non-financial resources required to implement and sustain an intervention”, thus reinforcing that feasibility is a distinct decision criterion from cost and cost-effectiveness and, as such, it should be considered alongside these but separately from them in priority setting (Gericke et al., 2005).

The definitions of feasibility discussed so far concentrate on the health services supply side and can be considered as synonymous of 'health system constraints'. Some recent literature looking at the sub-optimal application of cost-effectiveness analysis recommendations focuses instead on the *political feasibility* of interventions. In their attempt at explaining how cost-effectiveness evidence is sometimes disregarded in priority setting, Hauck and colleagues consider five classes of political economic forces – the median voter model, interest groups, bureaucratic decision-making, decentralization and equity – that limit the options of decision-makers in terms of what is feasible in a specific context (Hauck and Smith, 2015, Hauck et al., 2016). Decision criteria stemming from these political forces relate to the objectives of interventions, not to their overall impact. Hence, for the purpose of this work, I have adopted the distinction proposed in section 1.1 between:

- *feasibility of implementation*, relating to health system constraints of any nature that affect impact at scale, including budget availability and demand-side constraints on intervention uptake; and
- *political feasibility*, relating to policy objectives, which determine whether or not an intervention is considered in the first place.

2.1.2 Health systems strengthening frameworks

The above distinction highlights how feasibility can be determined by the health system's *software* elements, which include for example norms and values, governance, political commitment and effective bureaucracies, and are more likely to affect political feasibility; as well as by the more tangible *hardware* elements that are necessary to the direct provision of health services, such as workforce, supplies and information systems, that are more likely to affect feasibility of implementation (Sheikh et al., 2011). As discussed in Chapter 1, some health system constraints, usually those depending on hardware elements, are more amenable than others to being relieved with additional investments, particularly in the short- to medium-term.

The Alma-Ata declaration, with its focus on primary health care, is often interpreted as advocating a holistic approach to investing in health systems to improve a wide range of population health outcomes (WHO, 1978). The dichotomy between system-wide ('horizontal') and disease-specific ('vertical') investments has been ubiquitous in global health for several decades (World Bank, 1993), with vertical disease control programmes receiving the largest share of financial resources for health in LMICs through the early 2000s (England, 2007). Over time, it became apparent that vertical programmes have potentially large opportunity costs in terms of the more comprehensive health system investments forgone that could strengthen whole service delivery platforms (Garrett, 2007, Martinez Alvarez et al., 2016, Yu et al., 2008). The health systems strengthening (HSS) label was therefore embraced by key donors and global health leaders in the last decade, marking a renewed interest in horizontal approaches as a vehicle for improving health systems performance and efficiency (Hafner and Shiffman, 2013).

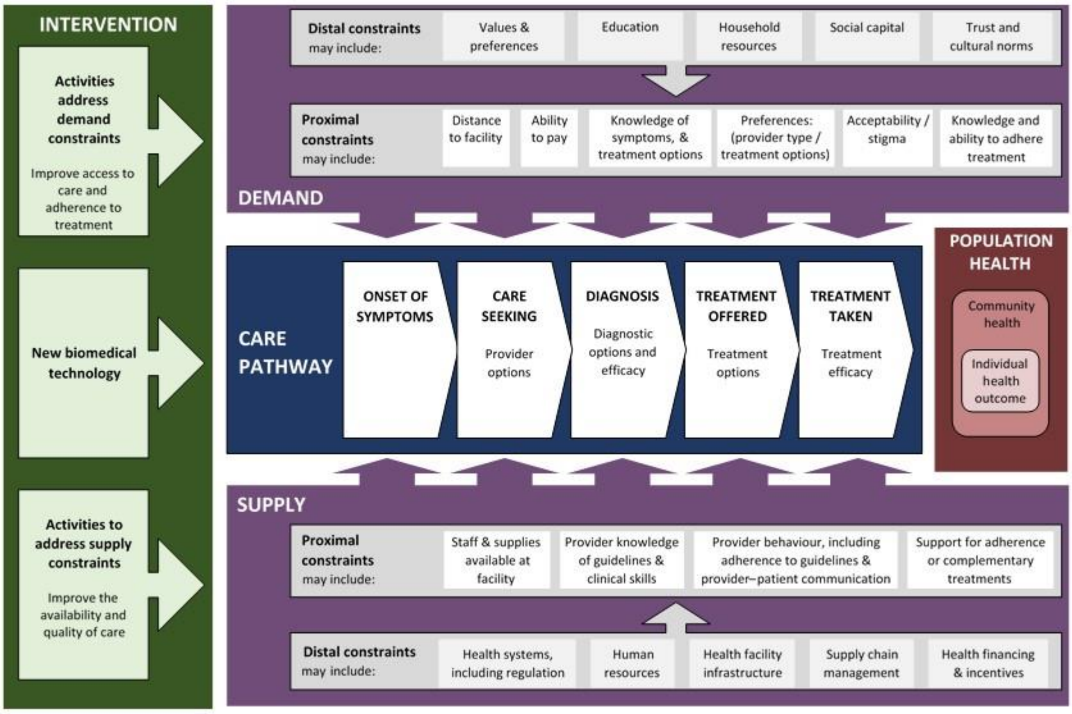
As a result of this shift, analysts' attention has been drawn to assessments of HSS to address two types of priority setting questions (Vassall et al., 2019):

1. What specific actions are needed to enable health systems to deliver interventions at scale (Fenwick et al., 2008, van Baal et al., 2016, Walker et al., 2014);
2. How to balance resource allocation between horizontal and vertical programmes (Hauck et al., 2019, Morton et al., 2016).

These enabling investments, which I refer to as 'relaxing health system constraints' throughout this work, are now recognised as a key concern for priority setting exercises such as defining health benefits packages, whose intended goal is to expand coverage of essential services to the whole population to achieve Universal Health Coverage (UHC) (Ochalek et al., 2018).

Several frameworks have been put forward to identify the HSS investments necessary to complement the roll out of new technologies and intervention packages. For example, Schwartländer and colleagues proposed an investment framework for HIV programmes that lists both programme-related (e.g. procurement and distribution, research and innovation) and social enablers (e.g. political commitment and advocacy, stigma reduction) that are critical for the scale-up of basic programme activities (Schwartlander et al., 2011). A broader framework, targeting the roll out of new technologies in LMICs, illustrates the pathway of a patient through the cascade of care, from case detection to treatment outcome, showing how health system constraints impact progress at each stage (Figure 1) (Vassall et al., 2016). This framework distinguishes between demand and supply constraints and, within each group, it identifies proximal and distal constraints to the cascade. Proximal constraints on the supply side take the form of input shortages or provider behaviours that directly influence service availability, and are in turn determined by distal constraints inherent to the system's organisational structure. Similarly, on the demand side, patients are resource and behaviourally constrained from accessing services appropriately and this is, in turn, driven by underlying norms and values, levels of education and socio-economic wellbeing.

Figure 1. Framework of interventions including HSS



Source: (Vassall et al., 2016)

One last set of frameworks that can be used to identify HSS requirements is derived from the theory-driven programme management and evaluation approaches introduced in section 2.1.1 Feasibility and health system constraints. These frameworks, which include programme theory and realist evaluation, reflect a broad understanding of interventions as complex and adaptive, and recognise the central role of the interaction between the intervention and the context in shaping successful implementation (Anderson and Hardwick, 2016, Mangham-Jefferies et al., 2014, Mukumbang et al., 2018, Mukumbang et al., 2016). However, the frameworks may not specifically incorporate a pre-conceived concept of the health system, which makes them ill-suited for identifying specific constraints to be included in economic analyses. Moreover, the focus on interface in the complex interventions literature does not extend to costs, which are instead treated as either a characteristic of the intervention or of the context, rather than of their dynamic interaction (Pitt, 2020).

For this reason, this thesis will use the framework by Vassall and colleagues, which was developed specifically to assist economic evaluations (Vassall et al., 2016), as the basis for identifying the relevant health system constraint for a given context and interventions, and it will explore alternative methodologies for expanding the framework to include dynamic interactions (Verguet et al., 2019).

2.1.3 Extra-welfarism, allocative efficiency and opportunity costs

From a health economics viewpoint, the importance of constraints for priority setting stems from the insight that, without accounting for the enabling investments to relax them, the efficiency of new interventions cannot be accurately assessed. Efficiency refers to the relationship between inputs and outputs, so that an investment is efficient to the extent that resources are being used in a way that maximises value for money (Williams, 1988). If resources could be reallocated in a way that increases the health outcomes produced, for example by investing in an alternative intervention that uses less of a constrained input, or by investing horizontally in a service delivery platform to improve outcomes for a range of interventions, then the initial investment is considered inefficient.

Value-for money-assessments in health economics take an extra-welfarist approach. This, according to Brouwer and colleagues, differs from welfarism in four ways (Brouwer et al., 2008): "(i) it permits the use of outcomes other than utility; (ii) it permits the use of sources of valuation other than the affected individuals; (iii) it permits the weighing of outcomes (whether utility or other) according to principles that need not be preference-based and (iv) it permits interpersonal comparisons of well-being in a variety of dimensions". This distinction is key for priority setting in health care as, under welfarism, the unit for valuing outcomes is the individual, the distribution of welfare across society is irrelevant and any reallocation that would make any individuals worse off is rejected as inefficient (Brouwer et al., 2008, Coast et al., 2008). Under extra-welfarism, instead, resource allocations that might increase the welfare of a large portion of society at the expense of a handful of individuals would be judged *allocatively efficient*, in that they maximise the welfare of the community (Palmer and Torgerson, 1999).

In addition to setting the decision rule for efficient health care resource allocation, extra-welfarism allows for the consideration of other decision criteria that are not preference-based, such as equity or feasibility. The societal perspective it adopts also has implications for the definition of the opportunity costs that should be considered in economic evaluations. These opportunity costs should represent the true social value of the second-best use of resources forgone (Drummond et al., 2005, Sandmann et al., 2018).

2.2 ECONOMIC METHODS FOR PRIORITY SETTING AND CONSTRAINTS

In health economic evaluations, the value of new interventions is normally assessed by conducting pairwise comparisons between alternatives and selecting the more effective interventions whose incremental cost-effectiveness ratio (ICER) fall below a cost-effectiveness threshold (Drummond et al., 2015). This standard decision rule relies on several assumptions (Birch and Gafni, 1992, Claxton et al., 2015, van Baal et al., 2018), including that:

- the health budget is the only constraint and maximisation of health outcomes the only objective;
- costs and effects of new interventions are independent of other interventions being adopted;
- interventions exhibit constant returns to scale and are perfectly divisible;
- the cost-effectiveness threshold is known and corresponds to the opportunity cost of the comparator being displaced by the investment in the new intervention;
- we have perfect information on the effectiveness-cost ratios of all interventions currently implemented and can select the least effective one to disinvest from;
- the new intervention consumes a relative small share of the health care budget and thus only has a marginal impact on the opportunity cost threshold.

However, as these assumptions are by definition a simplification of reality, they rarely hold in practice. New interventions often represent a large proportion of the available funds and therefore have a non-marginal impact on opportunity costs (Lomas et al., 2018). This is of particular concern in LMICs, where health budgets are limited and new investments may represent a larger relative share (Mills, 2014). Secondly, there are often ethical constraints that prevent interventions from being rationed, thus breaking the divisibility assumption (Cleary et al., 2011); and divestment is usually not an option that is considered politically viable, and often happens by stealth or consequence rather than deliberate action, not least due to lack of routine information on the effectiveness-cost ratios of existing interventions within a health system and on the applicable opportunity cost threshold (Ochalek et al., 2018). Lastly, and of greatest relevance for the scope of this thesis, policymakers often apply several criteria other than health maximisation when making decisions and are faced with different constraints, not all of which can be removed by increasing the health care budget, at least in the short run. Moreover, in the presence of health system constraints, returns to scale might not be constant; and the ICER of a new intervention may well depend on any HSS investments made in the delivery platform on which it relies (Hauck et al., 2019). In other words, any non-financial constraints determining feasibility fall outside of the standard economic evaluation framework. Therefore, a crucial question is whether they can be accommodated within the estimation of opportunity costs or whether feasibility should be weighed against cost-effectiveness as an additional decision criterion.

Modifications to economic evaluation methods have been proposed for dealing with additional priority setting objectives, particularly equity and social protection, including recommending consistent use of the societal perspective (Wilkinson et al., 2016), assessing cost-effectiveness in different population groups (Asaria et al., 2015a, Asaria et al., 2015b) and calculating metrics representing the incremental cost per poverty case averted to be presented alongside the ICER of new interventions (Verguet et al., 2015a, Verguet et al., 2013, Verguet et al., 2015b). Feasibility however, both as a decision criterion (political feasibility) and as a constraint to implementation, has rarely been the subject of explicit and systematic consideration in economic analyses.

In simple terms, the consideration of constraints into priority setting approaches requires a combination of these four core steps (see Figure 2 in Chapter 3):

1. Identifying and characterising the relevant constraints;
2. Gathering evidence about the pathways and extent to which constraints apply to the relevant intervention strategies within the local context;
3. Ranking strategies by incorporating in the analysis either
    a. A quantification of the impact of constraints on the costs and/or effectiveness of interventions OR
    b. A weighting (formal or informal) based on the impact and relative importance of constraints;
4. Deliberation, combining evidence produced by the analysis and the views of stakeholders.

Steps 3 and 4 are governed by the overarching priority setting process. Different priority setting approaches can be distinguished by: (i) the way they incorporate cost-effectiveness; (ii) the extent and way in which they arrive at the optimal combination of interventions algorithmically; and (iii) the process they use to involve stakeholders.

The following sections provide an overview of the theoretical frameworks that are available for incorporating constraints in economic evaluation and that this research draws on.

2.2.1 Incorporating constraints within cost-effectiveness analysis

A first set of priority setting approaches aim to incorporate as much information as possible in the ICERs for different intervention strategies.

Mathematical programming

The first of these approaches is mathematical programming, defined as "that branch of mathematics dealing with techniques for maximizing or minimizing an objective function subject to linear, non-linear, and integer constraints on the variables" (Dantzig and Thapa, 1997). Given a mathematical expression of existing health system constraints, whether financial or non-financial, this technique can be used to maximise cost-effectiveness under the constraint(s) and/or to achieve multiple policy goals using multi-objective optimisation (Cleary et al., 2010, Epstein et al., 2007). A recent application of this approach sought to assist policymakers to define a health benefits package that is simultaneously efficient (maximising population health) and averts catastrophic health expenditure to the largest possible extent, by using multi-objective optimisation across different choice sets (Karsu and Morton, 2021). Another example by Hontelez and colleagues aimed to inform priority setting for disease control using a transmission model to assess the cost-effectiveness of expanding HIV treatment eligibility in sub-Saharan Africa under a series of constrained scenarios (Hontelez et al., 2016). In this application, a scenario where a set of unspecified constraints affecting the pace of intervention scale-up restricts the output of a stochastic micro-simulation model was compared to several scenarios where once-off health system improvement costs were factored in to achieve different levels of implementation of the modified treatment guidelines (Hontelez et al., 2016).

Mathematical programming can be used to address both types of priority setting decisions around HSS introduced in section 2.1.2 Health systems strengthening frameworks: (1) incremental investment decisions, around the specific HSS actions needed to deliver the intervention at scale; and (2) sectoral investment decisions, on how to balance resources between horizontal and vertical HSS. A summary of published theoretical frameworks, the priority setting decision problems and constraints they address is provided in Table 1.

Table 1. Summary of published theoretical frameworks for addressing HSS

Framework	**Decision problem**	**Implementation issue addressed**	**Interaction with other interventions**
Value of implementation (Fenwick et al., 2008)	Used for decision type 1. Two stage decision: (1) approve technology; (2) approve costs to implement it at different coverage levels	Any	No explicit consideration of spill over outcomes of HSS (but also not ruled out). Can be used for multiple interventions
(van Baal et al., 2018)	Used for decision type 1 One stage decision: to invest in intervention or not, given current performance of the health system	HS constraints leading to input constraints in the short run	NA
(Morton et al., 2016)	Used for decision type 2 One stage: to allocate investment across intervention and HSS	HSS to improve productivity (health benefits per investment) generically	Can be used for multiple interventions
(Hauck et al., 2019)	Used for decision type 2 One stage: to allocate investment across intervention and HSS	Different HSS models for platforms to: a) improve efficiency b) increase capacity c) increase reach	Can be used for multiple interventions

Source: (Vassall et al., 2019)

Value of implementation is a framework that explicitly considers the additional 'implementation activities' required for replicating in real-world settings (actual implementation) the effectiveness observed in optimal clinical trial conditions (perfect implementation) (Fenwick et al., 2008, Kim and Basu, 2017). It is thus best suited for answering questions on incremental investments (type 1). In this static framework, value of implementation is defined as the incremental net benefit of the implementation activity and it is calculated as the difference between the expected value of actual implementation and the cost of the implementation activity (Walker et al., 2014). The value of implementation, expressed in either monetary or health units, can be incorporated in the ICER and it is linked to the value of the intervention being evaluated: the higher the value of the intervention, the greater the potential scope for investment in encouraging uptake to bridge the gap between expected and perfect implementation. However, while the value of implementation theory views investment decisions in interventions and enablers as simultaneous rather than sequential (Hoomans et al., 2009), it still essentially treats the intervention as separate from the implementation activities within a static frame. Moreover, the value of implementation literature is mostly focussed on priority setting for health technologies in high-income countries, and on implementation activities to relieve proximal constraints to intervention uptake (e.g. patient and provider knowledge) (Faria et al., 2014). The only LMIC application seeks to advise the government of Malawi on the definition of a health benefits package and considers the maximum investment in HSS for each intervention in the package for it to remain cost-effective (Ochalek et al., 2018). The maximum value of the HSS investment to relieve constrains is equals the cost per disability-adjusted life-year (DALY) averted at the current implementation level, multiplied by the DALYs averted at 100% coverage (Ochalek et al., 2018). Thus, this approach does not require the definition of the specific health system constraints that apply in the context. However, the approach does require information on the current opportunity cost of all interventions currently implemented in the health sector, which is not routinely available in many countries. Moreover, while the application in Malawi addresses a decision on balancing investments across new interventions and HSS, the interventions are viewed individually and, due to the fact that the specific constraints and HSS types are not defined, the spill-over effects of any HSS on other interventions cannot be taken into account in this instance. In the absence on guidance on identifying and operationalising health system constraints, the approach cannot be used prospectively for addressing priority setting questions around HSS investment at the sectoral level.

Van Baal and colleagues also address priority setting decisions around incremental investments in new technologies by proposing an adjustment to the ICER reflecting the extent to which the new technology makes use of physical inputs such as human resources that may be scarce in the short run (van Baal et al., 2018). The authors point out that a situation where an input is constrained is equivalent to having two separate health care budgets, one for the constrained input and one for the unconstrained input, each with its own cost-effectiveness threshold equivalent to its opportunity cost. For example, if human resources are constrained, then an intervention that requires additional nursing time will have a higher opportunity cost in terms of health gains foregone compared to investing the same amount in other inputs that are not constrained. The authors thus demonstrate how, in the presence of constant returns to scale and an efficient inputs mix, the ICER can be adjusted by weighting the cost of the constrained input to reflect its higher opportunity cost compared to other inputs. To carry out the adjustment, they posit that the ratio of the shadow price of the constrained input to non-constrained inputs can be identified as the ratio of the cost of the constrained input to the unconstrained input per health care unit produced observed during the delivery of the intervention (van Baal et al., 2018). Revill and colleagues applied this method to revise the ICER of routine viral load monitoring for differentiating ART delivery, an intervention that is costly but has the potential to decrease demand for constrained human resource time by reducing the number of clinic visits (Revill et al., 2018). This application shows that the method is empirically feasible. However, it relies on the assumption that input costs accurately represent current relative opportunity costs of inputs. This is unlikely to hold in LMICs, given data scarcity on the relationship between costs, outputs and outcomes. Another setting-specific limitation is that the approach relies on the estimation of health sector opportunity cost-based thresholds. More general limitations are the assumption of constant returns to scale, and the fact that the approach does not present policymakers with a choice set that includes relaxing nonfinancial constraints.

Finally, Morton, Hauck and colleagues put forward theoretical frameworks for answering questions on sectoral priority setting, to balance vertical investments in disease-specific interventions with horizontal HSS investments to strengthen service delivery platforms to improve multiple health outcomes. Morton and colleagues consider the case where HIV, TB and malaria services are delivered under vertical programmes but share a common (horizontal) platform (Morton et al., 2016). They propose a mathematical model with an objective function that maximises health benefits subject to a budget given that: a) each intervention exhibits constant returns to scale; b) interventions are independent from one another; c) costs can be disaggregated into health system and service delivery costs; and, d) all costs are incurred within a fixed time period.

$$
\begin{aligned}
\max \quad & \sum_{j\in J} w_j y_j^{\gamma} \sum_{i\in I(j)} v_{i,j} x_{i,j} \\
s.t. \quad & \textstyle\sum_{j\in J} y_j + \sum_{j\in J} \sum_{i\in I} c_{i,j} x_{i,j} \leq b \qquad (1) \\
& p_j \leq y_j \leq P_j \\
& 0 \leq x_{i,j} \leq 1 \\
& \qquad\qquad \forall j \in J \qquad\qquad \forall i \in I\,(j)\, \forall j \in J
\end{aligned}
$$

In their model, captured in equation 1, I is the index of interventions (e.g. antiretroviral therapy delivery, provision of bed nets for malaria) within the vertical disease programmes J, the v and c terms represent the benefits and costs of each intervention, respectively, x is the proportion of each intervention that is implemented and y represents expenditure on HSS. The weighted power term $w_j y_j^{\gamma}$ models the effectiveness of the health system for programme j given an investment of y_j. The parameterisation of the power term alters the extent to which the production function between HSS (strengthening the platform) and health outcomes is concave. As the parameter for the power term increases, so does the optimal proportion of HSS investment to the total investment. Characterising the impact of HSS in this non-linear objective function allows economies of scope to be reflected.

Hauck and colleagues expand on the work by Morton to characterise different types of HSS reflecting different objectives related to health maximisation (Hauck et al., 2019). Once again, the health system is viewed as a platform where investment may impact multiple health outcomes. However, Hauck and colleagues distinguish between different types of HSS: 1) to improve the efficiency of existing shared platforms (as for Morton et *al*.); 2) to relax capacity constraints (expanding on van Baal et *al*.); or 3) to expand coverage by investing in new platforms. As with Morton, they develop a range of mathematical models that determine the optimal balance between investment in HSS and service delivery for each of these mechanisms for health outcome improvement (Hauck et al., 2019).

Linkage of health system and disease transmission models

An alternative approach to mathematical programming for incorporating constraints within the ICER combines health system models, either operational or system dynamics, with infectious disease transmission models (Curran et al., 2016, Langley et al., 2014, Lin et al., 2011). The health system model outputs are then used to restrict transmission model outputs, which, in turn, are used to generate estimates of intervention effect and of total costs by attaching unit costs. In this way, costs and effect estimates reflect real-world implementation levels in the presence of constraints. Given the level of detail on the context required to parametrise health system models, this approach is potentially data intensive. However, it has the advantage of explicitly capturing specific constraints and analysing the mechanisms by which they impact interventions by linking process to outcomes. Due to the mechanical complexity of linking disease transmission and health system models, to date this approach has only had limited application in economic evaluation.

2.2.2 Incorporating constraints alongside cost-effectiveness analysis

Secondly, economists have looked to multi-criteria decision analysis (MCDA) as a set of tools for informing policy-makers considering other criteria in decision processes alongside (but external to) cost-effectiveness analysis (Baltussen et al., 2010, Peacock et al., 2009). According to Peacock and colleagues, "The primary aim of MCDA is to develop models of decision-maker objectives and their value trade-offs so that alternatives under consideration can be compared with each other in a consistent and transparent manner. A key principle is that decisions between different interventions should be consistent with stakeholders' objectives" (Peacock et al., 2009). A key requirement of MCDA for deciding on resource allocation is that researchers cooperate with policy-makers to define a set of locally relevant decision criteria through semi-structured discussion (Peacock et al., 2009). In this case, 'feasibility' constraints for different interventions are considered alongside costs, impact and other decision criteria. MCDA can then weight these criteria and use them to rank interventions in an algorithmic or in a more deliberative way, combining qualitative and quantitative information. The algorithmic approach would necessitate the quantification of the constraints, whereas more deliberative methods may use descriptive evidence and expert elicitation, followed by a qualitative interpretation of the relative importance of criteria/constraints and of their effect on the intervention strategies being examined (Dolan, 2010, Goetghebeur et al., 2008). For this reason, compared to mathematical programming and to algorithmic MCDA techniques, deliberative MCDA methods can more easily accommodate considerations around policy objectives and intervention feasibility that are not immediately quantifiable.

There are several MCDA methods that require the quantification of constraints. These include, for example, 'even swaps', where decision makers quantify the changes required for making options equivalent (e.g. a patient would be willing to accept a 50% increase in the price of a drug to obtain a 10% increase in its effectiveness at halting disease progression); multi-attribute utility analysis, which involves generating and using utility functions to describe how well the options meet the criteria; and discrete choice experiments, which cannot be designed without some prior quantification of the performance of each decision option (e.g. a contraception method) according to the decision criteria (e.g. efficacy at preventing sexually transmitted infections) (Dolan, 2010, Marsh et al., 2013).

In summary, in those approaches that are embedded in cost-effectiveness analysis the relative importance of constraints is captured in the ranking of interventions based on ICERs. In algorithmic MCDA, it is captured through value-based or discrete choice mathematical approaches used to rank interventions (e.g. utility functions, direct weighting or discrete choice experiments). The non-algorithmic MCDA methods bypass the ranking stage and the importance of objectives and constraints is established entirely through deliberation with experts and stakeholders (Goetghebeur et al., 2012, Goetghebeur et al., 2008, Tromp et al., 2018).

2.2.3 Informing priority setting

The choice of priority setting approach not only determines the way cost-effectiveness is treated analytically, but also impacts the procedures for decision criteria and constraints identification as well as the deliberation process with stakeholders. In particular, which stakeholders to include and how they should be approached to elicit preferences and opinions can be defined in a process with multiple steps that are specific to the context and intervention. The mode and extent to which deliberation is organised can also take different forms.

Designing deliberative processes to support resource allocation decisions can be particularly challenging in LMICs, where priority setting is not fully institutionalised (it may not happen in group settings) and decision-making can be subject to power dynamics that are unique to each setting, decision-making level and policy cycle. Particular challenges were documented in contexts where the decision process is less based on evidence and more *ad hoc*, the gap between health care needs and available resources is wide and decisions are the result of power dynamics favouring a minority of stakeholders, as is often the case in LMICs (Baltussen et al., 2013, Barasa et al., 2016). In this sense, an important obstacle to the routine application of priority setting is that, while the aim is to arrive at a decision on resource allocation that is rational, there is no guarantee about its fairness unless conditions are put in place to ensure that a wide range of stakeholders are involved and that all relevant decision criteria are considered (Baltussen et al., 2013). To overcome the risk of providing incomplete information to policy-makers and ensure a fair process, Baltussen and colleagues have proposed to supplement the application of MCDA techniques with the use of an accountability for reasonableness (A4R) framework, in what they term an 'evidence-informed deliberative process' (Baltussen et al., 2016, Baltussen et al., 2017, Tromp et al., 2018). The A4R framework poses four conditions to the priority setting process: (a) relevance, ensuring all stakeholders are involved and in agreement on the reasons at the basis of decisions; (b) publicity, to ensure transparency on the rationale for decisions; (c) revisions, to reassess the initial outcomes in light of any new evidence; and (d) leadership, to regulate the process and ensure enforcement of these conditions (Daniels and Sabin, 2008).

However, guidance is not clearly outlined on how to identify all relevant stakeholders and ensure their participation in priority setting.

In contrast, using mathematical optimisation approaches may require less involvement of stakeholders in key aspects of the decision process; and may lack transparency. Compounding this challenge are data scarcity, which can be an issue in populating models and characterising constraints and their effects, coupled with sometimes limited capacity on the part of decision-makers to absorb the evidence generated using complex and unfamiliar techniques (van Baal et al., 2018). Process limitations may also be particularly acute when used to incorporate constraints or intervention feasibility aspects that are difficult to define quantitively. Qualitative impressions or judgements may instead be limited in cases where decisions are not taken by consumers/patients but by policy makers, who do not directly experience the constraints nor the consequences of their choices.

REFERENCES

ANDERSON, R. & HARDWICK, R. 2016. Realism and resources: Towards more explanatory economic evaluation. *Evaluation (Lond),* 22**,** 323-341. 10.1177/1356389016652742.

ASARIA, M., GRIFFIN, S. & COOKSON, R. 2015a. Distributional cost-effectiveness analysis: A tutorial. *Med Decis Making,* 36**,** 8-19.

ASARIA, M., GRIFFIN, S., COOKSON, R., WHYTE, S. & TAPPENDEN, P. 2015b. Distributional cost-effectiveness analysis of health care programmes - a methodological case study of the UK bowel cancer screening programme. *Health Econ,* 24**,** 742-54.

BALTUSSEN, R., JANSEN, M. P., MIKKELSEN, E., TROMP, N., HONTELEZ, J., BIJLMAKERS, L. & VAN DER WILT, G. J. 2016. Priority setting for Universal Health Coverage: We need evidence-informed deliberative processes, not just more evidence on cost-effectiveness. *Int J Health Policy Manag,* 5**,** 615-618.

BALTUSSEN, R., JANSEN, M. P. M., BIJLMAKERS, L., GRUTTERS, J., KLUYTMANS, A., REUZEL, R. P., TUMMERS, M. & VAN DER WILT, G. J. 2017. Value assessment frameworks for HTA agencies: The organisation of evidence-informed deliberative processes. *Value in Health,* 20**,** 256-60.

BALTUSSEN, R., MIKKELSEN, E., TROMP, N., HURTIG, A., BYSKOV, J., OLSEN, O., BAEROE, K., HONTELEZ, J. A., SINGH, J. & NORHEIM, O. F. 2013. Balancing efficiency, equity and feasibility of HIV treatment in South Africa - development of programmatic guidance. *Cost Eff Resour Alloc,* 11**,** 26

BALTUSSEN, R., YOUNGKONG, S., PAOLUCCI, F. & NIESSEN, L. 2010. Multi-criteria decision analysis to prioritize health interventions: capitalizing on first experiences. *Health Policy,* 96**,** 262-264.

BARASA, E. W., CLEARY, S., ENGLISH, M. & MOLYNEUX, S. 2016. The influence of power and actor relations on priority setting and resource allocation practices at the hospital level in Kenya: a case study. *BMC Health Services Research,* 16**,** 536.

BIRCH, S. & GAFNI, A. 1992. Cost effectiveness/utility analyses. Do current decision rules lead us to where we want to be? *J Health Econ,* 11**,** 279-296.

BROUWER, W. B., CULYER, A. J., VAN EXEL, N. J. & RUTTEN, F. F. 2008. Welfarism vs. extra-welfarism. *J Health Econ,* 27**,** 325-38. 10.1016/j.jhealeco.2007.07.003.

CLAXTON, K., MARTIN, S., SOARES, M., RICE, N., SPACKMAN, E., HINDE, S., DEVLIN, N., SMITH, P. C. & SCULPHER, M. 2015. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. *Health Technol Assess,* 19**,** 1-503, v-vi. 10.3310/hta19140.

CLEARY, S., MOONEY, G. & MCINTYRE, D. 2010. Equity and efficiency in HIV-treatment in South Africa: the contribution of mathematical programming to priority setting. *Health Econ,* 19**,** 1166-1180.

CLEARY, S. M., MOONEY, G. H. & MCINTYRE, D. E. 2011. Claims on health care: A decision-making framework for equity, with application to treatment for HIV/AIDS in South Africa. *Health Policy Plan,* 26**,** 464-470.

COAST, J., SMITH, R. D. & LORGELLY, P. 2008. Welfarism, extra-welfarism and capability: the spread of ideas in health economics. *Soc Sci Med,* 67**,** 1190-8. 10.1016/j.socscimed.2008.06.027.

CURRAN, M., HOWLEY, E. & DUGGAN, J. An analytics framework to support surge capacity planning for emerging epidemics. 2016. Association for Computing Machinery, Inc, 151-155.

DANIELS, N. & SABIN, J. E. 2008. Accountability for reasonableness: an update. *BMJ,* 337**,** a1850. 10.1136/bmj.a1850.

DANTZIG, G. B. & THAPA, M. N. 1997. *Linear programming 1: Introduction,* New York, Springer-Verlag.

DOLAN, J. G. 2010. Multi-criteria clinical decision support: A primer on the use of multiple criteria decision making methods to promote evidence-based, patient-centered healthcare. *Patient,* 3**,** 229-248.

DRUMMOND, M. F., SCULPHER, M., CLAXTON, K., STODDART, G. & TORRANCE, G. 2015. *Methods for the economic evaluation of health care programmes*, Oxford University Press.

DRUMMOND, M. F., SCULPHER, M. J., TORRANCE, G. W., O'BRIEN, B. J. & STODDART, G. L. 2005. *Methods for the economic evaluation of health care programmes,* Oxford, Oxford University Press.

ENGLAND, R. 2007. The dangers of disease specific aid programmes. *BMJ,* 335**,** 565. https://doi.org/10.1136/bmj.39335.520463.94.

EPSTEIN, D., CHALABI, Z., CLAXTON, K. & SCULPHER, M. 2007. Efficiency, equity and budgetary policies: informing decisions using mathematical programming. *Med Decis Making,* 27**,** 128-137.

FARIA, R., WALKER, S., WHYTE, S., DIXON, S., PALMER, S. & SCULPHER, M. 2014. Getting cost-effective technologies into practice: the value of implementation. An application to novel anticoagulants in the prevention of stroke and systemic embolism. Policy Research Unit in Economic Evaluation of Health & Care Interventions (EEPRU).

FENWICK, E., CLAXTON, K. & SCULPHER, M. 2008. The value of implementation and the value of information: combined and uneven development. *Med Decis Making,* 28**,** 21-32. 10.1177/0272989X07308751.

GARRETT, L. 2007. The challenge of global health. *Foreign Affairs* [Online]. Available: https://www.foreignaffairs.com/articles/2007-01-01/challenge-global-health [Accessed July/August 2007].

GERICKE, C. A., KUROWSKI, C., RANSON, M. K. & MILLS, A. 2005. Intervention complexity - a conceptual framework to inform priority-setting in health. *Bull World Health Organ,* 83**,** 285-293.

GOETGHEBEUR, M. M., WAGNER, M., KHOURY, H., ERICKSON, L. J. & RINDRESS, D. 2012. Bridging Health Technology Assessment (HTA) and efficient care decision making with Multicriteria Decision Analysis (MCDA): Applying the EVIDEM framework to medicines appraisal. *Med Decis Making*.

GOETGHEBEUR, M. M., WAGNER, M., KHOURY, H., LEVITT, R. J., ERICKSON, L. J. & RINDRESS, D. 2008. Evidence and Value: Impact on DEcisionMaking--the EVIDEM framework and potential applications. *BMC Health Serv Res,* 8**,** 270. 10.1186/1472-6963-8-270.

GUINDO, L. A., WAGNER, M., BALTUSSEN, R., RINDRESS, D., VAN TIL, J., KIND, P. & GOETGHEBEUR, M. M. 2012. From efficacy to equity: Literature review of decision criteria for resource allocation and healthcare decisionmaking. *Cost Eff Resour Alloc,* 10.

HAFNER, T. & SHIFFMAN, J. 2013. The emergence of global attention to health systems strengthening. *Health Policy Plan,* 28**,** 41-50. 10.1093/heapol/czs023.

HANSON, K., RANSON, M. K., OLIVEIRA-CRUZ, V. & MILLS, A. 2003. Expanding access to priority health interventions: a framework for understanding the constraints to scaling up. *J Int Dev,* 15**,** 1-14.

HAUCK, K., MORTON, A., CHALKIDOU, K., CHI, Y. L., CULYER, A., LEVIN, C., MEACOCK, R., OVER, M., THOMAS, R., VASSALL, A., VERGUET, S. & SMITH, P. C. 2019. How can we evaluate the cost-effectiveness of health system strengthening? A typology and illustrations. *Soc Sci Med,* 220**,** 141-149.

HAUCK, K. & SMITH, P. C. 2015. The politics of priority setting in health: A political economy perspective. *CGD Working Paper 414.* Washington, DC: Center for Global Development

HAUCK, K., THOMAS, R. & SMITH, P. C. 2016. Departures from cost-effectiveness recommendations: The impact of health system constraints on priority setting. *Health Systems & Reform,* 2**,** 61-70.

HONTELEZ, J. A. C., CHANGE, A. Y., OGBUOJI, O., DE VLAS, S. J., BARNIGHAUSEN, T. & ATUN, R. 2016. Changing HIV treatment eligibility under health system constraints in sub-Saharan Africa: investment needs, population health gains, and cost-effectiveness. *AIDS,* 30**,** 2341-2350.

HOOMANS, T., SEVERENS, J. L., EVERS, S. M. & AMENT, A. J. 2009. Value for money in changing clinical practice: should decisions about guidelines and implementation strategies be made sequentially or simultaneously? *Med Decis Making,* 29**,** 207-16. 10.1177/0272989X08327397.

KARSU, O. & MORTON, A. 2021. Trading off health and financial protection benefits with multiobjective optimization. *Health Econ,* 30**,** 55-69. 10.1002/hec.4176.

KIM, D. D. & BASU, A. 2017. New Metrics for Economic Evaluation in the Presence of Heterogeneity: Focusing on Evaluating Policy Alternatives Rather than Treatment Alternatives. *Med Decis Making,* 37**,** 930-941. 10.1177/0272989X17702379.

KIM, J. J., SALOMON, J. A., WEINSTEIN, M. C. & GOLDIE, S. J. 2006. Packaging health services when resources are limited: The example of a cervical cancer screening visit. *PLoS Med,* 3**,** e434.

LANGLEY, I., LIN, H., EGWAGA, S., DOULLA, B., KU, C., MURRAY, M., COHEN, T. & SQUIRE, S. B. 2014. Assessment of the patient, health system, and population effects of Xpert MTB/RIF and alternative diagnostics for tuberculosis in Tanzania: an integrated modelling approach. *Lancet Glob Health,* 2**,** e581-91.

LIN, H. H., LANGLEY, I., MWENDA, R., DOULLA, B., EGWAGA, S., MILLINGTON, K. A., MANN, G. H., MURRAY, M., SQUIRE, S. B. & COHEN, T. 2011. A modelling framework to support the selection and implementation of new tuberculosis diagnostic tools. *Int J Tuberc Lung Dis,* 15**,** 996-1004. 10.5588/ijtld.11.0062.

LOMAS, J., CLAXTON, K., MARTIN, S. & SOARES, M. 2018. Resolving the "Cost-Effective but Unaffordable" Paradox: Estimating the Health Opportunity Costs of Nonmarginal Budget Impacts. *Value Health,* 21**,** 266-275. 10.1016/j.jval.2017.10.006.

MANGHAM-JEFFERIES, L., WISEMAN, V., ACHONDUH, O. A., DRAKE, T. L., CUNDILL, B., ONWUJEKWE, O. & MBACHAM, W. 2014. Economic evaluation of a cluster randomized trial of interventions to improve health workers' practice in diagnosing and treating uncomplicated malaria in Cameroon. *Value Health,* 17**,** 783-91. 10.1016/j.jval.2014.07.010.

MARSH, K., DOLAN, P., KEMPSTER, J. & LUGON, M. 2013. Prioritizing investments in public health: a multi-criteria decision analysis. *J Public Health (Oxf),* 35**,** 460-6. 10.1093/pubmed/fds099.

MARTINEZ ALVAREZ, M., BORGHI, J., ACHARYA, A. & VASSALL, A. 2016. Is Development Assistance for Health fungible? Findings from a mixed methods case study in Tanzania. *Soc Sci Med,* 159**,** 161-169.

MIKKELSEN, E., HONTELEZ, J. A. C., JANSEN, M. P. M., BÄRNIGHAUSEN, T., HAUCK, K., JOHANSSON, K. A., MEYER-RATH G., OVER, M., DE VLAS, S. J., VAN DER WILT, G. J., TROMP, N., BIJLMAKERS, L. & BALTUSSEN, R. M. P. M. 2017. Evidence for scaling up HIV treatment in sub-Saharan Africa: A call for incorporating health systems constraints. *PLoS Med,* 14**,** e1002240.

MILLS, A. 2014. Health care systems in low- and middle-income countries. *N Engl J Med,* 370**,** 552-7. 10.1056/NEJMra1110897.

MORTON, A., THOMAS, R. & SMITH, P. C. 2016. Decision rules for allocation of finances to health systems strengthening. *J Health Econ,* 49**,** 97-108.

MUKUMBANG, F. C., MARCHAL, B., VAN BELLE, S. & VAN WYK, B. 2018. "Patients Are Not Following the [Adherence] Club Rules Anymore": A Realist Case Study of the Antiretroviral Treatment Adherence Club, South Africa. *Qual Health Res,* 28**,** 1839-1857. 10.1177/1049732318784883.

MUKUMBANG, F. C., VAN BELLE, S., MARCHAL, B. & VAN WYK, B. 2016. Realist evaluation of the antiretroviral treatment adherence club programme in selected primary healthcare facilities in the metropolitan area of Western Cape Province, South Africa: a study protocol. *BMJ Open,* 6**,** e009977. 10.1136/bmjopen-2015-009977.

OCHALEK, J., REVILL, P., MANTHALU, G., MCGUIRE, F., NKHOMA, D., ROLLINGER, A., SCULPHER, M. & CLAXTON, K. 2018. Supporting the development of a health benefits package in Malawi. *BMJ Glob Health,* 3**,** e000607. 10.1136/bmjgh-2017-000607.

PALMER, S. & TORGERSON, D. J. 1999. Economic notes: definitions of efficiency. *BMJ,* 318**,** 1136. 10.1136/bmj.318.7191.1136.

PEACOCK, S., MITTON, C., BATE, A., MCCOY, B. & DONALDSON, C. 2009. Overcoming barriers to priority setting using interdisciplinary methods. *Health Policy,* 92**,** 124-132.

PITT, C. K. 2020. *Promoting transferability: Insights from economic evaluations of public health interventions to tackle malaria in central Senegal.* PhD, London School of Hygiene & Tropical Medicine.

REVILL, P., WALKER, S., CAMBIANO, V., PHILLIPS, A. & SCULPHER, M. J. 2018. Reflecting the real value of health care resources in modelling and cost-effectiveness studies - The example of viral load informed differentiated care. *PLoS One,* 13**,** e0190283.

SANDMANN, F. G., ROBOTHAM, J. V., DEENY, S. R., EDMUNDS, W. J. & JIT, M. 2018. Estimating the opportunity costs of bed-days. *Health Econ,* 27**,** 592-605. 10.1002/hec.3613.

SCHWARTLANDER, B., STOVER, J., HALLETT, T., ATUN, R., AVILA, C., GOUWS, E., BARTOS, M., GHYS, P. D., OPUNI, M., BARR, D., ALSALLAQ, R., BOLLINGER, L., DE FREITAS, M., GARNETT, G., HOLMES, C., LEGINS, K., PILLAY, Y., STANCIOLE, A. E., MCCLURE, C., HIRNSCHALL, G., LAGA, M., PADIAN, N. & INVESTMENT FRAMEWORK STUDY, G. 2011. Towards an improved investment approach for an effective response to HIV/AIDS. *Lancet,* 377**,** 2031-41. 10.1016/S0140-6736(11)60702-2.

SENDI, P. P. & BRIGGS, A. H. 2001. Affordability and cost-effectiveness: decision-making on the cost-effectiveness plane. *Health Econ,* 10**,** 675-680.

SHEIKH, K., GILSON, L., AGYEPONG, I. A., HANSON, K., SSENGOOBA, F. & BENNETT, S. 2011. Building the field of health policy and systems research: framing the questions. *PLoS Med,* 8**,** e1001073. 10.1371/journal.pmed.1001073.

TROMP, N. & BALTUSSEN, R. 2012. Mapping of multiple criteria for priority setting of health interventions: An aid for decision makers. *BMC Health Services Research,* 12**,** 454.

TROMP, N., PRAWIRANEGARA, R., SIREGAR, A., WISAKASANA, R., PINXTEN, L., PINXTEN, J., PUTRA, A. L., LESMANA, D. S., JANSEN, M., HONTELEZ, J., MAURITS, S., MAHARANI, F., BIJLMAKERS, L. & BALTUSSEN, R. 2018. Translating international HIV treatment guidelines into local priorities in Indonesia. *Trop Med Int Health,* 23**,** 279-294.

VAN BAAL, P., MORTON, A. & SEVERENS, J. L. 2018. Health care input constraints and cost effectiveness analysis decision rules. *Soc Sci Med,* 200**,** 59-64. 10.1016/j.socscimed.2018.01.026.

VAN BAAL, P., THONGKONG N. & SEVERENS, J. L. 2016. Human resource constraints and the methods of economic evaluation of health care technologies. *iDSI Methods Working Group.* Rotterdam.

VASSALL, A., BOZZANI, F. & HANSON, K. 2019. Considering Health-Systems Constraints in Economic Evaluation in Low- and Middle-Income Settings. *Oxford Research Encyclopaedias*

VASSALL, A., MANGHAM-JEFFERIES, L., GOMEZ, G. B., PITT, C. & FOSTER, N. 2016. Incorporating demand and supply constraints into economic evaluation in low-income and middle-income countries. *Health Econ,* 25**,** 95-115. 10.1002/hec.3306.

VERGUET, S., FELDHAUS, I., JIANG KWETE, X., AQIL, A., ATUN, R., BISHAI, D., CECCHINI, M., GUERRA JR, A. A., HABTEMARIAM, M. K., JBAILY, A., KARANFIL, O., KRUK, M. E., HANEUSE, S., NORHEIM, O. F., SMITH, P. C., TOLLA, M. T., ZEWDU, S. & BUMP, J. 2019. Health system modelling research: towards a whole-health-system perspective for identifying good value for money investments in health system strengthening. *BMJ Glob Health,* 4**,** e001311.

VERGUET, S., LAXMINARAYAN, R. & JAMISON, D. T. 2015a. Universal public finance of tuberculosis treatment in India: an extended cost-effectiveness analysis. *Health Econ,* 24**,** 318-332.

VERGUET, S., MURPHY, S., ANDERSON, B., JOHANSSON, K. A., GLASS, R. & RHEINGANS, R. 2013. Public finance of rotavirus vaccination in India and Ethiopia: An extended cost-effectiveness analysis. *Vaccine,* 31**,** 4902-4910.

VERGUET, S., OLSON, Z., D.,, BABIGUMIRA, J. B., DESALEGN, D., JOHANSSON, K. A., KRUK, M. E., LEVIN, C. E., NUGENT, R. A., PECENKA, C., SHRIME, M. G., MEMIRIE, S. T., WATKINS, D. A. & JAMISON, D. T. 2015b. Health gains and financial risk protection afforded by public financing of selected interventions in Ethiopia: an extended cost-effectiveness analysis. *Lancet Glob Health,* 3**,** e288-e296.

WALKER, S., FARIA, R., WHYTE, S., DIXON, S., PALMER, S. & SCULPHER, M. 2014. Getting cost-effective technologies into practice: the value of implementation. Report on framework for valuing implementation initiatives. Policy Research Unit in Economic Evaluation of Health & Care Interventions (EEPRU).

WHO 1978. Declaration of Alma-Ata. *WHO Chron,* 32**,** 428-30.

WILKINSON, T., SCULPHER, M., CLAXTON, K., REVILL, P., BRIGGS, A., CAIRNS, J. A., TEERAWATTANANON, Y., ASFAW, E., LOPERT, R., CULYER, A. J. & WALKER, D. G. 2016. The International Decision Support Initiative Reference Case for Economic Evaluation: An aid to thought. *Value in Health,* 19**,** 921-28.

WILLIAMS, A. 1988. Priority setting in public and private health care. A guide through the ideological jungle. *Journal of Health Economics,* 7**,** 173-83.

WORLD BANK 1993. World Development Report 1993: Investing in health. New York.

YU, D., SOUTEYRAND, Y., BANDA, M. A., KAUFMAN, J., PERRIËNS, J. H. & 2008. Investment in HIV/AIDS programs: Does it help strengthen health systems in developing countries? *Globalization and Health,* 4.

CHAPTER 3: BUILDING RESOURCE CONSTRAINTS AND FEASIBILITY CONSIDERATIONS IN MATHEMATICAL MODELS FOR INFECTIOUS DISEASE: A SYSTEMATIC LITERATURE REVIEW

Citation

BOZZANI, F. M., VASSALL, A. & GOMEZ, G. B. 2021. Building resource constraints and feasibility considerations in mathematical models for infectious disease: A systematic literature review. *Epidemics,* Under review.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

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

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	232851	**Title**	Ms
First Name(s)	Fiammetta Maria		
Surname/Family Name	Bozzani		
Thesis Title	Incorporating feasibility in priority setting: A case study of tuberculosis control in South Africa		
Primary Supervisor	Prof. 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

Where was the work published?	Epidemics		
When was the work published?	March 2021		
If the work was published prior to registration for your research degree give a brief rationale for its inclusion	n/a		
Have you retained copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the lead author of this paper. I designed the literature review with input from my co-authors, and was primarily responsible for running the search and extracting and analysing data. I drafted the manuscript, incorporated feedback from co-authors and was responsible for submission to the journal and for carrying out the revisions recommended during the peer review process.

SECTION E

Student Signature	[redacted]
Date	14th March 2021

Supervisor Signature	[redacted]
Date	01/06/2021

3.1 ABSTRACT

Priority setting for infectious disease control is increasingly concerned with physical input constraints and other real-world restrictions on implementation and on the decision process. These health system constraints determine the ‘feasibility’ of interventions and hence impact. However, considering them within mathematical models places additional demands on model structure and relies on data availability. This review aims to provide an overview of published methods for considering constraints in mathematical models of infectious disease.

We systematically searched the literature to identify studies employing dynamic transmission models to assess interventions in any infectious disease and geographical area that included non-financial constraints to implementation. Information was extracted on the types of constraints considered and how these were identified and characterised, as well as on the model structures and techniques for incorporating the constraints.

A total of 36 studies were retained for analysis. While most dynamic transmission models identified were deterministic compartmental models, stochastic models and agent-based simulations were also successfully used for assessing the effects of non-financial constraints on priority setting. Studies aimed to assess reductions in intervention coverage (and programme costs) as a result of constraints preventing successful roll-out and scale-up, and/or to calculate costs and resources needed to relax these constraints and achieve desired coverage levels. We identified three approaches for incorporating constraints within the analyses: (i) estimation within the disease transmission model; (ii) linking disease transmission and health system models; (iii) optimising under constraints (other than the budget).

The review highlighted the viability of expanding model-based priority setting to consider health system constraints. We show strengths and limitations in current approaches to identify and quantify locally relevant constraints, ranging from simple assumptions to structured elicitation and operational models. Overall, there is a clear need for transparency in the way feasibility is defined as a decision criterion for its systematic operationalisation within models.

3.2 INTRODUCTION

The launch of the Sustainable Development Goals, with their focus on Universal Health Coverage, has accelerated a shift in priority setting for health care interventions. The traditional focus on comparing the incremental cost-effectiveness of finite sets of interventions is being complemented with ranking and optimisation exercises across diseases and, in some cases, the whole health sector. Examples include defining essential benefits packages, disease-specific strategic plans and national health insurance coverage schemes for expanding access to health care and avoiding catastrophic costs for patients and households (Jamison et al., 2018). At the same time, it is being increasingly recognised that priority setting should take into account a range of non-financial constraints in any given setting and intervention area (Vassall et al., 2016) while considering multiple objectives alongside efficiency and effectiveness, such as equity and social protection.

Traditionally, the health care budget is the sole constraint considered in resource allocation models. However, policymakers contend with several other constraints affecting *feasibility of implementation*, both on the supply (health system) and demand (patient) sides, when selecting interventions. These constraints may limit the pace of intervention scale-up (e.g. human resources scarcity in the short run); may be insurmountable even with increased resourcing (e.g. prioritisation of specific population groups, or an ethical obligation to provide treatment to all those in need); or may incur costs that are not observable when interventions are tested in research settings. Failure to account for such setting- and intervention-specific influences on the priority setting process itself and on the implementation of the resulting recommendations can result in unfeasible health interventions being recommended and, ultimately, in evidence being disregarded by decision-makers (Hauck et al., 2016, Mikkelsen et al., 2017).

Mathematical models exploring complex systems have made a vital contribution to advancements in priority setting for infectious diseases. The recent development of user-friendly dynamic transmission models to prioritise new health technologies for infectious disease control increasingly allows policymakers to account for setting-specific variations in factors such as epidemiological characteristics and input types and prices (Houben et al., 2016, Lubell et al., 2008, Stegmuller et al., 2017). Moreover, model-based priority setting may allow analysts to consider other country- and intervention-specific non-financial constraints that bind resource allocation decisions. For example, while transmission modelling analyses recommend intensified screening of all clinic patients for reaching the End TB Strategy targets in South Africa, this intervention is highly human resource (HR) intensive and increases the use of diagnostics downstream in the tuberculosis (TB) care cascade (Menzies et al., 2016). Thus, it might be a sub-optimal option compared to others in the TB portfolio when constraints on these inputs are taken into account. In this example, the effect of the constraints on intervention impact is parametrised in the model through changes in the rates of transitions between different compartments or states (the example of human resource constrains for TB care in South Africa is illustrated graphically in the Supplementary material (Figure 4)). However, this may not be the only existing approach to the inclusion of constraints in these analyses.

The aim of this review is to establish how locally relevant non-financial constraints have been incorporated in model-based impact and cost-effectiveness analyses of infectious disease control interventions. In particular, we describe the constraints considered and how these were characterised and quantified in the models. Ultimately, we aim to discuss suitable model structures and techniques for implementing the constraints within them.

3.3 MATERIALS AND METHODS

A systematic search of the published literature was conducted to identify studies published before November 2020, that employ dynamic transmission models to assess infection control interventions in any disease and geographical area and that consider non-financial constraints to implementation. Reporting of results follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement and checklist (Liberati et al., 2009).

3.3.1 Search strategy

The MEDLINE and Embase databases were searched via the OvidSP platform for English language, full text studies on human subjects. The Scopus database was also searched without imposing any limits. The search strategy combined keywords on infectious diseases, dynamic transmission modelling, economic evaluation, priority setting and health systems research, including constraints and feasibility of health interventions. The following Medical Subject Heading (MeSH) terms were ‘exploded’ in MEDLINE and Embase: “Infectious Disease Transmission”, “Public Health Systems Research”, “Systems Analysis”, “Theoretical Models”, “Economic Models”, “Decision Support Techniques”. The full search strategy for each database and number of records retrieved (with and without limits, where applicable) are presented in the Supplementary material. A hand search of the reference lists of retained articles was also conducted to identify other potentially relevant literature.

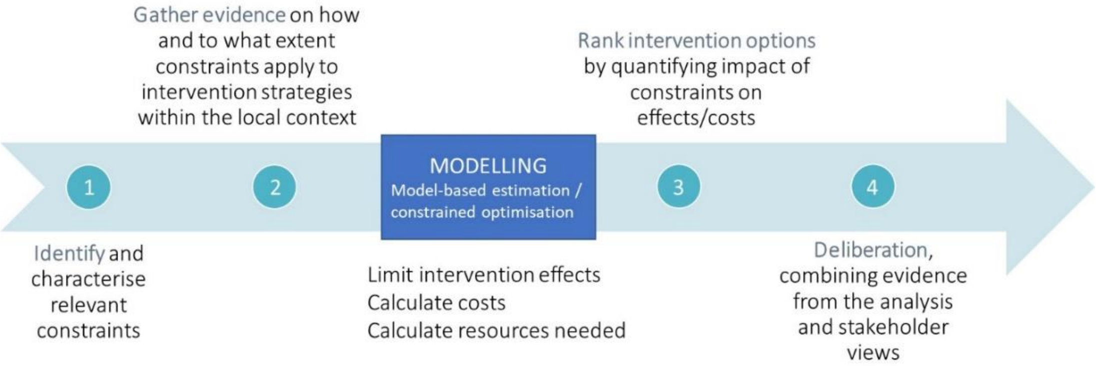
3.3.2 Screening, data extraction and analysis

Search results were exported to EndNote (v. X8) to eliminate duplicates. The abstract and titles of all unique records were then screened and articles were further excluded based on the following criteria: (i) language other than English; (ii) topic not related to human health; (iii) no reference to the application of health system constraints and infectious disease models; (iv) ineligible article type (clinical and/or pragmatic trials, feasibility or pilot or demonstration studies, editorials, conference proceedings, comments, letters and notes). The full texts of remaining articles were then reviewed and retained if they made reference to a formal method of applying non-financial constraints in priority setting using a mathematical model of infectious disease transmission. Articles using 'static' mathematical models or other model types and those that did not consider any constraints other than the budget or financial constraint were discarded.

Data was extracted from the retained records in the following categories: geographical and disease area of interest, type of intervention and level of the health system at which implementation occurred, transmission model structure, model population and projection timeframe, presence and type of economic analysis (including optimisation under a budget constraint), demand- and supply-side non-financial constraints considered as well as methods for identifying and quantifying the constraints, aim of the modelling exercise and formal method of incorporating the constraints in the analysis. The data was summarised using descriptive statistics and a thematic analysis of the contents of the articles was carried out to answer the study question.

For characterising how health system constraints were incorporated in models we drew on the work of Vassall and colleagues, who distinguished between proximal constraints, such as HR and pharmaceutical shortages, and distal constraints, such as cultural norms, values and regulations (Vassall et al., 2016). We then described how these constraints were analysed at different stages in the priority setting process using the framework shown in Figure 2. Steps 1 and 2 refer to the identification and characterisation of health system constraints that apply to the intervention of interest in the specific context; steps 3 and 4 refer to the assessment of the constraints' impact on intervention effects and/or costs, and to how this evidence is used in the deliberation process, highlighting how the views of stakeholders may still play a role alongside the quantitative evidence from modelling.

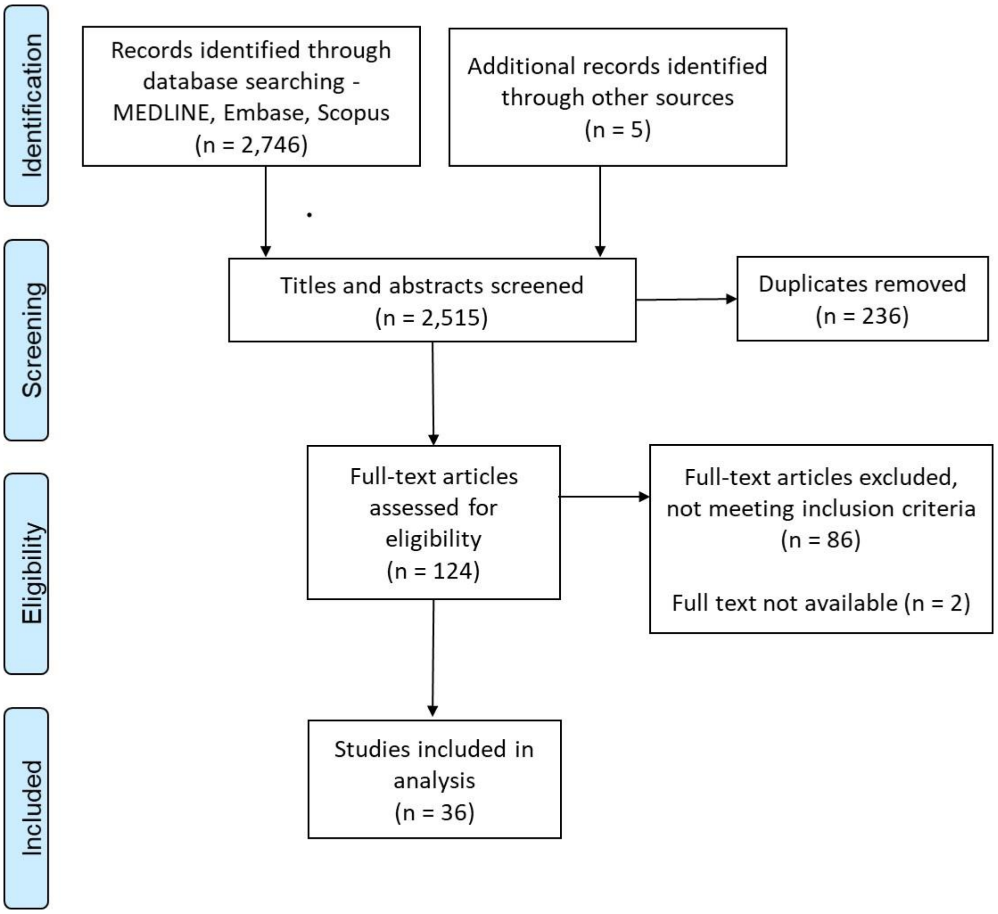
Figure 2. Framework for incorporating health system constraints in priority setting



3.4 RESULTS

We identified 2,751 unique citations, of which approximately one in 20 were eligible for full text screening. The PRISMA flow chart with details of the study screening and selection process is shown in Figure 3.

Figure 3. Flow chart of screening and selection process



After the selection process was completed, 36 studies were retained for analysis. The study characteristics, aims and model structures of all selected papers are summarised in Table 2. Approximately one third of the studies focused on a single country, predominantly in the low- and middle-income group, while eight studies were global in focus and a further three regional (two from sub-Saharan Africa and one from South-East Asia). Another seven studies, mostly from high-income settings, looked at one single municipality or health facility within a country. The disease area most represented in the literature was pandemic influenza, followed by human immunodeficiency virus (HIV) and TB.

Table 2. Study characteristics and mathematical model structure

Lead author (year)	Setting	Disease area	Intervention	Level of health system	Study aim	Transmission model structure	Economic analysis
(Adisasmito et al., 2015)	Local - Bali, Indonesia	Influenza	Pandemic influenza case management capabilities strengthening	Decentralised	Simulate influenza spread at the district level given existing resource gaps to inform preparedness planning	Density-dependent deterministic compartmental model (SEAIR)	-
(Alistar et al., 2013)	Country - not specified	HIV	Multiple, user-defined HIV control interventions	National	Develop a model to guide setting-specific resource allocation across interventions along the HIV cascade	Frequency-dependent deterministic compartmental model (HIV disease stages and treatment status)	Cost-effectiveness analysis
(Anderson et al., 2014, Anderson et al., 2018)	Country - Kenya	HIV	Combination prevention interventions	Decentralised	Model the effect of prioritising key population and of short-term funding cycles on HIV prevention	Frequency-dependent deterministic compartmental model (susceptible, acute-, latent infection, pre-AIDS, AIDS)	Cost analysis
(Bärnighausen et al., 2016)	Country - South Africa	HIV	Treatment as prevention (TaSP)	National	Model the effects of TaSP on universal ART coverage	Frequency-dependent deterministic compartmental model (susceptible, HIV infection stages)	-
(Barker et al., 2017)	Regional - sub-Saharan Africa	HIV	ART differentiated care models	National	Model efficiency gains from different service delivery options	Frequency-dependent deterministic compartmental model (AIDS Impact Model, Estimation Projection Package)	Cost analysis
(Bottcher et al., 2015)	Global	Influenza	Epidemic preparedness	National	Investigate the effects of disease-induced resource constraints on epidemic spreading	Density-dependent deterministic compartmental model (bSIS, recovery rate mediated by resources availability)	-
(Bozzani et al., 2018, Bozzani et al., 2020a, Sumner et al., 2019a)	Country - South Africa	TB	Changes to screening and diagnostic algorithm	National	Develop a pragmatic approach for empirical estimation of health system constraints from routine data to parametrise models	Density-dependent deterministic compartmental model (susceptible, latent infection, active disease)	Cost and cost-effectiveness analysis

(Chen et al., 2019)	Country – not specified	Sexually transmitted infection epidemic	Epidemic control	National	Model the effects of resource availability on rate of infection	Frequency-dependent deterministic compartmental model (SIS, recovery rate mediated by resources availability)	-
(Cruz-Aponte et al., 2011)	Global	Influenza	Flu vaccination campaign during outbreak	National	Develop an accurate model of vaccine stockpiles for epidemic preparedness	Density-dependent deterministic compartmental model (SIR-like model including vaccines supply and numbers vaccinated)	-
(Curran et al., 2016)	Global	General epidemic outbreak	Surge capacity planning	National	Develop a conceptual framework for integrating big data analytics with simulation, to provide real-time analysis of health system capacity during epidemics	Density-dependent deterministic compartmental model (SEIR)	-
(Dalgiç et al., 2017)	Local - Seattle, US	Influenza	Flu vaccination campaign during outbreak	National	Compare age-specific vaccination strategies derived from agent-based simulation and from a deterministic compartmental model	Agent-based simulation and density-dependent deterministic compartmental model (SEIR), enhanced with mesh-adaptive direct search (MADS) algorithm to iteratively improve intervention strategies	Cost analysis
(Ferrer et al., 2014)	Local - France	All-cause ICU visits	Strategies to cope with nurses shortages	Service	Explore impact of management strategies against nurse shortages on pathogen transmission within the ICU	Agent-based simulation	-
(Hecht and Gandhi, 2008)	Global	HIV	AIDS vaccination	National	Model determinants of demand, uptake dynamics and potential revenues from vaccine candidates	Discrete deterministic linear predictive model (vaccinated are a fraction of population in need dynamically estimated based on numbers of susceptibles who have access given constraints)	Cost analysis
(Hontelez et al., 2016)	Regional - sub-Saharan Africa	HIV	ART scale-up (changing eligibility thresholds)	National	Model resource requirements to achieve ART coverage targets	Agent-based simulation	Cost-effectiveness analysis

(Krumkamp et al., 2011)	Country - Thailand	Influenza	Epidemic preparedness	Decentralised	Simulate characteristics of an influenza outbreak and identify resource needs and gaps	Density-dependent deterministic compartmental model (SEAIR)	-
(Langley et al., 2014, Lin et al., 2011)	Country - Tanzania	TB	New diagnostic technologies for parasitic disease	National	Model intervention effects on operational performance of the health system to accurately assess impact and cost-effectiveness	Deterministic compartmental model (SIR-like). Active diseases states of the model are expanded to include pathway from onset to diagnosis and linkage to treatment from operational model	Cost-effectiveness analysis
(Marks et al., 2017)	Global	Yaws	Eradication campaign (mass azythromycin treatment followed by case finding and targeted treatment)	National	Determine the feasibility and optimal strategy for yaws eradication	Stochastic compartmental model (Markov model with susceptibles and primary, latent and secondary infection)	-
(Martin et al., 2015a, Martin et al., 2015b)	Local - New York state, US	HIV	Policy change to increase HIV testing and linkage to care	Decentralised	Assess health outcomes and health system resources needs under different policy implementation scenarios	Stock and flow model with transmission rates that vary by HIV infection stage and ART status	-
(Martin et al., 2011)	Country - UK	HCV	Antiviral treatment among injecting drug users	National	Assess optimal treatment strategy for different economic and policy objectives	Frequency-dependent deterministic compartmental model (susceptible, chronically infected, treated)	Cost analysis
(McKay et al., 2018)	Local - US	HIV	HIV counselling	Service	Describe the relationship between HR, intervention delivery and health outcomes by simulating different HR availability scenarios and observing effects on the other variables	Agent-based simulation	-
(Peak et al., 2020)	Country – not specified	SARS-CoV-2	Epidemic preparedness	National	Compare effectiveness of individual quarantine and active monitoring at reducing effective reproductive number to below 1, under different feasibility scenarios	Density-dependent deterministic compartmental model (bSIS, recovery rate mediated by resources availability)	-

(Putthasri et al., 2009)	Country - Thailand	Influenza	Modest pandemic mitigation	Decentralised	Define and quantify pandemic preparedness resources at the provincial level and estimate gaps under different scenarios	Density-dependent deterministic compartmental model	-
(Rudge et al., 2012)	Regional - South-East Asia	Influenza	Epidemic preparedness	Decentralised	Estimate and compare resource gaps and their potential consequences in six countries	Density-dependent deterministic compartmental model (SEAIR)	-
(Salomon et al., 2006)	Global	TB	Introduction of short-course regiments using new drugs	National	Examine the expected benefits of shorter drug regimens	Deterministic compartmental model (SIR-like model with treatment compartments)	-
(Sébille and Valleron, 1997)	Global	Nosocomial bacterial infection	Staff handwashing compliance to prevent transmission from patient contacts	Service	Develop a simulation of resistant pathogens spread in the hospital unit	Agent-based simulation	-
(Shattock et al., 2016)	Country - Zambia	HIV	Multiple (model guides priority setting across the HIV cascade)	National	Assess time-varying optimal resource allocations for fixed and variable annual budgets and for various time horizons for measuring outcomes	Frequency-dependent deterministic compartmental model	-
(Shim et al., 2011)	Country - US	Influenza	Seasonal influenza vaccination	National	Investigate age-dependent optimal vaccine distribution against influenza H1N1 influenza from the individual and population perspectives	Density-dependent deterministic compartmental model (SLIR)	Cost analysis
(Stenberg et al., 2017)	Global	Health-related SDG targets	Multiple - 187 interventions targeting health-related SDGs and health systems strengthening	National	Estimate resource needs for strengthening health systems to reach universal health coverage in the SDG era	One Health tool, incorporating the interlinked epidemiological reference models for various disease areas (AIM, TIME, LiST)	Cost analysis

(Stopard et al., 2019)	Country – provinces across Tanzania (Benin, South Africa limited implementation)	HIV	Multiple - behavioural change communication, pre-exposure prophylaxis, voluntary medical male circumcision and universal test-and-treat services	National	To investigate the impact of ‘real-world’ constraints on the resource allocation and possible health gains nationally	Frequency-dependent deterministic compartmental model	Optimisation
(Verma et al., 2020)	Country – India	SARS-CoV-2	Treatment	National	Forecast need for hospital resources and assess surge capacity of health system	Density-dependent deterministic compartmental model (modified SEIR model with age-specific mixing patterns)	-
(Zhang et al., 2020)	Country – not specified	Generic epidemic outbreak	Vaccination	National	Assess optimal vaccination policy in a resource-limited environment	Density dependent deterministic compartmental model (SIR with vaccination compartment)	-

AIM: AIDS Impact Model; AIDS: Acquired Immunodeficiency Syndrome; ART: Anti-Retroviral Therapy; CEA: Cost-Effectiveness Analysis; FTE: Full-Time Equivalent; HCV: Hepatitis C Virus; HR: Human Resources; ICU: Intensive Care Unit; LiST: Lives Saved Tool; QALY: Quality-Adjusted Life-Years; SDG: Sustainable Development Goals

3.4.1 Model structures

The majority of included studies used deterministic compartmental models of disease transmission, as shown in Table 2. However, all mathematical model structures commonly used to characterise the epidemiology of disease transmission were represented in the review, including agent-based simulations and stochastic models. Choice of model structure was determined by the characteristics of the disease, intervention and setting under study, rather than by the characteristics and objectives of the constrained analysis. For example, agent-based models were best suited for investigating nosocomial pathogen transmission (Ferrer et al., 2014, Sébille and Valleron, 1997), while stochastic models were used for cohort analyses assessing the impact of eradication campaigns (Marks et al., 2017) or measures to contain SARS-Cov-2 outbreaks (Peak et al., 2020). The structural decision may have been different if the focus had been the constrained analysis. For example, a compartmental model where the compartments reflect different levels of the health system in addition to disease progression and transmission could improve the analysis of human resource constraints. More details on the model structures represented are provided in the Supplementary material.

3.4.2 Health system constraints and policy objectives

The types of health system constraints considered in the models and the objectives of the constrained analyses are described in Table 3. These ranged from constraints on service delivery inputs, mostly human resources and supplies, but also capital constraints such as equipment and hospital beds, to constraints on the demand for services (e.g. vaccine hesitancy) and other constraints on decision-making that affect the resource allocation process.

Table 3. Constrained analysis characteristics

Lead author (year)	Constrained analysis objective	Non-financial constraints	Constraints identification	Constraints parametrisation and data sources	Approach for modelling constraints	Constraints implementation, details	Scenarios description
(Adisasmito et al., 2015)	Feasibility assessment - produce realistic intervention impact estimates given health system constraints	HR, bed space, equipment, pharmaceutical supplies	Literature	Literature and secondary data analysis (AsiaFluCap survey)	Transmission model-based estimation - Calculate resource requirements	Transmission model linked to resource calculator to estimate requirements during outbreak. Model calculates depletion rate of resources based on average requirements to treat one case, estimated through a mix of data from literature and routine sources. Needs are compared to capacity, estimated through a survey administered as part of AsiaFluCap project	Two scenarios with different hospitalization and mortality rates
(Alistar et al., 2013)	Efficient resource allocation - maximising impact given health system constraints	Political constraint on decision-making	Assumption	Assumption	Transmission model-based estimation - Limit effects and calculate costs along the cascade	REACH is an Excel-based user-friendly model helping policy makers allocate resources across different HIV control interventions. It comprises transmission dynamics and optimisation function. Optimisation done under budget constraint only, but political/social/ethical constraints on allocation of resources can be specified in the user interface. Outputs sheet includes estimates of health care resources needed to support the allocations	-
(Anderson et al., 2014, Anderson et al., 2018)	Feasibility assessment and efficient resource allocation - produce realistic	Political constraint on decision-making, demand side barriers to access	Assumption	Assumption	Transmission model-based estimation - Limit effects and calculate costs along the cascade	Constraints determine the way funds are allocated to key populations (MSM, other men, FSW, other women), geographical areas and throughout 5-year funding cycles (fully flexible, frontloaded, constant or back-loaded). Intervention choice optimised under the	For key populations and districts (paper 1), all possible intervention scenarios compared by constructing health production functions

	intervention impact estimates and maximise impact given health system constraints					different resulting budget constraints. Constraints to implementation also parametrised in the form of uptake limits to certain intervention components	for a given cost. For spending cycle (paper 2), 5 scenarios: 2 with complete spending flexibility (one of which with intervention change at 10 years), choices optimized over 30-year period; 3 with front-loaded, equal and back-loaded funding cycles, respectively, and choices optimised over each 5-year cycle
(Bärnighausen et al., 2016)	Feasibility assessment - produce realistic intervention impact estimates given health system constraints	HR	Assumption	Literature	Transmission model-based estimation - Limit effects and calculate resource requirements along the cascade	Given current HR supply, number of patients treated is computed assuming fixed ratios for each cadre to patient. Model projects the impact of reallocating scarce HR to varying patient distributions in the different HIV disease stages and can estimate potential shortages	200 scenarios varying assumptions around HIV transmission probabilities, ART effect, retention and adherence. Two sets of constraints scenarios: one where allocation of HR is proportional to number of patients in TaSP and standard ART (treatment for advanced disease stages) pools, respectively; one where more HR allocated to pool with patients at more

						advanced disease stages
(Barker et al., 2017)	Feasibility assessment - produce realistic intervention impact estimates given health system constraints	HR	Assumption	Secondary analysis of data from Tanzania and Mozambique on time spent by facility health workers delivering ART	Transmission model-based estimation - Calculate resource requirements	Model estimates total facility staff FTE needed for different ART differentiated care models, based on previous estimates of time spent delivering ART in Africa. An analysis of constraints is not presented because differentiated care models are expected to lead to cost and HR savings	-
(Bottcher et al., 2015)	Feasibility assessment - produce realistic intervention impact estimates given health system constraints	Political constraint on decision-making, recurrent supplies	Assumption	Assumption	Transmission model-based estimation - Limit intervention effects	Model projects a global budget that increases by one unit with each additional healthy individual per unit of time and partially constrains recovery when available budget is insufficient for covering 'costs of healing'	-
(Bozzani et al., 2018, Bozzani et al., 2020a, Sumner et al., 2019a)	Feasibility assessment and efficient resource allocation - produce realistic intervention impact estimates and maximise impact given health system constraints	HR, diagnostic equipment	Expert opinion	Secondary data collection from routine sources including district health information system (DHIS) and other Department of Health and Nursing Council records	Transmission model-based estimation - Limit effects and calculate resource requirements along the cascade	Unit costs and staff FTE to deliver different services are attached to model outputs to limit intervention effects once threshold of available resources is exceeded. Diagnostic constraint parametrised as maximum ratio of tests to TB notifications. Costs of 'relaxing' the constraints to achieve target coverage is calculated.	3 scenarios (least limiting, medium and most limiting) considered for each constraint (budget, diagnostic and HR), respectively, based on projections of future resource availability

(Chen et al., 2019)	Feasibility assessment - produce realistic intervention impact estimates given health system constraints	Resources that are necessary to contain an epidemic (not specified)	Assumption	Assumption	Transmission model-based estimation - Limit intervention effects	A value R_c, representing the level of resources in the system, is identified, whereby the epidemic can be effectively contained. If $R<R_c$ the disease becomes widespread, recovery rate varies with time depending on average amount of resources that each infected individual receives	Scenarios explored with different levels of health system resourcing
(Cruz-Aponte et al., 2011)	Feasibility assessment - produce realistic intervention impact estimates given health system constraints	Vaccine stockouts	Assumption	Assumption	Transmission model-based estimation - Limit intervention effects	Vaccine administration limited by daily maximum number. Vaccination campaign ends a) after some prescribed duration of time; or b) when stockpile is depleted. Results are compared with those from alternative model that ends campaign when target proportion of population is vaccinated.	Three scenarios varying the number of vaccines administered in a time period (56- , 28- , and 3-day campaign with different daily administration limits)
(Curran et al., 2016)	Efficient resource allocation - maximising impact given health system constraints	HR, supplies and infrastructure	Group model building - System dynamics modelling techniques	Assumption	Transmission and system dynamics models linkage - Limit effects system-wide	The paper outlines possible ways of integrating transmission dynamics modelling with data generated from population surveys and sentinel surveillance and with system dynamics models to predict resource capacity during epidemic outbreaks and assist with resource allocation based on predicted pathogen spread	Multiple scenarios with varying disease transmission rates and health system capacity can be analysed
(Dalgiç et al., 2017)	Efficient resource allocation - maximising impact given health system constraints	Vaccine stockouts	Assumption	Assumption	Constrained optimisation - Limit intervention effects	Optimise vaccine allocation in different age groups subject to constrained availability. Different objectives (minimise total costs, total infections, total deaths, total years of life lost)	Several vaccine coverage and delayed response time scenarios

(Ferrer et al., 2014)	Feasibility assessment - produce realistic intervention impact estimates given health system constraints	HR	Assumption	Primary data collection at 5 ICUs on bed occupancy and staffing conditions	Transmission model-based estimation - Limit intervention effects	Model includes estimates of nurses' contact time with patients, which has an effect on pathogen spread. Daily rate of nurse absenteeism varied to adopt a fixed value between 10-40% and different coping mechanisms modelled	Systematic analysis of pathogen dissemination under different scenarios of pathogens circulating, level of nurses shortage and shortage management strategy
(Hecht and Gandhi, 2008)	Feasibility assessment - produce realistic intervention impact estimates given health system constraints	Political constraint on decision-making, demand side barriers to access	Literature and expert opinion	Assumptions based on expert consultation	Transmission model-based estimation - Limit intervention effects	Global demand for vaccine forecast by adding up demand estimates for individual country profiles	Four vaccine profile scenarios based on variations in efficacy, duration of protection and cost
(Hontelez et al., 2016)	Efficient resource allocation - maximising impact given health system constraints	HR, infrastructure, demand-side barriers to access	Assumption	Assumptions made on effects of constraints on ART coverage. Costs of one-off investment needed to relax constraints calculated from routine AIDS spending reports	Transmission model-based estimation - Limit effects and calculate costs system-wide	Model calculates total investment needs, population health gains and cost-effectiveness of scaling-up new ART eligibility guidelines, including removal of health system constraints	Scenarios reflecting pessimistic, realistic and optimistic future health system developments, in which constraints apply to different extents

(Krumkamp et al., 2011)	Efficient resource allocation - maximising impact given health system constraints	HR, pharmaceuticals supplies and other consumables	Assumption	Expert opinion and primary data collection (AsiaFluCap survey)	Transmission model-based estimation - Limit effects and calculate resource requirements along the cascade	Model constrains epidemic containment based on availability of resources and calculates resource depletion per hospital case. Resource usage data and impact of constraints estimated from a mix of survey data and expert opinion	Different epidemic control strategies modelled (antivirals stockpiling for critical cases, contact reductions)
(Langley et al., 2014, Lin et al., 2011)	Efficient resource allocation - maximising impact given health system constraints	HR, diagnostic pathway bottlenecks, demand-side barriers to access	Group model building - Operational modelling techniques	Primary data collected from two diagnostic centres in Tanzania and calibrated using National TB programme reports	Transmission and operational models linkage - Limit intervention effects	Operational model outputs used to parametrise transmission model and vice versa. Operational component uses discrete-event simulation approach to model patient and sputum sample pathways	Different diagnostic algorithms modelled
(Marks et al., 2017)	Feasibility assessment - produce realistic intervention impact estimates given health system constraints	Demand-side barriers to access	Assumption	Assumption	Transmission model-based estimation - Limit intervention effects	Eradication modelled under a range of plausible targeted treatment coverage estimates (65%-95%). Mass treatment compliance modelled as a random non-systematic process where every patient has the same, independent likelihood of receiving treatment	3 transmission scenarios modelled (low, medium, high) based on literature and expert opinion
(Martin et al., 2015a, Martin et al., 2015b)	Feasibility assessment - produce realistic intervention impact estimates given health system constraints	Implementation' constraints, demand-side barriers to access	Group model building - System dynamics modelling techniques	Literature and expert opinion	Transmission and system dynamics models linkage - Limit intervention effects	Scenario analysis where the flow of patients along the HIV testing and care cascade is determined by different sets of assumptions regarding policy implementation. These were defined in consultation with experts and based on the literature, by developing a system dynamics model that assesses the impact and relationships of different policy components	3 policy 'implementation' scenarios (low, high, perfect) and 3 testing policy scenarios (annual, five-year and no repeat offer of testing) combined to generate 9 unique combinations of policy

							conditions in addition to the base case
(Martin et al., 2011)	Efficient resource allocation - maximising impact given health system constraints	Political constraint on decision-making	Assumption	Assumption	Constrained optimisation - Limit effects and calculate costs along the cascade	Optimal treatment strategy for HCV is examined under different economic and policy objectives: 1) minimise costs and QALY loss; 2) minimise prevalence; 3) minimise costs and QALY loss while achieving 20% time prevalence reduction; 4) minimise costs while achieving 20% time prevalence reduction	Analysis is repeated for a combination of annual budget constraints and two HCV baseline prevalences (30% and 45%)
(McKay et al., 2018)	Feasibility assessment - produce realistic intervention impact estimates given health system constraints	HR	Assumption	Model parametrised with trial and implementation studies data and informed by published organizational and intervention sustainability models	Transmission model-based estimation - Limit effects and calculate resource requirements along the cascade	Model predicts the level of preventive services a health agency can provide given different combinations of i) staff positions; ii) turnover rates; iii) timing in training.	N/A
(Peak et al., 2020)	Feasibility assessment - produce realistic intervention impact estimates given health system constraints	Barriers to effective contact tracing and quarantine interventions, including untrained monitoring of symptoms	Assumption	Assumption	Transmission model-based estimation - Limit intervention effects	R0 is estimated based on the implementation of quarantine and active monitoring in high- vs low-feasibility settings	Analysis compares a high- (90% contacts traced and quarantined or monitored, reducing infectiousness by up to 90%) and a low-feasibility setting (delays in locating contacts, imperfect quarantine)

(Putthasri et al., 2009)	Efficient resource allocation - maximising impact given health system constraints	HR, supplies and infrastructure	Expert opinion	Expert opinion	Transmission model-based estimation - Calculate resource requirements	Actual and projected resources per case multiplied by the number of case-patients estimated by previous modelling exercises under different scenarios. Resource gaps estimated at the provincial level	3 epidemic (human-to-human transmission) scenarios analysed, with specific numbers of index cases and contacts: 1) from case-patients to caregivers; 2) localised clusters; 3) transmission resulting in substantial number of cases
(Rudge et al., 2012)	Feasibility assessment and efficient resource allocation - produce realistic intervention impact estimates and maximise impact given health system constraints	HR, bed space, equipment, pharmaceutical supplies	Multi-criteria decision analysis - Delphi consensus process with a panel of 24 experts integrated with literature review	Primary data collection at health facilities to enumerate available resources. Gaps estimated based on literature on resource needs	Transmission model-based estimation - Calculate resource requirements	Available quantities of resources estimated through a survey sent out to hospitals, district health offices and ministries of health. Additional model parameters describing clinical pathway of infected individuals, conditional upon availability of resources	Model runs: i) available resources; ii) unlimited resources (to calculate gaps and compare with availability data from survey)
(Salomon et al., 2006)	Feasibility assessment - produce realistic intervention impact estimates given health system constraints	HR, infrastructure	Assumption	Assumption	Transmission model-based estimation - Limit intervention effects	Constraints not explicitly modelled, but scenarios are analysed where it is assumed that the intervention reduces constraints to case detection, thus improving case detection rates	Scenarios were modelled with varying assumptions about case detection coverage (including one where constraints are relaxed), cure rates and DOTS scale-up

(Sébille and Valleron, 1997)	Feasibility assessment - produce realistic intervention impact estimates given health system constraints	Pharmaceutical supplies, political constraint on decision-making	Assumption	Assumption	Transmission model-based estimation - Limit intervention effects	Scenarios with different risk of patient-to-staff transmission based on whether procurement of two essential antibiotics is simultaneous (both available), sequential (only one available at a given time, then the other) or a mix of the two	Software allows for different assumptions to be specified before running simulations (e.g. drug procurement policy, staff handwashing compliance)
(Shattock et al., 2016)	Efficient resource allocation - maximising impact given health system constraints	Political constraint on decision-making	Assumption	Assumption	Transmission model-based estimation - Limit intervention effects	Time-varying optimization i.e. minimising objective function (cumulative HIV infections) associated with the budget allocation, such that: i) total programme spending equals a pre-defined budget (either constant, front-loaded etc.) at each time point; or ii) total spending across the optimisation period is equal to pre-defined budget, but total spending at each point is optimally determined	4 optimization scenarios illustrating policy decisions where time considerations matter: 1) optimal 10-years allocation assuming baseline budget is annually available with no constraints to programme-specific allocation; 2) as in 1, but programme-specific funding cannot vary by more than 30% compared to baseline; 3) as in 1, but annual optimal allocation determined based on implementation and ethical constraints; 4) optimal 5-years allocation but cumulative new infections assessed

							after 5, 10 or 15 years, again within constraints
(Shim et al., 2011)	Efficient resource allocation - maximising impact given health system constraints	Demand-side barriers to access	Assumption	Assumption	Transmission model-based estimation - Limit intervention effects	Decision to vaccinate characterised as a game, where monetary payoff for different age groups is modelled based on different individual strategies as well as on the average behaviour of the population	Two strategies modelled to calculate payoff to vaccinated and non-vaccinated: Nash and utilitarian
(Stenberg et al., 2017)	Efficient resource allocation - maximising impact given health system constraints	HR, infrastructure, demand-side barriers to access	Assumption	Assumption	Transmission model-based estimation - Calculate intervention costs	Tracer interventions identified for each of the relevant SDGs, then gap estimated between current provision and universal coverage and country-specific programme costs multiplied by this gap. Costs estimated from the One Health Tool and from the literature. Progress towards 2030 targets adjusted by level of 'strength' of the health system (conflict, vulnerable, low-income, lower middle-income, upper middle-income)	Two financial space scenarios in each country, reflecting uncertainty around health systems' absorption capacity: i) ambitious, strengthening system towards global benchmarks and expanding coverage of full service package to 95%; ii) progress, not all SDG targets met by 2030 but improvements can be achieved by scaling up services delivered through the lower platforms
(Stopard et al., 2019)	Efficient resource allocation - incidence minimizing	Political constraints on decision making (earmarking, externally	Assumption	Assumption	Transmission model-based estimation - Calculate intervention costs and impact	Constraints are modelled through initial conditions in each scenario representing minimum coverage by subgroups within the transmission model	Four scenarios of real-world constraints: 1) earmarking, where the first intervention funded would be PrEP for heterosexual

		imposed targets, minimising change to current program)					women (excluding FSWs); 2) targets, where 90% of PLHIV must receive UTT; 3) minimising change, baseline allocation represents an allocation at national level; and 4) all constraints simultaneously
(Verma et al., 2020)	Feasibility assessment - produce realistic intervention impact estimates given health system constraints	Hospital beds, ICU beds and mechanical ventilation equipment	Assumption	Secondary data	Transmission model-based estimation - Limit effects and calculate resource requirements along the cascade	Available capacity estimated from public records, including for private sector. Capacity needs calculated based on requirements per case and turnover times from the literature. Capacity requirements during surge are based on model projections under different lockdown scenarios. Surge capacity compared to available capacity to estimate gap.	Different lockdown/social distancing scenarios
(Zhang et al., 2020)	Efficient resource allocation - maximising impact given health system constraints	Vaccines availability	Assumption	Assumption	Constrained optimisation - Limit intervention effects	Optimise allocation of limited vaccines in order to minimise the number of infections	N/A

AIDS: Acquired Immunodeficiency Syndrome; ART: Anti-Retroviral Therapy; FTE: Full-Time Equivalent; HCV: Hepatitis C Virus; HR: Human Resources; ICU: Intensive Care Unit; QALY: Quality-Adjusted Life-Years; SDG: Sustainable Development Goals

The majority of articles relied on assumptions for identifying the constraints that applied to the setting and programme area of interest (n=25, 66%) and for quantifying the extent to which the constraints impacted intervention effects (n=21, 55%). For constraints identification, other sources were stakeholder elicitation in the form of expert opinion (n=5), system dynamics modelling (n=3), the literature (n=1) and multi-criteria decision analysis using Delphi consensus (n=1). Finally, two articles by Lin, Langley and colleagues described an operational model of the TB diagnostic pathway in Tanzania to identify bottlenecks and shortages, which was 'linked' to a transmission model; i.e. the operational model generated estimates of programmatic variables such as prevalence of treatment default and number of diagnostic centre visits, that were then used to parametrise the transmission model (Langley et al., 2014, Lin et al., 2011). Those studies that relied on data collection for parametrising constraints impact mostly used secondary sources (n=7) or a mix of primary data collection and routine sources or expert opinion (n=6). For example, modelling done using the AsiaFluCap simulator identified the resources needed for pandemic influenza response through expert elicitation (Rudge et al., 2012) and estimated available quantities and resource use per patient in the study countries through a survey integrated with data from the published literature (Adisasmito et al., 2015, Krumkamp et al., 2011).

Non-financial constraints influencing health providers' ability to deliver health services were considered in two thirds of included studies (n=28) (Adisasmito et al., 2015, Alistar et al., 2013, Barker et al., 2017, Bärnighausen et al., 2016, Bottcher et al., 2015, Bozzani et al., 2018, Bozzani et al., 2020b, Chen et al., 2019, Cruz-Aponte et al., 2011, Curran et al., 2016, Dalgiç et al., 2017, Ferrer et al., 2014, Krumkamp et al., 2011, Langley et al., 2014, Lin et al., 2011, Martin et al., 2011, McKay et al., 2018, Peak et al., 2020, Putthasri et al., 2009, Rudge et al., 2012, Salomon et al., 2012, Sébille and Valleron, 1997, Shattock et al., 2016, Stopard et al., 2019, Sumner et al., 2018, Verma et al., 2020, Zhang et al., 2020), while only two studies considered constraints to the demand for health services (Hecht and Gandhi, 2008, Shim et al., 2011), and six articles considered both demand- and supply-side factors (Anderson et al., 2014, Anderson et al., 2018, Hontelez et al., 2016, Marks et al., 2017, Martin et al., 2015a, Martin et al., 2015b, Stenberg et al., 2017). The models that exclusively include demand-side constraints both focus on vaccines: one study projected the public and private demand for an AIDS vaccine candidate under different vaccine characteristics (efficacy, duration of protection, price), performance (acceptability, compliance) and country-level profile scenarios (including political ability and motivation to implement HIV/AIDS prevention programmes) (Hecht and Gandhi, 2008); the second study subdivided model compartments based on individual decisions to vaccinate against seasonal influenza, to assess the effects of vaccine hesitancy on coverage and to derive optimal vaccine allocation across age groups under a Nash (own interest) versus a utilitarian strategy (optimal for the population) (Shim et al., 2011).

Most commonly, the analyses that focussed on limits to the supply of health services incorporated a combination of HR, capital, equipment (infrastructure, hospital beds, logistics, ventilators etc.) and supplies constraints (drugs, vaccines and diagnostic consumables). These physical input constraints are not explicitly defined in a limited number of the analyses. For example, the 3S Surge System model for outbreak capacity planning consists of broadly defined 'staff, stuff and structure' (Curran et al., 2016) while three studies talk about non-specific resources necessary for controlling the spread of an epidemic (Bottcher et al., 2015, Chen et al., 2019, Peak et al., 2020) and other analyses refer to generic 'implementation' constraints that reduce the achievable coverage of interventions (Hontelez et al., 2016, Martin et al., 2015a, Martin et al., 2015b).

A second set of supply-side non-financial constraints groups are distal factors deriving from political and social values and practices that determine how budgets are allocated, what activities are considered feasible or acceptable, and broader societal policy objectives that the system can pursue. Examples of models that allow for considering these constraints include the Resource Allocation for Controlling HIV tool, which allows users to specify interventions that cannot be implemented due to social, political or ethical concerns, or that have to receive a minimum/maximum level of funding for historical or strategic reasons (Alistar et al., 2013); the Optima model, which lets users analyse different budget allocation scenarios (constant, front-loaded, rear-loaded or initially scaled-up/down then later scaled-down/up over the funding cycle) (Shattock et al., 2016); and model developed by Stopard and colleagues, that examines different constraints to the efficient allocation of resources for HIV prevention, including externally imposed targets or limited capacity to modify existing programmes (Stopard et al., 2019). One set of studies in this group considers policy constraints both on the funding cycle (varying the flexibility of spending and the time horizon over which choices are to be optimised) and on how funds are allocated across key populations and geographical areas (Anderson et al., 2014, Anderson et al., 2018).

3.4.3 Modelling approaches integrating non-financial constraints

As shown in Table 3, the rationale for considering health system constraints in the modelling studies was two-fold, with studies seeking to do one, or a combination, of the following: i) carry out a *feasibility assessment*, by producing realistic estimates of intervention impact (and costs) given the constraints; ii) guide *efficient priority setting*, by allocating resources in a way that maximises intervention impact given the constraints. Following from these objectives, the analytical approaches for considering constraints in the modelling studies can be grouped into two categories. The first category includes constrained estimation exercises, where intervention implementation is modelled at the maximum attainable coverage given the constraints. Effects (and costs) are thus limited at the level of the specific intervention, the disease cascade or the health system as a whole (Bottcher et al., 2015, Chen et al., 2019, Cruz-Aponte et al., 2011, Ferrer et al., 2014, Hecht and Gandhi, 2008, Marks et al., 2017, Peak et al., 2020, Salomon et al., 2006, Sébille and Valleron, 1997, Shattock et al., 2016, Shim et al., 2011, Stopard et al., 2019, Zhang et al., 2020).

The second category is unconstrained estimation, where interventions are modelled at full coverage but the gap in current resources for reaching that coverage is quantified in monetary or physical units, such as staff full-time equivalent (FTE) (Adisasmito et al., 2015, Barker et al., 2017, Putthasri et al., 2009, Rudge et al., 2012, Stenberg et al., 2017, Verma et al., 2020). Some of the studies in the review adopted a combination of these approaches, calculating both constrained impact estimates and the costs or resource requirements for relaxing the constraints (Alistar et al., 2013, Anderson et al., 2014, Anderson et al., 2018, Bärnighausen et al., 2016, Bozzani et al., 2018, Bozzani et al., 2020b, Hontelez et al., 2016, Krumkamp et al., 2011, McKay et al., 2018, Sumner et al., 2019b). For example, Bozzani, Sumner and colleagues presented an analysis of different TB screening and diagnosis algorithms in South Africa under several constraints scenarios limiting effects along the TB prevention and care cascade to varying degrees, then modelled the additional staff FTE and costs of purchasing extra quantities of diagnostic consumables required to relax the constraints and achieve target coverage, observing any differences in the cost-effectiveness ranking of the screening options with and without constraints (Bozzani et al., 2018, Bozzani et al., 2020b, Sumner et al., 2019b).

In practice, constrained and unconstrained model-based estimation was most commonly achieved by combining transmission model outputs with unit costs (to address financial constraints) and other input per unit estimates, such as nurse FTE per output, to calculate resource usage at different intervention coverage levels and any additional requirements to relax constraints (Adisasmito et al., 2015, Alistar et al., 2013, Anderson et al., 2018, Barker et al., 2017, Bärnighausen et al., 2016, Bottcher et al., 2015, Bozzani et al., 2018, Bozzani et al., 2020b, Cruz-Aponte et al., 2011, Ferrer et al., 2014, Hecht and Gandhi, 2008, Hontelez et al., 2016, Krumkamp et al., 2011, Marks et al., 2017, McKay et al., 2018, Putthasri et al., 2009, Rudge et al., 2012, Salomon et al., 2006, Sébille and Valleron, 1997, Shattock et al., 2016, Shim et al., 2011, Stenberg et al., 2017, Sumner et al., 2019b, Verma et al., 2020). For instance, the agent-based model by McKay et *al*. analysed the relationship between HIV outcomes and staffing levels at a health agency by simulating changes over time in the number of HR positions, turnover rates and length of time for training newly recruited staff, and observing the effect of this HR constraint on the effectiveness of a prevention intervention (McKay et al., 2018).

A related approach adopted to incorporate constraints was the 'linkage' of disease transmission models with health system models, such as system dynamics (Curran et al., 2016, Martin et al., 2015a, Martin et al., 2015b) or operational models (Langley et al., 2014, Lin et al., 2011). In this approach, model-based estimation relied on the health system models to generate estimates of the impact of constraints on intervention effects, which were then used to parametrise the transmission models. As an example, Curran and colleagues illustrated possible ways of integrating transmission models with system dynamics models to regulate the flows impacting on infection dynamics based on system capacity (Curran et al., 2016).

The last approach to integrate constraints was optimisation under a constraint other than the available budget. This approach was followed by two studies that sought to prioritise among different strategies, one for flu vaccine allocation in different age groups and one for HCV treatment, under different policy objectives such as minimising total incidence/prevalence, total deaths or total utility losses (Dalgiç et al., 2017, Martin et al., 2011, Zhang et al., 2020).

3.5 DISCUSSION AND CONCLUSIONS

Incorporating health system elements that influence the priority setting process for disease control interventions, either by limiting the pace and scale of implementation or by otherwise determining their feasibility (as in the case of political or ethical constraints), is an increasingly common practice in the modelling literature. The main objectives of the studies reviewed were to constrain mathematical model outputs to approximate real-world implementation and to guide efficient resource allocation in the presence of constraints. They thus generated priority setting evidence that is more functional to the country-level planning cycle, in contrast to the 'perfect implementation' evidence generated by trials, trial-based economic evaluations and traditional target-driven modelling exercises (Menzies et al., 2019, Mikkelsen et al., 2017). One key advantage of these constrained analyses is that, by comparing target and actual implementation, the models allow analysts to calculate the resources needed for 'relaxing' the constraints, thus providing policymakers with a more accurate estimate of the value for money of investing in a given intervention implemented at full scale.

Although the characteristics of the interventions and of the relative constraints are context-specific, there were patterns across settings in this review. For example, there was no distinction between demand-side and supply-side constraints in terms of the policy questions asked, whether about real-world impact or efficient investments (or both), and of the model structures used to explore them. Disease areas were also equally represented across models and similar objectives were pursued, for instance, by a study using an agent-based simulation to explore the allocation of flu vaccines in the presence of physical stockouts and a study using a SIR-like model to assess antiviral treatment strategies under different policy objectives (Dalgiç et al., 2017, Martin et al., 2011).

Constraints incorporation was achieved in two main ways, both of which can be accommodated by all mathematical model types: (i) model-based estimation, whereby limitations to intervention coverage were applied on the basis of either demand- or supply-side factors; (ii) optimisation, under a non-financial constraint or policy objective. The former was the most common approach overall, while the latter can be exclusively applied in analyses seeking to guide efficient resource allocation. Approaches for identifying the applicable constraints and quantifying the extent of their impact varied in terms of strength, from unspecified assumptions to primary data collection, for example for building an operational model, and to structured stakeholder elicitation methods such as for systems dynamics modelling. Model-based estimation approaches thus varied according to the constraints quantification methods, and the dynamic transmission models were parametrised either in standard ways, using primary or secondary data, or through 'linkage' with the health system models (operational or system dynamics). The examples of model linkage in our sample are all from studies assessing interventions involving policy changes, such as a new HIV testing and linkage to care model, that are amenable to distal constraints more easily identified and quantified through group model building exercises involving a wide range of stakeholders.

This review builds on previous theoretical work on conceptualising and operationalising constraints (Vassall et al., 2016), but does not attempt to define the *feasibility* decision criterion. This concept and its influence on priority setting have been ill-defined in the literature and may encompass a range of aspects such as affordability, physical constraints that directly restrict access to services or technologies and arbitrary beliefs held by decision-makers and the wider environment that limit implementation in some way (Guindo et al., 2012, Tromp and Baltussen, 2012). In this review, the focus was restricted to non-financial constraints but the definition of constraints was kept deliberately broad to capture all relevant incorporation approaches. The search strategy returned a number of records dealing with political, social and ethical constraints on the decision-making process, since it contained keywords around priority setting and decision-making criteria. We therefore introduced a working distinction between constraints on physical inputs and political constraints, including policy objectives. This latter category could, for example, include principles such as equity in cases where this objective is treated in the analysis as a *de facto* constraint to the roll-out or scale-up of an intervention, as in the study assessing the effects of prioritising key populations when delivering combination HIV prevention in Kenya (Anderson et al., 2014).

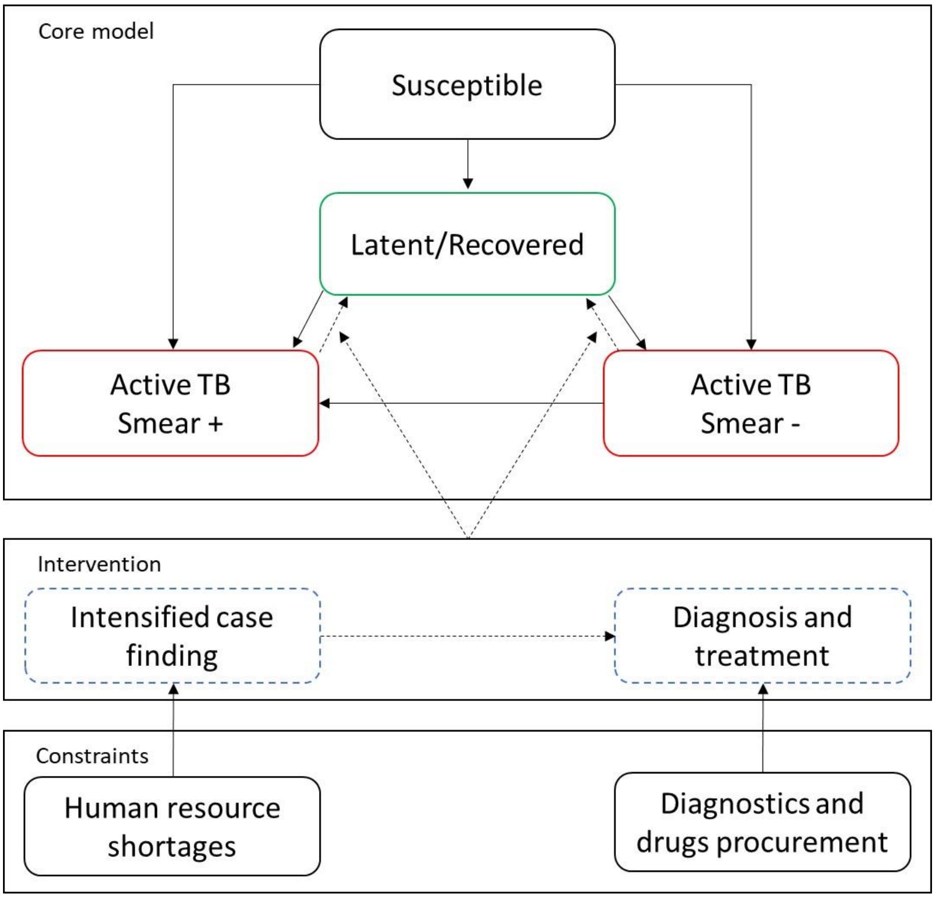
In conclusion, this review has shown that the inclusion of non-financial health system constraints in mathematical model-based priority setting can be accommodated within all model structures that are commonly used in epidemiological analyses. Despite the additional complexity, the enhanced models produce valuable information, including estimates of the costs of relaxing the constraints i.e. the true cost of the intervention at scale. As modelling techniques become more sophisticated and user-friendly and data availability improves, it will become increasingly possible to parametrise the models using real-time surveillance data, thus making the identification and quantification of constraints more viable and making models more locally relevant and accessible for decision-makers within the policy timeframe (Alistar et al., 2013, Masoodian and Luz, 2017). However, further research is needed to categorise health system constraints, to assist their systematic operationalisation in models.

SUPPLEMENTARY MATERIAL

S1. PARAMETRISING CONSTRAINTS IN MATHEMATICAL MODELS, AN EXAMPLE

Figure 4 illustrates the model transitions affected by human resource constraints along the tuberculosis care cascade (dashed lines).

Figure 4. Example of modelling constrains impact on intervention effects



Adapted from (Houben et al., 2016). Dashed lines represent transitions impacted by constraints

S2. LITERATURE SEARCH FILTERS AND RESULTS

S.2.1 Medline and Embase

Medline and Embase were searched via OvidSP on 9th May 2019. The search was updated on 9th November 2020, to include all records published since the original search. Search results are summarised below (in brackets, results with limits applied: full text, humans)

		Medline	Embase
Search terms for infectious disease			
1.	exp Infectious Disease Transmission/	70,882 (10,670)	48,356 (30,128)
2.	(infection or (infectious disease*) or outbreak or vaccin* or immuni#ation or (human immunodeficiency virus) or (HIV) or tuberculosis or (TB) or (antimicrobial resistance) or (AMR) or malaria or dengue or (mosquito-transmitted) or (mosquito-borne) or cholera or ebola or (hepatitis A) or (hepatitis B) or varicella or rubella or meningococc* or pneumococc* or influenza or (respiratory syndrome) or (SARS) or (h?emorragic fever) or (human papilloma virus) or (HPV) or chlamydia).ti,ab.	1,835,247 (327,181)	2,722,116 (379,371)
3.	or/1-2	1,863,174 (307,816)	2,740,461 (346,632)
Search terms for health systems research			
4.	exp Public Health Systems Research/	36 (4)	85 (8)
5.	exp Systems Analysis/	89,479 (8,702)	22,687 (1,212)
6.	(((health system*) and (building block*)) or ((health system*) adj3 research) or HPSR).ti,ab.	922 (152)	1,363 (196)
7.	((health system* adj3 constraint*) or (resource* constraint*) or (resource* adj2 gap*) or (resource* adj1 need) or (demand adj3 constraint*) or (supply adj3 constraint*) or (implementation adj3 constraint*) or ((scal* up) and constraint*) or (capacity constraint*) or ((staffing or (human resource*) or HR or time) and (constraint* or shortage*))).ti,ab.	24,262 (3,292)	42,580 (5,265)
8.	(((feasib* or unfeasib*) adj3 intervention*) or (intervention adj3 (feasib* or unfeasib*))).ti,ab.	3,162 (639)	5,806 (1,077)
9.	Or/4-8	117,266 (12,709)	72,204 (7,723)
Search terms for mathematical modelling, economic evaluation and priority setting			
10.	exp Theoretical Models/	1,788,166 (196,565)	10,463 (4,798)
11.	exp Economic Models/	15,261 (2,422)	5,406 (230)

12. exp Decision Support Techniques/	77,974 (10,735)	26,393 (3,494)
13. ((mathematic* or simulation or dynamic* or compartment* or (agent-based) or systems* or stochastic or deterministic or epidemic or epidemiologic* or transmission or cost*) and (model* or modeling* or modelling*)).ti,ab.	534,555 (60,627)	853,142 (79,899)
14. ((decision-mak*) or (decision adj3 criteria) or (priorit* or (priority-setting))).ti,ab.	219,849 (35,767)	365,451 (53,550)
15. ((economic evaluation) or (cost-effectiveness) or (cost-benefit) or (cost-utility) or (benefit-cost) or (cost-minimi#ation) or (health technology assessment) or (HTA)).ti,ab.	67,767 (12,638)	118,778 (17,176)
16. (multi-criteria adj1 decision adj1 analysis).ti,ab.	308 (32)	626 (38)
17. Or/10-17	2,351,214 (277,229)	1,459,721 (146,532)
18. 3 and 9 and 18	**2,259 (461)**	**985 (215)**

S.2.2 Scopus

Search terms for infectious disease

1. TITLE-ABS-KEY (“Infectious Disease Transmission”) (10,742)
2. TITLE-ABS-KEY (infection or (infectious disease*) or outbreak or vaccin* or immuni?ation or (“human immunodeficiency virus”) or (HIV) or tuberculosis or (TB) or (“antimicrobial resistance”) or (AMR) or malaria or dengue or (“mosquito-transmitted”) or (“mosquito-borne”) or cholera or ebola or (“hepatitis A”) or (“hepatitis B”) or varicella or rubella or meningococc* or pneumococc* or influenza or (“respiratory syndrome”) or (SARS) or (h*morragic fever) or (“human papilloma virus”) or (HPV) or chlamydia) (3,974,834)
3. #1 OR #2 (3,974,834)

Search terms for health systems research

4. TITLE-ABS-KEY (“Public Health Systems Research”) (153)
5. TITLE-ABS-KEY (“Systems Analysis”) (169,032)
6. TITLE-ABS-KEY ((“health system*” and “building block*”) or (“health system*” W/3 research) or HPSR) (1,968)
7. TITLE-ABS-KEY ((“health system*” W/3 constraint*) or “resource* constraint*” or (resource* W/2 gap*) or (resource* W/1 need) or (demand W/3 constraint*) or (supply W/3 constraint*) or (implementation W/3 constraint*) or (“scal* up” and constraint*) or “capacity constraint*” or “time constraint” or ((staffing or “human resource*” or HR) and (constraint* or shortage*))) (65,508)
8. TITLE-ABS-KEY (((feasib* or unfeasib*) W/3 intervention*) or (intervention W/3 (feasib* or unfeasib*))) (6,494)
9. #4 OR #5 OR #6 OR #7 OR #8 (247,157)

Search terms for mathematical modelling, economic evaluation and priority setting

10. TITLE-ABS-KEY (“Theoretical Models”) (252,432)
11. TITLE-ABS-KEY (“Economic Models”) (20,385)
12. TITLE-ABS-KEY (“Decision Support Techniques”) (19,186)
13. TITLE-ABS-KEY ((mathematic* or simulation or dynamic* or compartment* or (“agent-based”) or systems* or stochastic or deterministic or epidemic or epidemiologic* or transmission or cost*) and (model* or modeling* or modelling*)) (6,212,320)
14. TITLE-ABS-KEY ((decision-mak*) or (decision W/3 criteria) or (priorit* or (“priority-setting”))) (11,001,863)
15. TITLE-ABS-KEY ((“economic evaluation”) OR (“cost effectiveness”) OR (“cost benefit”) OR (“cost utility”) OR (“benefit cost”) OR (“cost minimi?ation”) OR (“health technology assessment”) OR (“HTA”)) (487,891)
16. TITLE-ABS-KEY (“multi criteria decision analysis”) (3,349)
17. #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 (16,962,390)
18. #3 AND #9 AND #17 (**2,602**)

S.2.3 Details on the structure of mathematical models analysed

This section aims to describe the mathematical model structures used to incorporate health system constraints in more detail. The focus is on influenza and HIV models, as the disease areas most represented in the review and presenting the widest variety of modelling approaches.

The majority of studies captured in this review used deterministic compartmental models of disease transmission. Models of influenza and SARS-Cov-2 transmission typically presented a SIR (susceptible, infected, recovered) or SEIR/SEAIR (as for SIR, but with explicit compartments for exposed and asymptomatic individuals) structure (Adisasmito et al., 2015, Curran et al., 2016, Krumkamp et al., 2011, Putthasri et al., 2009, Rudge et al., 2012), with the addition of a vaccination compartment where required by the analysis (Cruz-Aponte et al., 2011, Dalgiç et al., 2017, Shim et al., 2011). One analysis of influenza vaccine allocation aimed to compare the results of the deterministic compartmental model with those generated using agent-based simulation, to assess whether the strategies prioritised by the two models were different in any practical scenarios (Dalgiç et al., 2017). One influenza outbreak model presented a SIS structure (susceptible, infected, susceptible), where the rate at which individuals recovered and became susceptible again freed up resources, and the level of resources in the system in turn influenced the rate of recovery (Bottcher et al., 2015). Two models of nosocomial pathogens spread used agent-based simulation: one study analysing the impact of measures to address nurse shortages in the intensive care unit (ICU) ran 500-day simulations parametrised with data from a sample of ICUs in France (Ferrer et al., 2014); while another study used a Monte Carlo simulation model of the interactions between different patient and facility staff profiles (Sébille and Valleron, 1997).

All TB transmission models presented a SIR structure, with or without an additional compartment for latent infection and further stratified by other relevant characteristics including HIV and smear microscopy status as well as drug resistance (Bozzani et al., 2018, Bozzani et al., 2020b, Langley et al., 2014, Lin et al., 2011, Salomon et al., 2006, Sumner et al., 2019b). The majority of HIV transmission models in the sample were also compartmental, with the most common structure distinguishing between age- and sex-stratified infected and uninfected compartments further subdivided by any relevant risk groups (Alistar et al., 2013, Anderson et al., 2014, Anderson et al., 2018, Bärnighausen et al., 2016, Shattock et al., 2016, Stopard et al., 2019). Two studies, one assessing differentiated antiretroviral therapy (ART) models and one looking at interventions targeting all health-related sustainable development goals (SDGs), generated projections using the AIDS Impact Model (AIM), which automatically aggregates transmission rates across all risk groups in the population and does not produce stratified outputs (Barker et al., 2017), and other models in the user-friendly interface Spectrum suite of software (Stenberg et al., 2017). One study aimed to build a linear predictive model of the demand for an HIV vaccine candidate in different countries based on its acceptability, parametrised as a function of vaccine efficacy and duration of protection as well as other local characteristics that determined the level of demand in different target populations (Hecht and Gandhi, 2008). Lastly, two papers analysing the effects of a new HIV testing and care policy in New York state, US, utilised a stock and flow model where transmission rates varied across different 'HIV stage' stocks, determined by CD4 counts derived from the literature; the model was then calibrated to local data and the transmission rates were used as fixed parameters in the stock and flow model, which is a system of integral and differential equations solved in a continuous, rather than a discrete simulation (Martin et al., 2015a, Martin et al., 2015b).

With regards to other disease areas, a model of hepatitis C virus (HCV) transmission among injecting drug users presented a SIR structure (Martin et al., 2011), while a stochastic Markov model of community transmission of yaws treated each disease stage as a discrete compartment, with infection rates dependent on transmission probability and number of infectious individuals (Marks et al., 2017).

REFERENCES

ADISASMITO, W., HUNTER, B. M., KRUMKAMP, R., LATIEF, K., RUDGE, J. W., HANVORAVONGCHAI, P. & COKER, R. J. 2015. Pandemic influenza and health system resource gaps in bali: An analysis through a resource transmission dynamics model. *Asia-Pacific Journal of Public Health,* 27**,** NP713-NP733. 10.1177/1010539511421365.

ALISTAR, S. S., BRANDEAU, M. L. & BECK, E. J. 2013. REACH: A practical HIV resource allocation tool for decision makers. *International Series in Operations Research and Management Science.* Springer New York LLC. 10.1007/978-1-4614-6507-2_10.

ANDERSON, S. J., CHERUTICH, P., KILONZO, N., CREMIN, I., FECHT, D., KIMANGA, D., HARPER, M., MASHA, R. L., NGONGO, P. B., MAINA, W., DYBUL, M. & HALLETT, T. B. 2014. Maximising the effect of combination HIV prevention through prioritisation of the people and places in greatest need: a modelling study. *Lancet,* 384**,** 249-56.

ANDERSON, S. J., GHYS, P. D., OMBAM, R. & HALLETT, T. B. 2018. Frontloading HIV financing maximizes the achievable impact of HIV prevention. *Journal of the International AIDS Society,* 21 (3) (no pagination). http://dx.doi.org/10.1002/jia2.25087.

BARKER, C., DUTTA, A. & KLEIN, K. 2017. Can differentiated care models solve the crisis in HIV treatment financing? Analysis of prospects for 38 countries in sub-Saharan Africa. *Journal of the International AIDS Society,* 20. 10.7448/IAS.20.5.21648.

BÄRNIGHAUSEN, T., BLOOM, D. E. & HUMAIR, S. 2016. Human resources for treating HIV/AIDS: Are the preventive effects of antiretroviral treatment a game changer? *PLoS ONE,* 11 (10) (no pagination). http://dx.doi.org/10.1371/journal.pone.0163960.

BOTTCHER, L., WOOLLEY-MEZA, O., ARAUJO, N. A., HERRMANN, H. J. & HELBING, D. 2015. Disease-induced resource constraints can trigger explosive epidemics. *Scientific Reports,* 5**,** 16571. https://dx.doi.org/10.1038/srep16571.

BOZZANI, F. M., MUDZENGI, D., SUMNER, T., GOMEZ, G. B., HIPPNER, P., CARDENAS, V., CHARALAMBOUS, S., WHITE, R. & VASSALL, A. 2018. Empirical estimation of resource constraints for use in model-based economic evaluation: an example of TB services in South Africa. *Cost Eff Resour Alloc,* 16**,** 27. https://doi.org/10.1186/s12962-018-0113-z.

BOZZANI, F. M., SUMNER, T., MUDZENGI, D., GOMEZ, G. B., WHITE, R. & VASSALL, A. 2020a. Informing Balanced Investment in Services and Health Systems: A Case Study of Priority Setting for Tuberculosis Interventions in South Africa. *Value in Health,* 23**,** 1462-1469. 10.1016/j.jval.2020.05.021.

BOZZANI, F. M., SUMNER, T., MUDZENGI, D., GOMEZ, G. B., WHITE, R. & VASSALL, A. 2020b. Informing balanced investment in services and health systems: A case study of priority setting for tuberculosis interventions in South Africa. *Value in Health*.

CHEN, X., ZHOU, T., FENG, L., LIANG, J., LILJEROS, F., HAVLIN, S. & HU, Y. 2019. Nontrivial resource requirement in the early stage for containment of epidemics. *Physical Review E,* 100. 10.1103/PhysRevE.100.032310.

CRUZ-APONTE, M., MCKIERNAN, E. C. & HERRERA-VALDEZ, M. A. 2011. Mitigating effects of vaccination on influenza outbreaks given constraints in stockpile size and daily administration capacity. *BMC Infectious Diseases,* 11. 10.1186/1471-2334-11-207.

CURRAN, M., HOWLEY, E. & DUGGAN, J. An analytics framework to support surge capacity planning for emerging epidemics. 2016. Association for Computing Machinery, Inc, 151-155.

DALGIÇ, Ö. O., ÖZALTIN, O. Y., CICCOTELLI, W. A. & ERENAY, F. S. 2017. Deriving effective vaccine allocation strategies for pandemic influenza: Comparison of an agent-based simulation and a compartmental model. *PLoS ONE,* 12. 10.1371/journal.pone.0172261.

FERRER, J., BOELLE, P. Y., SALOMON, J., MILIANI, K., L'HÉRITEAU, F., ASTAGNEAU, P. & TEMIME, L. 2014. Management of nurse shortage and its impact on pathogen dissemination in the intensive care unit. *Epidemics,* 9**,** 62-69. 10.1016/j.epidem.2014.07.002.

GUINDO, L. A., WAGNER, M., BALTUSSEN, R., RINDRESS, D., VAN TIL, J., KIND, P. & GOETGHEBEUR, M. M. 2012. From efficacy to equity: Literature review of decision criteria for resource allocation and healthcare decisionmaking. *Cost Eff Resour Alloc,* 10.

HAUCK, K., THOMAS, R. & SMITH, P. C. 2016. Departures from cost-effectiveness recommendations: The impact of health system constraints on priority setting. *Health Systems & Reform,* 2**,** 61-70.

HECHT, R. & GANDHI, G. 2008. Demand forecasting for preventive AIDS vaccines: Economic and policy dimensions. *PharmacoEconomics,* 26**,** 679-697. 10.2165/00019053-200826080-00005.

HONTELEZ, J. A. C., CHANGE, A. Y., OGBUOJI, O., DE VLAS, S. J., BARNIGHAUSEN, T. & ATUN, R. 2016. Changing HIV treatment eligibility under health system constraints in sub-Saharan Africa: investment needs, population health gains, and cost-effectiveness. *AIDS,* 30**,** 2341-2350.

HOUBEN, R. M. G. J., LALLI, M., SUMNER, T., HAMILTON, M., PEDRAZZOLI, D., BONSU, F., HIPPNER, P., PILLAY, Y., KIMERLING, M., AHMEDOV, S., PRETORIUS, C. & WHITE, R. G. 2016. TIME Impact – a new user-friendly tuberculosis (TB) model to inform TB policy decisions. *BMC Medicine,* 14**,** 1-10. 10.1186/s12916-016-0608-4.

JAMISON, D. T., ALWAN, A., MOCK, C. N., NUGENT, R., WATKINS, D., ADEYI, O., ANAND, S., ATUN, R., BERTOZZI, S., BHUTTA, Z., BINAGWAHO, A., BLACK, R., BLECHER, M., BLOOM, B. R., BROUWER, E., BUNDY, D. A. P., CHISHOLM, D., CIEZA, A., CULLEN, M., DANFORTH, K., DE SILVA, N., DEBAS, H. T., DONKOR, P., DUA, T., FLEMING, K. A., GALLIVAN, M., GARCIA, P. J., GAWANDE, A., GAZIANO, T., GELBAND, H., GLASS, R., GLASSMAN, A., GRAY, G., HABTE, D., HOLMES, K. K., HORTON, S., HUTTON, G., JHA, P., KNAUL, F. M., KOBUSINGYE, O., KRAKAUER, E. L., KRUK, M. E., LACHMANN, P., LAXMINARAYAN, R., LEVIN, C., LOOI, L. M., MADHAV, N., MAHMOUD, A., MBANYA, J. C., MEASHAM, A., MEDINA-MORA, M. E., MEDLIN, C., MILLS, A., MILLS, J. A., MONTOYA, J., NORHEIM, O., OLSON, Z., OMOKHODION, F., OPPENHEIM, B., ORD, T., PATEL, V., PATTON, G. C., PEABODY, J., PRABHAKARAN, D., QI, J., REYNOLDS, T., RUACAN, S., SANKARANARAYANAN, R., SEPULVEDA, J., SKOLNIK, R., SMITH, K. R., TEMMERMAN, M., TOLLMAN, S., VERGUET, S., WALKER, D. G., WALKER, N., WU, Y. & ZHAO, K. 2018. Universal health coverage and intersectoral action for health: key messages from Disease Control Priorities, 3rd edition. *Lancet,* 391**,** 1108-1120. 10.1016/S0140-6736(17)32906-9.

KRUMKAMP, R., KRETZSCHMAR, M., RUDGE, J. W., AHMAD, A., HANVORAVONGCHAI, P., WESTENHOEFER, J., STEIN, M., PUTTHASRI, W. & COKER, R. 2011. Health service resource needs for pandemic influenza in developing countries: A linked transmission dynamics, interventions and resource demand model. *Epidemiology and Infection,* 139**,** 59-67. 10.1017/S0950268810002220.

LANGLEY, I., ADAMS, E., DOULLA, B. & SQUIRE, S. B. 2014. Operational modelling to guide implementation and scale-up of diagnostic tests within the health system: Exploring opportunities for parasitic disease diagnostics based on example application for tuberculosis. *Parasitology,* 141**,** 1795-1802. 10.1017/S0031182014000985.

LIBERATI, A., ALTMAN, D. G., TETZLAFF, J., MULROW, C., GØTZSCHE, P. C., IOANNIDIS, J. P., CLARKE, M., DEVEREAUX, P. J., KLEIJNEN, J. & MOHER, D. 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med,* 6**,** e1000100. 10.1371/journal.pmed.1000100.

LIN, H. H., LANGLEY, I., MWENDA, R., DOULLA, B., EGWAGA, S., MILLINGTON, K. A., MANN, G. H., MURRAY, M., SQUIRE, S. B. & COHEN, T. 2011. A modelling framework to support the selection and implementation of new tuberculosis diagnostic tools. *Int J Tuberc Lung Dis,* 15**,** 996-1004. 10.5588/ijtld.11.0062.

LUBELL, Y., HOPKINS H., WHITTY, C. J., STAEDKE, S. G. & MILLS, A. 2008. An interactive model for the assessment of the economic costs and benefits of different rapid diagnostic tests for malaria. *Malaria J,* 7**,** 21.

MARKS, M. E., FUNK, S., MITJA, O., FITZPATRICK, C., ASIEDU, K., SOLOMON, A. W. & MABEY, D. C. 2017. Mathematical modelling approaches to estimating the optimum strategy for the eradication of yaws. *American Journal of Tropical Medicine and Hygiene,* 93 (4 Supplement)**,** 26.

MARTIN, E. G., MACDONALD, R. H., SMITH, L. C., GORDON, D. E., TESORIERO, J. M., LAUFER, F. N., LEUNG, S. Y. J. & O'CONNELL, D. A. 2015a. Policy modeling to support administrative decisionmaking on the new york state HIV testing law. *Journal of Policy Analysis and Management,* 34**,** 403-423. 10.1002/pam.21797.

MARTIN, E. G., MACDONALD, R. H., SMITH, L. C., GORDON, D. E., TESORIERO, J. M., LAUFER, F. N., LEUNG, S. Y. J., ROWE, K. A. & O'CONNELL, D. A. 2015b. Mandating the offer of HIV testing in New York: Simulating the epidemic impact and resource needs. *Journal of Acquired Immune Deficiency Syndromes,* 68**,** S59-S67. 10.1097/QAI.0000000000000395.

MARTIN, N. K., PITCHER, A. B., VICKERMAN, P., VASSALL, A. & HICKMAN, M. 2011. Optimal control of hepatitis C antiviral treatment programme delivery for prevention amongst a population of injecting drug users. *PLoS ONE [Electronic Resource],* 6**,** e22309. https://dx.doi.org/10.1371/journal.pone.0022309.

MASOODIAN, M. & LUZ, S. Ecoepidemiological Simulation as a Serious Game Engine Module. *In:* BAMIDIS, P. D., KONSTANTINIDIS, S. T. & RODRIGUES, P. P., eds., 2017. Institute of Electrical and Electronics Engineers Inc., 193-194.

MCKAY, V. R., HOFFER, L. D., COMBS, T. B. & MARGARET DOLCINI, M. 2018. The dynamic influence of human resources on evidence-based intervention sustainability and population outcomes: An agent-based modeling approach. *Implementation Science,* 13. 10.1186/s13012-018-0767-0.

MENZIES, N. A., GOMEZ, G. B., BOZZANI, F., CHATTERJEE, S., FOSTER, N., GARCIA BAENA, I., LAURENCE, Y. & ET AL. 2016. Cost-effectiveness and resource implications of aggressive TB control in China, India and South Africa: a combined analysis of nine models. *Lancet Glob Health,* 4**,** e816–e826.

MENZIES, N. A., MCQUAID, C. F., GOMEZ, G. B., SIROKA, A., GLAZIOU, P., FLOYD, K., WHITE, R. G. & HOUBEN, R. M. G. J. 2019. Improving the quality of modelling evidence used for tuberculosis policy evaluation. *Int J Tuberc Lung Dis,* 23**,** 387-395.

MIKKELSEN, E., HONTELEZ, J. A. C., JANSEN, M. P. M., BÄRNIGHAUSEN, T., HAUCK, K., JOHANSSON, K. A., MEYER-RATH G., OVER, M., DE VLAS, S. J., VAN DER WILT, G. J., TROMP, N., BIJLMAKERS, L. & BALTUSSEN, R. M. P. M. 2017. Evidence for scaling up HIV treatment in sub-Saharan Africa: A call for incorporating health systems constraints. *PLoS Med,* 14**,** e1002240.

PEAK, C. M., KAHN, R., GRAD, Y. H., CHILDS, L. M., LI, R., LIPSITCH, M. & BUCKEE, C. O. 2020. Individual quarantine versus active monitoring of contacts for the mitigation of COVID-19: a modelling study. *The Lancet Infectious Diseases,* 20**,** 1025-1033. 10.1016/S1473-3099(20)30361-3.

PUTTHASRI, W., LERTIENDUMRONG, J., CHOMPOOK, P., TANGCHAROENSATHIEN, V. & COKER, R. 2009. Capacity of Thailand to contain an emerging influenza pandemic. *Emerging Infectious Diseases,* 15**,** 423-432. 10.3201/eid1503.080872.

RUDGE, J. W., HANVORAVONGCHAI, P., KRUMKAMP, R., CHAVEZ, I., ADISASMITO, W., CHAU, P. N., PHOMMASAK, B., PUTTHASRI, W., SHIH, C. S., STEIN, M., TIMEN, A., TOUCH, S., REINTJES, R., COKER, R. & ASIAFLUCAP PROJECT, C. 2012. Health system resource gaps and associated mortality from pandemic influenza across six Asian territories. *PLoS ONE [Electronic Resource],* 7**,** e31800. https://dx.doi.org/10.1371/journal.pone.0031800.

SALOMON, J. A., LLOYD-SMITH, J. O., GETZ, W. M., RESCH, S., SANCHEZ, M. S., PORCO, T. C. & BORGDORFF, M. W. 2006. Prospects for advancing tuberculosis control efforts through novel therapies. *PLoS Med,* 3**,** e273. 10.1371/journal.pmed.0030273.

SALOMON, J. A., VOS, T., HOGAN, D. R., GAGNON, M., NAGHAVI, M., MOKDAD, A., BEGUM, N., SHAH, R., KARYANA, M., KOSEN, S., FARJE, M. R. & ET AL. 2012. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet,* 15**,** 2129-43. 10.1016/S0140-6736(12)61680-8.

SÉBILLE, V. & VALLERON, A. J. 1997. A computer simulation model for the spread of nosocomial infections caused by multidrug-resistant pathogens. *Computers and Biomedical Research,* 30**,** 307-322. 10.1006/cbmr.1997.1451.

SHATTOCK, A. J., KERR, C. C., STUART, R. M., MASAKI, E., FRASER, N., BENEDIKT, C., GORGENS, M., WILSON, D. P. & GRAY, R. T. 2016. In the interests of time: improving HIV allocative efficiency modelling via optimal time-varying allocations. *J Int AIDS Soc,* 19**,** 20627. 10.7448/IAS.19.1.20627.

SHIM, E., MEYERS, L. A. & GALVANI, A. P. 2011. Optimal H1N1 vaccination strategies based on self-interest versus group interest. *BMC Public Health,* 11 Suppl 1**,** S4. https://dx.doi.org/10.1186/1471-2458-11-S1-S4.

STEGMULLER, A. R., SELF, A., LITVIN, K. & ROBERTON, T. 2017. How is the Lives Saved Tool (LiST) used in the global health community? Results of a mixed-methods LiST user study. *BMC Public Health,* 17**,** 773.

STENBERG, K., HANSSEN, O., EDEJER, T. T. T., BERTRAM, M., BRINDLEY, C., MESHREKY, A., ROSEN, J. E., STOVER, J., VERBOOM, P., SANDERS, R. & SOUCAT, A. 2017. Financing transformative health systems towards achievement of the health Sustainable Development Goals: a model for projected resource needs in 67 low-income and middle-income countries. *The Lancet Global Health,* 5**,** e875-e887. 10.1016/S2214-109X(17)30263-2.

STOPARD, I. J., MCGILLEN, J. B., HAUCK, K. & HALLETT, T. B. 2019. The influence of constraints on the efficient allocation of resources for HIV prevention. *AIDS,* 33**,** 1241-1246. 10.1097/QAD.0000000000002158.

SUMNER, T., BOZZANI, F., MUDZENGI, D., HIPPNER, P., CARDENAS, V., VASSALL, A. & WHITE, R. 2018. Incorporating resource constraints into mathematical models of TB: An example of case finding in South Africa. *Am J Epidemiol,* 188**,** 1155-1164. doi: 10.1093/aje/kwz038.

SUMNER, T., BOZZANI, F., MUDZENGI, D., HIPPNER, P., HOUBEN, R. M., CARDENAS, V., VASSALL, A. & WHITE, R. G. 2019a. Estimating the Impact of Tuberculosis Case Detection in Constrained Health Systems: An Example of Case-Finding in South Africa. *American Journal of Epidemiology,* 188**,** 1155-1164. 10.1093/aje/kwz038.

SUMNER, T., BOZZANI, F., MUDZENGI, D., HIPPNER, P., HOUBEN, R. M., CARDENAS, V., VASSALL, A. & WHITE, R. G. 2019b. Estimating the Impact of Tuberculosis Case Detection in Constrained Health Systems: An Example of Case-Finding in South Africa. *Am J Epidemiol,* 188**,** 1155-1164. 10.1093/aje/kwz038.

TROMP, N. & BALTUSSEN, R. 2012. Mapping of multiple criteria for priority setting of health interventions: An aid for decision makers. *BMC Health Services Research,* 12**,** 454.

VASSALL, A., MANGHAM-JEFFERIES, L., GOMEZ, G. B., PITT, C. & FOSTER, N. 2016. Incorporating demand and supply constraints into economic evaluation in low-income and middle-income countries. *Health Econ,* 25**,** 95-115. 10.1002/hec.3306.

VERMA, V. R., SAINI, A., GANDHI, S., DASH, U. & KOYA, S. F. 2020. Capacity-need gap in hospital resources for varying mitigation and containment strategies in India in the face of COVID-19 pandemic. *Infectious Disease Modelling,* 5**,** 608-621. 10.1016/j.idm.2020.08.011.

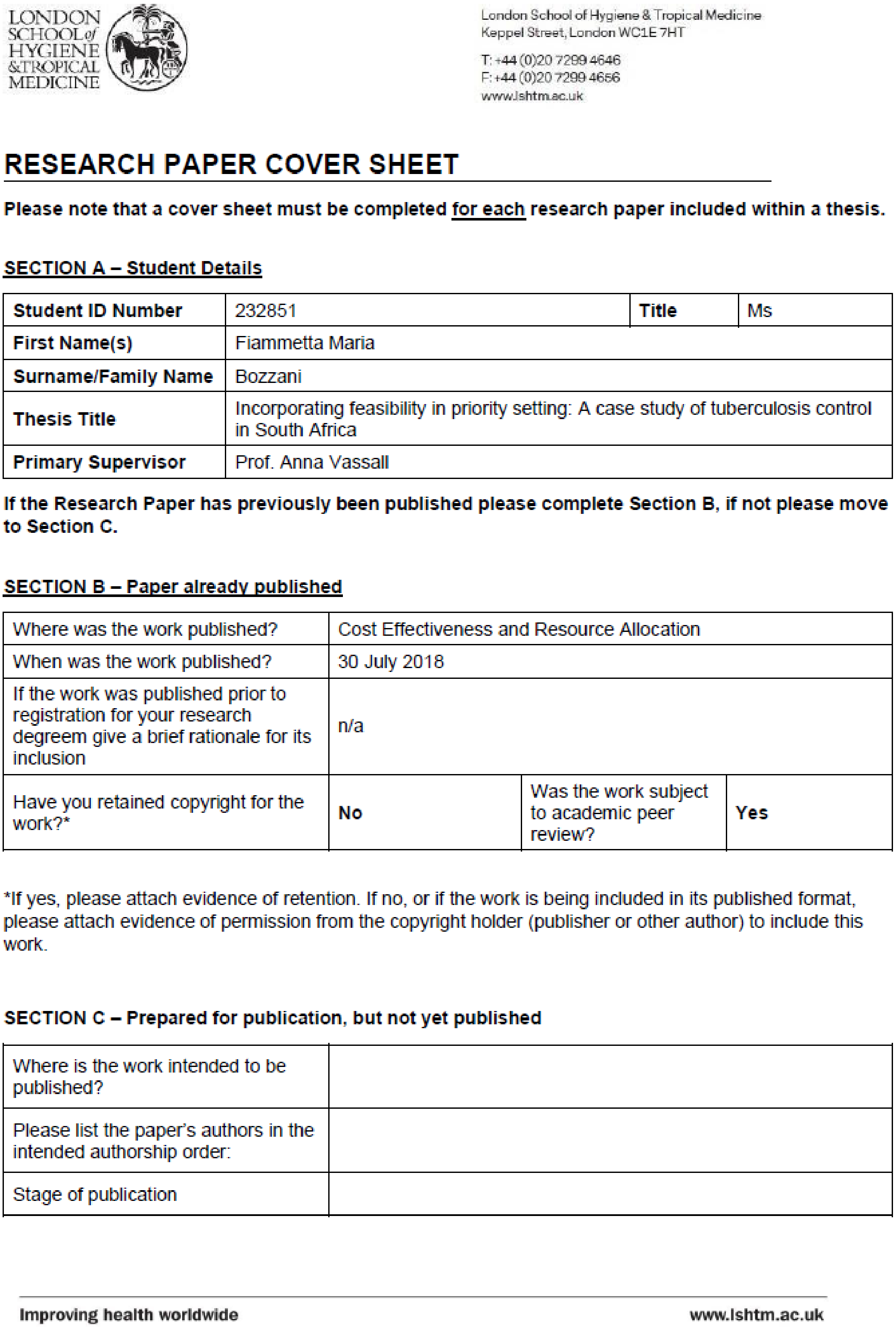
ZHANG, H., YANG, Z., PAWELEK, K. A. & LIU, S. 2020. Optimal control strategies for a two-group epidemic model with vaccination-resource constraints. *Applied Mathematics and Computation,* 371. 10.1016/j.amc.2019.124956.

CHAPTER 4: EMPIRICAL ESTIMATION OF RESOURCE CONSTRAINTS FOR USE IN MODEL-BASED ECONOMIC EVALUATION: AN EXAMPLE OF TB SERVICES IN SOUTH AFRICA

Citation

BOZZANI, F. M., MUDZENGI, D., SUMNER, T., GOMEZ, G. B., HIPPNER, P., CARDENAS, V., CHARALAMBOUS, S., WHITE, R. & VASSALL, A. 2018. Empirical estimation of resource constraints for use in model-based economic evaluation: an example of TB services in South Africa. *Cost Eff Resour Alloc,* 16**,** 27. https://doi.org/10.1186/s12962-018-0113-z.

Paper 2 cover sheet



LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

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

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

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	232851	**Title**	Ms
First Name(s)	Fiammetta Maria		
Surname/Family Name	Bozzani		
Thesis Title	Incorporating feasibility in priority setting: A case study of tuberculosis control in South Africa		
Primary Supervisor	Prof. 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

Where was the work published?	Cost Effectiveness and Resource Allocation		
When was the work published?	30 July 2018		
If the work was published prior to registration for your research degreem give a brief rationale for its inclusion	n/a		
Have you retained copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

Improving health worldwide www.lshtm.ac.uk

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the lead author of this paper, which descibes an analysis of costs and resource requirements for tuberculosis control based on a tuberculosis transmission model built by Dr Tom Sumner. I built the model for calculating costs and input constraints, designed the constraints scenarios in collaboration with my co-authors, coordinated data collection and analysed the data. I drafted the manuscript, incorporated feedback from co-authors and was responsible for submission to the journal and for carrying out the revisions recommended during the peer review process.

SECTION E

Student Signature	[redacted]
Date	14/03/2021

Supervisor Signature	[redacted]
Date	01/06/2021

4.1 ABSTRACT

Background: Evidence on the relative costs and effects of interventions that do not consider 'real-world' constraints on implementation may be misleading. However, in many low- and middle-income countries, time and data scarcity mean that incorporating health system constraints in priority setting can be challenging.

Methods: We developed a 'proof of concept' method to empirically estimate health system constraints for inclusion in model-based economic evaluations, using intensified case-finding strategies (ICF) for tuberculosis (TB) in South Africa as an example. As part of a strategic planning process, we quantified the resources (fiscal and human) needed to scale up different ICF strategies (cough triage and WHO symptom screening). We identified and characterised three constraints through discussions with local stakeholders: 1) financial constraint: potential maximum increase in public TB financing available for new TB interventions; 2) human resource constraint: maximum current and future capacity among public sector nurses that could be dedicated to TB services; and 3) diagnostic supplies constraint: maximum ratio of Xpert MTB/RIF tests to TB notifications. We assessed the impact of these constraints on the costs of different ICF strategies.

Results: It would not be possible to reach the target coverage of ICF (as defined by policy makers) without addressing financial, human resource and diagnostic supplies constraints. The costs of addressing human resource constraints is substantial, increasing total TB programme costs during the period 2016-2035 by between 7% and 37% compared to assuming the expansion of ICF is unconstrained, depending on the ICF strategy chosen.

Conclusions: Failure to include the costs of relaxing constraints may provide misleading estimates of costs, and therefore cost-effectiveness. In turn, these could impact the local relevance and credibility of analyses, thereby increasing the risk of sub-optimal investments.

4.2 INTRODUCTION

Frameworks for priority setting for the control of infectious diseases in low-and middle-income countries are evolving. In recent years, mathematical models of disease transmission have been increasingly used for supporting priority setting efforts in these settings (Houben et al., 2016, McGillen et al., 2016, Menzies et al., 2016). At the same time, the importance of considering both supply-side and demand-side constraints on the uptake, delivery and cost-effectiveness of global health interventions has been widely recognised (Hauck et al., 2016, Vassall et al., 2016). Understanding constraints is particularly relevant in low and middle-income countries, where non-financial constraints such as human resources scarcity may substantially impact the feasibility of implementation and pace of scale-up of interventions (Gericke et al., 2005, Hanson et al., 2003). Traditionally, model-based priority setting has incorporated and adapted to local demographic and epidemiological characteristics, but to date the explicit consideration of the impact of context-specific health system constraints on the costs and cost-effectiveness of global health interventions is often absent (Mikkelsen et al., 2017).

Several approaches have been proposed for incorporating both financial and non-financial resource constraints in model-based priority setting for infectious diseases. These allow the analyst to either restrict outputs to limit the impact of interventions, or to cost the relaxation of constraints. For limiting impact, some have adopted an 'integrated modelling' approach combining disease and operational (health systems) modelling. However, this approach has substantial data requirements as detailed knowledge of numerous processes across the health system is necessary to populate the operational model (Langley et al., 2014, Lin et al., 2011). Another approach is mathematical programming, which examines solutions that maximise global health objectives under a range of constraints (Bradley et al., 1977). Mathematical programming has the advantage of potentially dealing simultaneously with multiple constraints, such as equity and efficiency (Cleary et al., 2010, Epstein et al., 2007, Hontelez et al., 2016). However, combining this approach with infectious disease models is computationally complex and data-intensive (Hontelez et al., 2016). While mathematical programming has the potential to be widely applied in the presence of strengthened health information systems, the 'black box' nature of this approach may constitute a barrier for users and result in a process that lacks transparency for decision-makers (van Baal et al., 2016).

A gap remains for approaches to support decision-makers set priorities that assess the impact of constraints and that are feasible within planning timeframes and under considerable data scarcity. In this context, we present a proof of concept for a pragmatic method for the empirical estimation of both financial and non-financial constraints from routine data. Target users are analysts involved in priority setting to support national strategic planning processes, who wish to explicitly model the impact of selected constraints. This method was developed and piloted during the policy planning process for the 2017-2022 National Tuberculosis Plan (NTP) in South Africa, rather than in a research setting. We illustrate the approach in respect of facility-based tuberculosis (TB) case-finding strategies. Specifically, we present methods for estimating financial, human resource and diagnostic constraints, and demonstrate how these can be used in estimating the costs of the facility-based TB case finding strategies under constraints.

4.3 MATERIALS AND METHODS

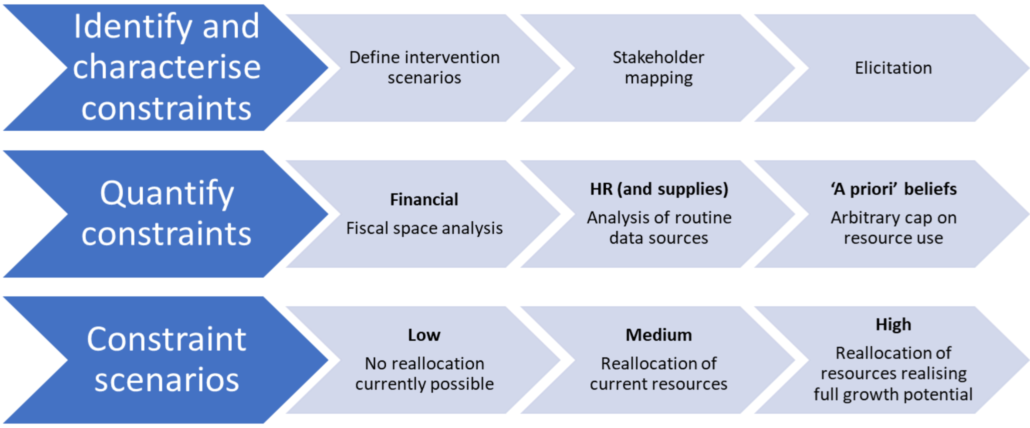
4.3.1 Study setting

South Africa faces one of the world's worst TB epidemics (Churchyard et al., 2014). TB programmes often rely on passive case-finding, focused on the screening of individuals presenting to health facilities with TB symptoms. This method has been shown to miss a large proportion of facility-based TB cases presenting with unrelated symptoms (Claassens et al., 2013). In 2015, Intensified Case Finding (ICF) for TB was adopted in South Africa for detecting TB cases among HIV-infected health facility attendees, who are screened for TB at each facility visit. During the previous year, the South African TB Think Tank was established with the purpose of advising the National Department of Health (NDoH) on TB policy and strategic planning (White et al., 2018). As part of this effort, an economic analysis to identify the optimal ICF and TB diagnostic strategy for South Africa was conducted. The ICF programme would be targeting over 100 million visits to primary health care facilities per year.

4.3.2 Identifying and characterising constraints

The analysis concentrated on supply- rather than demand-side constraints. The process of constraints estimation is described in Figure 5. Three constraints on health system resources relevant to TB service provision were identified through discussions with local stakeholders that primarily took place as part of the TB Think Tank meetings (NDoH TB programme managers and staff, technical assistants and local TB experts supporting the national planning processes). Stakeholders were selected based on their participation in the TB Think Tank. Individual discussions were held with 12 Think Tank members and group discussions were facilitated during Think Tank meetings, attended by an average of 25 stakeholders. In the context of policy meetings, no formal interview process was used. In addition to financial constraints, stakeholders consistently highlighted human resource and supplies constraints and agreed for these to be considered in the analysis.

Figure 5. Summary of constraints estimation process



4.3.3 Financial constraint

We conducted a fiscal space analysis for estimating the financial constraint for TB. Baseline levels of total public expenditure on TB were estimated using the most recent figures (2013) (National Department of Health and South Africa National AIDS Council, 2016). To convert South African Rand into US Dollars, we used the average official exchange rate over the three-year period to 2016 (13.9) (World Bank). For the NTP 2017-2022 period, we used the fiscal space model developed by Remme and colleagues (Remme et al., 2016). This model considers the increase in public spending from GDP growth, health prioritisation within the overall government budget as well as TB prioritisation within overall health spending, earmarked alcohol taxes and efficiency gains.

While in principle resources for TB could be allocated from the general health budget, the budgeting process is historically incremental. We therefore considered three scenarios (Table 4), including one where policy makers do not use all the fiscal space available to them. In the low constraint scenario (most limiting), the TB budget was assumed to grow at an annual rate of 1.7% in line with GDP growth only (Remme et al., 2016). This assumes that TB policy makers are unable to advocate for a greater share of the overall health budget. In the medium constraint scenario, we assumed that, between 2017 and 2022, an increased share (from 2% to 15%) of the health budget is allocated to TB to match the share of the burden of disease caused by TB, adjusted for TB mortality as reported by the NDoH (15%). In the high constraint scenario (least limiting), we assumed that 15% of a health budget that achieves its full fiscal space growth (3%) is allocated to TB. In all scenarios we assumed that, post 2022, TB expenditure would continue to grow by a constant rate of 1.7% per annum.

Table 4. Projected annual growth in budget and human resources for TB under different constraint scenarios, from most to least limiting

	Budget constraint			Human resource constraint		
Year	Low	Medium	High	Low	Medium	High
2015	-	-	-	-	-	-
2016	1.7%	1.7%	1.7%	0.9%	0.9%	0.9%
2017	1.7%	47.5%	51.8%	0.8%	4.2%	4.2%
2018	1.7%	32.2%	34.1%	0.8%	4.1%	4.1%
2019	1.7%	24.4%	25.4%	0.7%	3.9%	3.9%
2020	1.7%	19.6%	20.3%	0.7%	3.7%	3.7%
2021	1.7%	16.4%	16.9%	0.7%	3.6%	3.6%
2022	1.7%	1.7%	1.7%	0.6%	0.6%	3.1%
2023	1.7%	1.7%	1.7%	0.6%	0.6%	3.1%
2024	1.7%	1.7%	1.7%	0.6%	0.6%	3.1%
2025	1.7%	1.7%	1.7%	0.6%	0.6%	3.2%
2026	1.7%	1.7%	1.7%	0.5%	0.5%	3.2%
2027	1.7%	1.7%	1.7%	0.5%	0.5%	3.2%
2028	1.7%	1.7%	1.7%	0.5%	0.5%	3.2%
2029	1.7%	1.7%	1.7%	0.5%	0.5%	3.2%
2030	1.7%	1.7%	1.7%	0.5%	0.5%	3.3%
2031	1.7%	1.7%	1.7%	0.5%	0.5%	3.3%
2032	1.7%	1.7%	1.7%	0.5%	0.5%	3.3%
2033	1.7%	1.7%	1.7%	0.5%	0.5%	3.3%
2034	1.7%	1.7%	1.7%	0.5%	0.5%	3.3%
2035	1.7%	1.7%	1.7%	0.5%	0.5%	3.4%

4.3.4 Human resource constraint

In consultation with the NDoH, the constraint on human resources was characterised as the available annual full time equivalent (FTE) of nursing staff to provide all TB services, expressed in minutes of available nursing time. The constraint was applied to all TB services, as increased screening will also increase the use of other TB services along the patient pathway. Nurses are the main cadre of staff that deliver TB case detection, diagnosis and treatment in South Africa. The nursing cadres considered were professional (or registered) nurses, including TB and antiretroviral therapy nurses; and enrolled nurses, who are not specialised and carry out many of the same activities as registered nurses but do not prescribe drugs. The analysis was limited to nurse availability in primary health care (PHC) clinics and health centres.

The total FTE spent by nursing staff on TB in 2015 (baseline) was estimated from routine data available upon request (DHIS, Persal, Electronic TB Register). In addition, estimates were informed by ongoing or recently concluded costing studies that measured human resource use, published literature and personal communications with the NDoH (see technical appendix for further details). Projections on the growth of the nursing workforce in South Africa were informed by historical data available from the South African Nursing Council (South African Nursing Council).

Three human resource constraint scenarios were considered (Table 4). For the low (most limiting) constraint, we assumed TB policymakers are unable to re-allocate nurses from other services. In this case, the maximum annual minutes spent on TB were held at the current level and adjusted in future years based on population growth projections, holding the ratio of nurses trained per capita constant (United Nations Population Division, 2015). For the medium and high constraints, nurse time was allocated to TB according to the disease burden (from 6% to 15%) during the NTP period. This was calculated as the ratio of total deaths from TB among HIV-infected and -uninfected patients (WHO, 2015), to total deaths in South Africa (IHME, 2013). Post 2022, the low and medium constraint increased annually in line with population growth projections. The high (least limiting) constraint also took the historically rapid nursing workforce growth in South Africa into account.

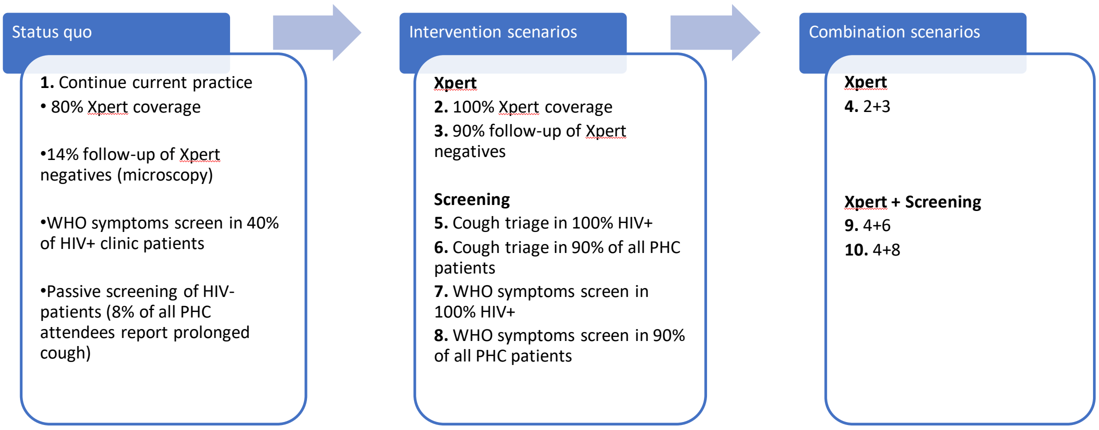
4.3.5 Diagnostic supplies constraint

Strengthening TB case-finding may have a substantial impact on diagnostic supplies requirements and related costs. While South Africa has demonstrated the capacity to rapidly scale up TB diagnostic volumes (Churchyard et al., 2015), in consultation with the NDoH we identified a constraint on the amount of TB diagnostic supplies (Xpert MTB/RIF tests) purchased annually. This constraint corresponds to the rule of thumb that has been used to set the TB diagnostic budget in previous years (South African NDoH, personal communication), which limits the TB programme to a ratio of 20 Xpert MTB/RIF tests for every case of TB diagnosed.

4.3.6 Estimating the costs of TB services considering constraints

We estimated TB service costs both under constraints and with relaxing of the constraints using a mathematical model of TB that estimates TB cases, TB mortality and the use of TB services (Sumner et al., 2019). The model was calibrated for the year 2015 and cost projections were generated for a 20-year period up to 2035. The model was used to calculate costs of introducing nine different ICF intervention options (described in Figure 6), by multiplying projected TB service volumes by the unit costs for all TB services and interventions.

Figure 6. Modelled interventions



Status quo

1. Continue current practice
- 80% Xpert coverage
- 14% follow-up of Xpert negatives (microscopy)
- WHO symptoms screen in 40% of HIV+ clinic patients
- Passive screening of HIV- patients (8% of all PHC attendees report prolonged cough)

Intervention scenarios

Xpert
2. 100% Xpert coverage
3. 90% follow-up of Xpert negatives

Screening
5. Cough triage in 100% HIV+
6. Cough triage in 90% of all PHC patients
7. WHO symptoms screen in 100% HIV+
8. WHO symptoms screen in 90% of all PHC patients

Combination scenarios

Xpert
4. 2+3

Xpert + Screening
9. 4+6
10. 4+8

In detail, the ICF intervention options examined involve screening two different populations (all clinic patients or only those that are HIV-infected) using either cough triage, a single question on whether the respondent has been coughing for at least two weeks, or the full WHO symptoms screener, whereby patients reporting either current cough, fever, weight loss or night sweats are referred for TB testing (WHO, 2013). Unit costs for TB services and interventions in South Africa were derived from previously published data or constructed using ingredients costing, as described in the Supplementary material. A discount rate of 3% was applied to future costs.

The model was first used to estimate costs of the ICF interventions in an unconstrained environment, expanding services to coverage levels defined by policy targets (as described elsewhere and in the supplementary material) (Sumner et al., 2019). Each constraint scenario was then applied independently. When constraints were exceeded, the model was re-run at a reduced coverage, such that the projected costs or (in the case of the human resource constraint) nurse time remained below the constraint over the entire time horizon. For the supplies constraint, coverage was limited once the ratio of diagnostic tests to TB notifications was exceeded. Results on the effects of the constraints on intervention impact and the resulting coverage gaps are described elsewhere by Sumner and colleagues (Sumner et al., 2019).

Relaxing the Xpert MTB/RIF constraint was assumed to have no costs aside from purchasing and deploying additional tests. Similarly, relaxing the financial constraints results in no additional costs compared to the unconstrained scenario. The additional costs of relaxing the human resource constraint were estimated as the cost of hiring and employing the extra nurses needed to supply the additional number of minutes required for the three constrained scenarios to reach the coverage and output levels achieved under the unconstrained scenario. Our estimations considered a mix of registered (51%) and enrolled (49%) nurses based on DHIS and South African Nursing Council data. In discussion with the NDoH, some of the extra minutes required to relax the constraints were supplied by existing private sector nurses, as the average monthly salary for public sector nurses is higher than that in the private sector (PayScale, 2017). The underlying assumption is that, currently, nurses join the private sector due to a lack of open positions in the better paying public sector. In the first year where the nurse minutes requirements exceeded availability under the constrained scenario, we assumed all minutes worked in primary health care by private sector nurses could be re-allocated to the public sector as needed. In subsequent years, we assumed the historical proportion of new graduates joining the private sector would join the public sector instead. All private sector nurses and nursing graduates were assumed to be registered nurses.

The additional minutes needed to relax the constraints that could not be covered by employing the current private sector workforce were costed by estimating the costs of increasing government-sponsored new graduates. Professional nurses spend a total of 48 months in training while enrolled nurses take 36 months to qualify (South African Nursing Council). Both cadres receive a monthly stipend of US$ 676 from the government to cover living expenses while in training. Once employed, a 10% mark-up on the annual salary of new graduates was factored in to take the transaction costs of employment into account. An additional 10% mark-up over basic pay was added for 30% of new nurses, representing the allowance received by those posted in rural areas (Reid, 2004).

4.4 RESULTS

4.4.1 Base case estimates of financial, human resources and number of Xpert MTB/RIFs

In 2015, we estimate a public expenditure for the TB programme of approximately U$ 415 million, of which US$ 310 million was spent on direct service provision and the rest on administration and other above-service-level activities. Changes in financial resource requirements for service provision over time in the absence of new interventions are shown in Table 5. The decrease in the costs of TB services over time under this scenario reflects the projected declining trend in the TB epidemic in South Africa.

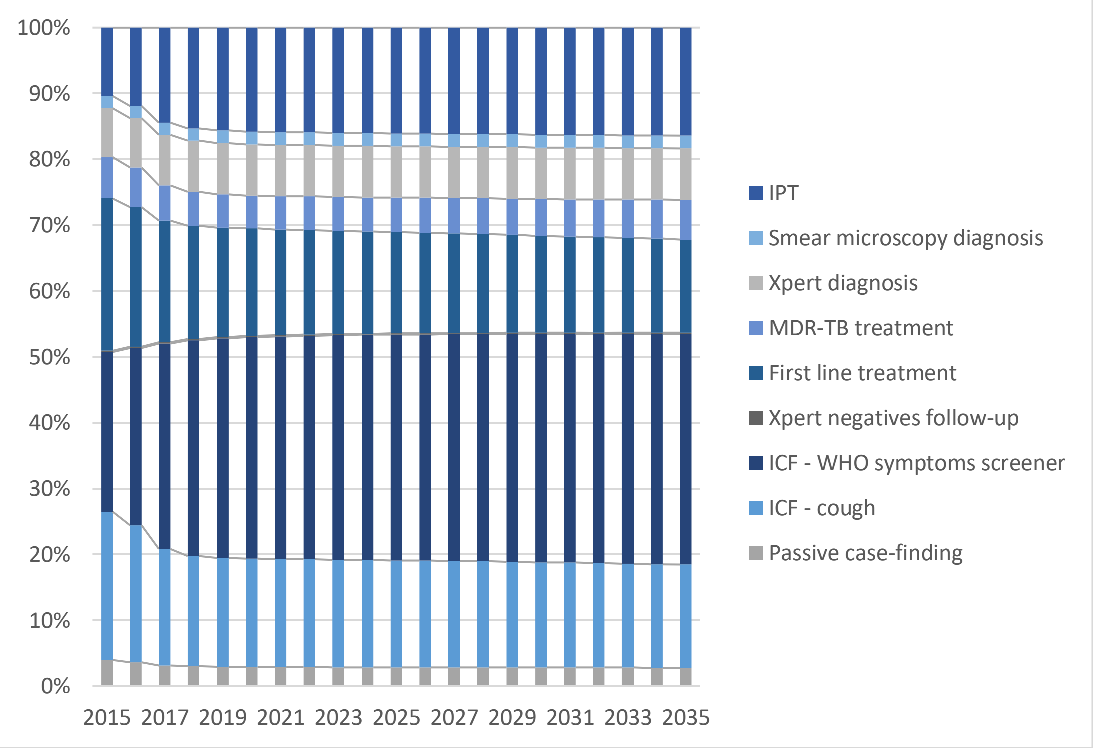
We estimate that the South African nursing workforce supplied approximately 209.5 million minutes to TB services in public primary health care facilities in 2015. Specialised TB nurses accounted for about 15% of total minutes for TB, while most TB service provision time was supplied by other professional nurses (51%) and enrolled nurses (34%). Figure 7 shows the distribution of staff time across different TB services under the base case, assuming no new intervention is introduced. Finally, the number of Xpert MTB/RIF tests in 2015 was estimated to be 3.2 million.

Table 5. base case financial resource requirements for TB services provision, 2016 US$

Year	Passive case finding	ICF – cough triage	ICF - WHO symptoms screener	Xpert negatives follow-up	First line treatment	MDR-TB treatment	Xpert MTB/RIF diagnosis	Smear microscopy diagnosis	IPT	**TOTAL**
2015	1,410,773	16,735,538	11,339,995	719,731	40,180,219	116,780,734	104,264,301	8,788,407	10,075,340	310,295,039
2016	1,361,274	16,163,576	13,152,808	713,400	38,432,227	116,926,226	110,340,641	9,300,580	12,055,578	318,446,309
2017	1,315,734	15,417,893	17,142,665	726,632	37,705,880	118,058,283	125,981,140	10,618,913	16,398,177	343,365,316
2018	1,275,370	14,936,907	18,332,255	712,543	35,898,981	114,934,319	129,548,686	10,919,620	17,722,633	344,281,313
2019	1,240,571	14,555,234	18,524,339	694,551	34,356,526	111,743,996	129,002,723	10,873,601	17,967,440	338,958,982
2020	1,209,293	14,214,061	18,368,678	676,625	33,071,298	109,171,196	127,087,494	10,712,167	17,835,516	332,346,329
2021	1,180,102	13,891,486	18,096,024	659,396	31,946,882	107,155,267	124,747,372	10,514,919	17,576,279	325,767,726
2022	1,152,180	13,578,567	17,787,797	642,850	30,920,793	105,540,398	122,303,518	10,308,927	17,277,749	319,512,780
2023	1,125,078	13,271,337	17,471,075	626,861	29,958,551	104,197,245	119,855,790	10,102,609	16,969,529	313,578,075
2024	1,098,620	12,968,654	17,155,575	611,357	29,044,267	103,043,788	117,439,480	9,898,939	16,662,200	307,922,880
2025	1,072,710	12,669,940	16,844,627	596,290	28,169,833	102,027,241	115,065,298	9,698,820	16,359,422	302,504,180
2026	1,047,337	12,375,476	16,540,194	581,648	27,331,230	101,115,987	112,741,285	9,502,929	16,063,288	297,299,373
2027	1,022,536	12,086,063	16,242,380	567,427	26,526,100	100,291,602	110,469,170	9,311,413	15,773,812	292,290,502
2028	998,299	11,801,897	15,950,333	553,607	25,752,333	99,540,603	108,244,943	9,123,934	15,490,056	287,456,007
2029	974,636	11,523,309	15,663,396	540,179	25,008,440	98,855,029	106,066,036	8,940,275	15,211,297	282,782,598
2030	951,549	11,250,556	15,380,642	527,129	24,292,808	98,228,624	103,928,488	8,760,101	14,936,554	278,256,451
2031	929,014	10,983,533	15,101,333	514,434	23,603,600	97,655,673	101,828,214	8,583,070	14,665,078	273,863,947
2032	907,022	10,722,349	14,824,025	502,070	22,938,847	97,130,242	99,758,485	8,408,613	14,395,348	269,587,000
2033	885,559	10,466,925	14,548,635	490,027	22,297,387	96,649,025	97,718,406	8,236,655	14,127,320	265,419,939
2034	864,608	10,217,086	14,275,791	478,295	21,678,167	96,209,490	95,710,021	8,067,369	13,861,714	261,362,541
2035	844,149	9,972,617	14,006,160	466,869	21,080,136	95,809,377	93,735,448	7,900,933	13,599,291	257,414,979

ICF: Intensified case-finding; MDR-TB: Multi-Drug Resistant Tuberculosis; IPT: Isoniazid Preventive Therapy

Figure 7. Base case human resource time for TB services provision, share of total minutes



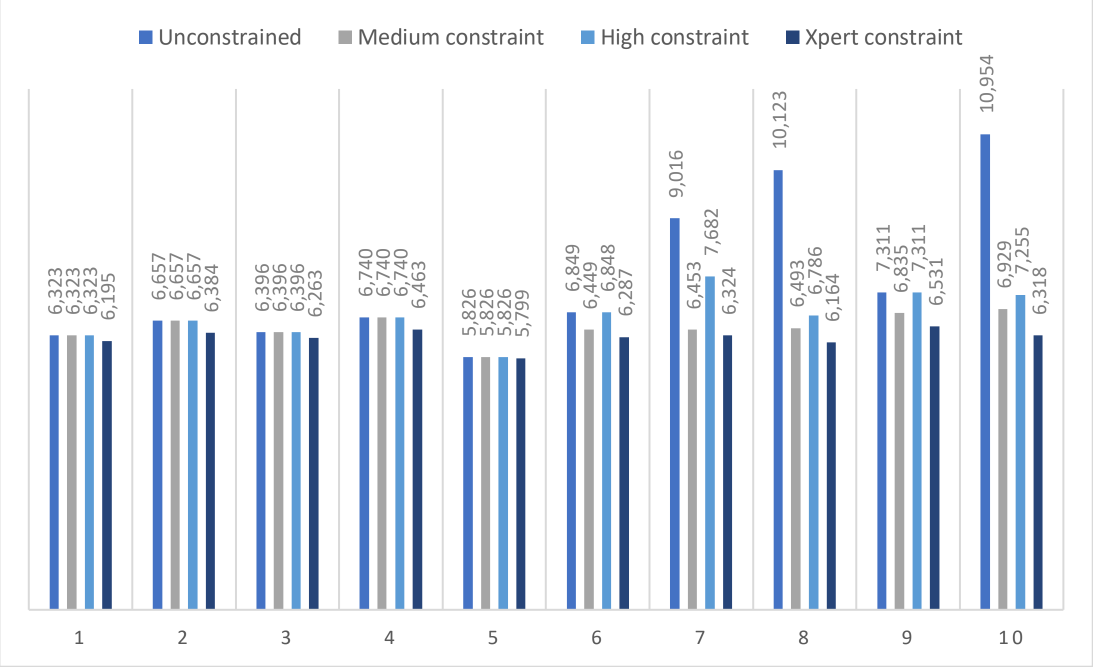
4.4.2 Constrained scenarios

The low (most limiting) budget and human resource constraints were exceeded by almost all interventions. These constraints were deemed unrealistic to overcome and thus not modelled further, as they made any expansion of case-finding infeasible without substantial disinvestment in other areas of TB care. Conversely, the high budget constraint was never exceeded. The impact of the other constrained scenarios on TB costs between 2016-2035 is presented in Figure 8. Under the medium budget constraint, all case-finding interventions could be 'afforded' with the exception of intervention 10 (combination of expanding Xpert MTB/RIF coverage, increasing adherence to the Xpert-negative algorithm and achieving 90% coverage of the WHO symptoms screener among all PHC clinic attendees). Under this scenario, there was a relatively small funding gap of approximately US$ 24.9 million over the period 2016-2035 for intervention 10 (Figure 8).

The human resource constraints do not impact interventions 2-5 (expanded Xpert MTB/RIF utilisation and increased adherence to the Xpert-negative algorithm, alone or in combination, and cough-based screening among all HIV-infected PHC clinic attendees, respectively). Interventions 6-8 (cough-based screening, both on its own among all PHC attendees and in combination with the strengthening of diagnostic algorithms) are impacted to a limited extent. Implementation of interventions 9 and 10 (combinations of strengthened diagnostic algorithms and ICF using cough triage or the WHO symptoms screener, respectively) is substantially constrained by human resource availability. If this constraint is not addressed, there is a difference in predicted TB costs of more than US$ 4 billion between the unconstrained and medium human resource constraint scenarios over the period 2016 to 2035 due to the restrictions on the level of TB services that the health system can supply.

The diagnostic supplies constraint restricts the coverage of all interventions, and similarly results in a reduction in costs by limiting access to TB services (Figure 8).

Figure 8. 2016-2035 budget requirements for interventions at reduced coverage under financial, human resource and Xpert constraints 2016 US$ (millions)



Interventions are described in Figure 6

4.4.3 Costs of relaxing the human resource constraint

The incremental nurse minutes that would be needed to relax the human resource constraints and match the intervention coverage achieved in the unconstrained scenario are presented in Table 6. We found that a maximum of 3.3 million nurse minutes, corresponding to the annual time supplied by approximately 1,300 nurses, can be switched from the private to the government sector between 2017, the year in which the National TB Plan case-finding interventions begin rolling out, and 2035. This is sufficient to cover the incremental needs of cough-based screening interventions (6 and 9) under all constrained scenarios, but does not meet the extra demand generated from strengthening the use of the WHO symptoms screener. Achieving 90% ICF coverage would require approximately 15% or 25% of all nurses in the South African public health system to work on TB if using cough triage or the WHO tool, respectively. The highest costs of relaxing the constraint arise under the medium constraint scenario for intervention 8, aimed at strengthening the use of the WHO symptoms screener among all PHC attendees. The costs of hiring and training a sufficient number of nurses in this scenario between 2017 and 2035 are approximately US$ 3.76 billion (US$ 187.9 million per year on average), corresponding to approximately 60% of the entire financial resource requirements for delivering the baseline TB services during the same period (US$ 316.2 million per year on average).

Table 6. Incremental nurse minutes and costs of relaxing the human resource constraints for impacted interventions

Interventions	Incremental nurse minutes needed	Nurse minutes available in private sector	Incremental salary costs	Incremental training costs	Total costs of relaxing constraint
Medium constraint					
6	391,839,546	3,288,019	202,071,898	260,963,844	463,035,742
7	2,092,347,066	3,288,019	1,080,038,659	1,464,587,472	2,544,626,131
8	3,223,758,889	3,288,019	1,664,183,076	2,094,657,776	3,758,840,851
9	427,006,436	3,288,019	220,228,454	284,203,098	504,431,552
10	3,184,770,361	3,288,019	1,644,053,420	2,066,650,290	3,710,703,709
High constraint					
6	273,592	273,592	121,813	183,109	304,922
7	1,043,322,764	3,288,019	538,430,664	730,965,942	1,269,396,606
8	2,951,942,738	3,288,019	1,523,845,239	1,925,170,799	3,449,016,039
9	266,569	266,569	118,686	178,280	296,967
10	2,914,419,377	3,288,019	1,504,472,045	1,898,371,197	3,402,843,241

4.5 DISCUSSION

We present a pragmatic approach using routine data and stakeholder opinions, applied in a policy context, that was used to inform decision-makers on the impact of supply-side constraints on ICF for TB in South Africa. We were able to produce estimates of constraints and apply these to TB transmission models to limit attainable service coverage and generate estimates of intervention costs, advancing the work conducted by Hontelez and colleagues (Hontelez et al., 2016), who considered a single, non-empirically defined cost of health systems strengthening. We provide an illustration of the work of Van Baal and colleagues, who recommend that human resource constraints should be considered in economic evaluation to avoid producing biased cost-effectiveness estimates that could mislead decision-makers (van Baal et al., 2016). In the South African setting we find that, when constraints are considered, substantial additional costs may be incurred to expand TB services, which will impact incremental cost-effectiveness ratios.

Conceptually, the constraints analysed in our approach may be considered as ‘policy’ constraints representing ‘fixity’ in resource use, which is primarily determined by policy choice rather than by the inherent characteristics of the resources. In this sense, our analysis highlighted the costs to TB programme managers of policies around financing and human resource planning. Likewise, our analysis could be used by those planning human resources to help estimate the health impact of those investments. Compared to other modelling approaches used in the literature, our method has relatively limited data requirements and is less computationally intensive than operational modelling (Langley et al., 2014, Lin et al., 2011). While the results may be less comprehensive and not provide formal optimisation within constraints compared to other methods, they can be used to promote deliberation to redefine the mix of health system strengthening with disease specific activities within intervention strategies.

As a proof of concept conducted in a pragmatic rather than research setting, our analysis has many limitations. Several of these need improvement as the methods are further applied. Firstly, our selection of constraints was informal, both in terms of the identification of stakeholders and of the list of constraints identified. This may underestimate the costs of addressing all constraints. Secondly, we assumed that unit costs and minutes per service remain constant during intervention scale-up and we do not consider the differential impact of constraints at different coverage levels. A third limitation is data quality for some of the routine information systems. For example, DHIS data on the annual hours worked by public sector nurses is not updated every year to reflect staff movements to the private sector, thus potentially overestimating nurse minutes supplied in the government sectors.

Our broad approach (stakeholder identification of constraints, routine data and stakeholder engagement to characterise them, independent application in the model and deliberation) is potentially generalisable to other settings. However, the way it is implemented is likely to be highly dependent on both local data sources and policy processes. In South Africa, formal processes for strategic planning are developing and there is no formal health technology assessment. In other settings, it may be possible to substantially improve both the elicitation and characterisation of constraints. Despite the shortcomings of our 'proof of concept' approach, the engagement of stakeholders through the whole process helps ensuring ownership, relevance and usefulness of the analysis. This work was used to inform the National TB Strategy, specifically to refine the staffing of ICF approaches (South Africa National AIDS Council, 2017, White et al., 2018). Moreover, the engagement of stakeholders can lay the foundation for further work to refine and develop the analysis, as iterative decisions are made during intervention scale-up.

SUPPLEMENTARY MATERIAL

S1. HUMAN RESOURCE CONSTRAINT ESTIMATION

S.1.1 Nursing workforce in South Africa

The number of nurses currently working in primary health care (PHC) and the number of students enrolled in nursing courses in South Africa were obtained from the South African Nursing Council (SANC)[1]. The SANC database includes all nurses registered for practice in the country in both public and private sectors. The register might thus include nurses who are currently working abroad and those who are retired or otherwise inactive, as well as those who are active but do not spend time with patients (e.g. SANC employees, nurses working for research institutions and on clinical trials etc.). Following the methods described in a published analysis (Econex, 2010), as well as in the latest strategy on human resources for health adopted by the National Department of Health (National Department of Health, 2012), the assumptions presented in Table 7 were used to derive an estimate of the number of active nurses working in PHC in the public sector.

Table 7. Nursing registration parameter assumptions

Parameter	**Value**	**Description**	**Source**
Annual attrition rate	-25%	Graduates who do not find postings and out migration	NDOH HRH strategy 2012-2017
Annual returning /immigration rate	+4%	Returning migrants and immigrant workers	Assumption
Annual retirement rate	-6%	Nurses leaving workforce	NDOH HRH strategy 2012-2017
Graduates joining private sector	-41%	Corresponds to share of private sector workers	NDOH HRH strategy 2012-2017
Inactive nurses	-18%	Share of nurses on SANC register not in contact with patients	Econex 2010

Nursing workforce growth projections for the twenty-year period between 2015 and 2035 were based on the observed rate of increase in employed nurses and nurses-in-training registered with SANC over the period 2006-2015. The average annual growth rate was then adjusted by the projected rate of population growth in South Africa[2]. The share of nurses

---

[1] http://www.sanc.co.za/stats.htm

[2] http://data.worldbank.org/data-catalog/population-projection-tables

working in PHC was assumed to be 94% of all nurses in the public sector[3]. The projected numbers of nurses and workforce growth over the period 2015 to 2035 are shown in Table 8.

---

[3] This is equal to the proportion of annual working days supplied by nurses in PHC over the total, from DHIS data obtained from the National Department of Health upon request

Table 8. Public sector nursing workforce growth projections, 2015-2035

Year	**PHC nurses**			**Average growth rate**
	Registered	**Enrolled**	**Auxiliaries**	
2015	51,279	27,492	28,812	-
2016	51,923	29,041	31,185	5.04%
2017	52,619	30,697	33,587	4.91%
2018	53,340	32,468	36,021	4.80%
2019	54,114	34,359	38,487	4.71%
2020	54,934	36,378	40,987	4,63%
2021	55,800	38,536	43,522	4,56%
2022	56,714	40,839	46,095	4,51%
2023	57,677	43,298	48,706	4.46%
2024	58,690	45,924	51,358	4.42%
2025	59,754	48,727	54,052	4.39%
2026	60,872	51,728	56,789	4.36%
2027	62,043	54,910	59,572	4.33%
2028	63,271	58,317	62,402	4.31%
2029	64,555	61,951	65,280	4.29%
2030	65,898	65,828	68,209	4.28%
2031	67,302	69,964	71,190	4.26%
2032	68,767	74,374	74,225	4.25%
2033	70,295	79,076	77,316	4.24%
2034	71,889	84,090	80,464	4.23%
2035	73,551	89,437	83,672	4.22%

S.1.2 Minutes per output of National TB Plan interventions

The minutes per day spent by nursing staff on different TB services and the number of patients receiving their services in one day were obtained from unpublished MERGE trial data that were collected for the economic evaluation (Kufa et al., 2014). These are summarised in Table 9.

Table 9. MERGE trial estimates of time spent on TB activities, minutes per day

HR cadre	**TB screening**	**Sputum collection**	**IPT**	**TB treatment***
Registered nurse, general	83	18	54	0
Registered nurse, TB	4	81	29	133
Enrolled nurse	24	0	18	0

* No difference observed between treatment for naïve and retreatment patients

The MERGE data likely underestimate the number of minutes that nursing staff spend on TB activities as these data rely on self-report, and a tendency to over-report the denominator (number of patients seen per day) was observed during data collection. Conversely, the self-report data do not account for multi-tasking, thus potentially leading to an overestimate, since an activity's duration is shorter when performed simultaneously with another activity.

The interventions defined as part of the National TB Plan modelling exercise were assigned a time per output based on their different components. The minutes per output for each TB service and intervention analysed are reported in Table 10, along with their source and calculation assumptions. Where the time per output of an activity was not available from MERGE, data was integrated with results from the XTEND trial analysis (Churchyard et al., 2015) and from a community-based contact-tracing programme in peri-mining communities funded through the Global Fund to Fight AIDS, TB and Malaria, as well as with personal communications with the National Department of Health.

S.1.3 Total nurse Full Time Equivalent spent on TB services in South Africa

The total minutes worked per day by registered nurses were calculated from the number of working days per year recorded by the District Health Information Software (DHIS). For enrolled nurses, minutes per day were estimated by multiplying the total working minutes by the number of practicing and newly graduated nurses registered with SANC in 2015[4]. Parameter assumptions and their sources are summarised in Table 11.

The share of TB nurses out of the total staff at PHC clinics as well as the time spent in contact with TB patients by the different cadres were calculated from MERGE trial data (Table 12).

---

[4] http://www.sanc.co.za/stats/Stat2015/Year%202015%20Provincial%20Distribution%20Stats.pdf

Table 10. Modelled interventions, minutes per output for professional and enrolled nurses

Activities	Unit	Nurse minutes	Source	Assumptions
Passive case finding	per patient screened	2.63	MERGE and XTEND trials	Average of cough question and full symptoms screener duration to account for reported suboptimal screening practices
Xpert MTB/Rif diagnosis	per suspect	3.16	MERGE trial	Minutes per suspect for sputum collection
Smear microscopy diagnosis	per suspect	3.16	MERGE trial	Minutes per suspect for sputum collection
Follow-up of HIV-infected Xpert negative patients	per HIV+ Xpert negative	8.61	MERGE trial	Sum of sputum collection time and duration of two visits, one for monitoring and one for results collection
Screening using cough triage	per patient screened	1.26	MERGE trial	MERGE uses nurses self-reported data. Screening time per patient, on average lower than in XTEND, was thought to reflect the suboptimal screening practice of cough triage instead of the recommended full WHO symptoms screener.
Screening using WHO symptoms screener	per patient screened	4.00	XTEND trial	XTEND data are from direct observation, and more likely to reflect the recommended practice.
First line TB treatment (initiation phase, 2 months)	per patient month	35.72	MERGE and XTEND trial	One monitoring visit with sputum collection and two for drug collection
First line TB treatment (continuation phase, 4 months))	per patient month	7.57	MERGE and XTEND trial	Three monitoring visits with sputum collection and two for drug collection
MDR-TB treatment, with DOTS (initiation phase, 6 months) *†	per patient month	237.04	MERGE and XTEND trial	25 visit with sputum collection and 132 for drug collection
MDR-TB treatment, with DOTS (continuation phase, 18 months) *†	per patient month	159.83	MERGE and XTEND trial	396 visits for drug collection
MDR-TB treatment (initiation phase, 6 months)	per patient month	84.47	MERGE and XTEND trial	25 visit with sputum collection for Xpert/microscopy + 31 for drug collection
MDR-TB treatment (continuation phase, 18 months)	per patient month	7.27	MERGE and XTEND trial	94 visits for drug collection
IPT	per patient month	5.54	MERGE trial	One visit per month and one sputum collection per year

ILTFU: Initial Loss to Follow-Up; IPT: Isoniazid Preventive Therapy

Note: shaded activities represent interventions that are being introduced or modified under the 2017-2022 National TB Plan, as opposed to routine services

* From personal communication from the National Department of Health: 20% of notified TB cases receive treatment under DOTS, others self-medicate and visit the clinic once a month to collect drugs.

† 40% of MDR patients receive decentralised treatment at clinics while the remaining 60% are hospitalised during the intense phase and then go on to receive decentralised care from clinics in the continuation phase. Given that the HR constraint only applies to PHC services, those services provided during the initiation phase on hospitalised MDR-TB patients were omitted from its calculation.

Table 11. Working days parameter assumptions

Parameter	**Description**	**Value**	**Source**
Annual days worked by registered nurses	FTE provided by PHC nursing staff over 12 months (July 2015 – June 2016	3,333,173	SA DHIS 2016
Annual working days	Allowing for annual leave, public holidays and sickness	223	Assumption
Daily minutes worked	Full-time work, 8 hours per day	480	Assumption

Table 12. Summary of MERGE trial data on human resources and time use

HR cadre	**Average per PHC facility, N (%)**	**Full time equivalent spent on TB, %**
Registered nurse, general	13 (33)	24%
Registered nurse, TB	1.5 (4)	70%
Enrolled nurse	2 (4)	15%

We then combined this percentage with the total number of minutes worked per day for all nurses to calculate the total annual Full Time Equivalent (FTE) spent on TB. This estimate of TB working time was calibrated to the total staff time spent on TB estimated by the transmission model at baseline, as we were not confident that the MERGE sites were representative of South Africa as a whole. The baseline model estimate was obtained by multiplying model outputs by the number of minutes to deliver a service estimated above (see section S.1.2). We used the time spent on providing TB treatment as the calibration parameter and we assessed the difference between the estimate generated from the MERGE data, calculated based on the observed number of patients per day at the study sites, and the predicted number of patients per year generated by the model.

We estimated that 25% of daily working hours are used as down time, resting and other activities not related to patient care. This was based on the difference in total working time calculated from alternative sources of self-reported data in the MERGE trial (number of TB patients per day and FTE spent on TB, multiplied by the minutes spent on each service and the total expected FTE, respectively).

S2. ECONOMIC MODEL

The cost model, including all unit costs of routine TB services and of the intensified case finding (ICF) interventions recommended for the 2017-2022 National TB Plan, was developed using data from the published literature as well as from ongoing studies conducted in South Africa. These costs were attached to transmission model outputs to generate estimates of the annual financial resource requirements of the national TB programme.

All costs were converted to 2016 US$ using the South African GDP deflator[5]. Table 13 reports all unit costs used in the economic model, as well as their sources and underlying assumptions.

---

[5] Statistics South Africa. Historical Consumer Price Index. Accessed on 1st May 2017. Available at: http://www.statssa.gov.za/publications/P0141/CPIHistory.pdf?

Table 13. Cost model

Intervention	Description	Unit	Unit cost of output (2016 US$)	Source
Nurse time	One minute of professional nurses' time	Per minute	0.34	Nicola Foster, unpublished XTEND data
Inpatient day	Cost of hospitalisation	Per bed-day	44.44	Edina Sinanovic, unpublished Xtend data
OPD visit	Nurse consultation, 12 minutes average duration	per event	4.08	Nicola Foster, unpublished XTEND data
IPT treatment	One OPD visit a month (at half cost as on HIV) + INH + Xpert cost every year	per month	7.81	Salome Charalambous, personal communication
First line TB treatment	Facility-based observation. 2 months intensive phase, 4 months continuation phase	per patient month	21.43	Treatment regimens from (The Aurum Institute, 2016). Drug prices from National Department of Health's master procurement catalogue - 8 April 2016[6]. Only 20% of patients are treated under DOTS, the rest visit facility once a month to collect drugs (Dr Lindiwe Mvusi, National Department of Health, personal communication).
MDR-TB treatment	6 months intensive phase, 18 months continuation phase	per patient month	359.06	As for first line treatment. Forty percent of patients are hospitalised during intensive phase, the rest receive fully decentralised treatment (Sinanovic et al., 2015).
TB diagnostics	Sum of costs of first and second line diagnostic tests, including visits and antibiotics *	per person diagnosed	53.65	Costs of first line diagnostics from (Cunnama et al., 2016). Costs of monitoring tests from Edina Sinanovic, unpublished XTEND data
WHO symptoms screener	4 minutes of a professional nurse	per suspect screened	1.36	Nicola Foster, unpublished XTEND data
Cough triage	1.3 minutes of professional nurse asking cough question	per suspect screened	0.68	MERGE trial

OPD: Out-patient Department; IPT: Isoniazid Preventive Therapy; INH: Isoniazid; MDR-TB: Multi-Drug Resistant Tuberculosis

Note: shaded activities represent interventions that are being introduced or modified under the 2017-2022 National TB Plan, as opposed to routine services

* Cost per person diagnosed calculated as a weighted average of the unit costs of each test from the XTEND trial, where the weights represent the probability of receiving each test experienced by diagnosed patients in the XTEND cohort

---

[6] Available at: http://www.health.gov.za/index.php/component/phocadownload/category/196. Accessed September 2016.

REFERENCES

BRADLEY, S. P., HAX, A. C. & MAGNANTI, T. L. 1977. *Applied mathematical programming*, Addison-Wesley Publishing Company.

CHURCHYARD, G. J., MAMETJA, L. D., MVUSI, L., NDJEKA, N., HESSELING, A. C., REID, A., BABATUNDE, S. & PILLAY, Y. 2014. Tuberculosis control in South Africa: Successes, challenges and recommendations. *S Afr Med J,* 104**,** 244-248.

CHURCHYARD, G. J., STEVENS, W. S., MAMETJA, L. D., MCCARTHY, K. M., CHIHOTA, V., NICOL, M. P., ERASMUS, L. K., NDJEKA, N. O., MVUSI, L., VASSALL, A., SINANOVIC, E., COX, H. S., DYE, C., GRANT, A. D. & FIELDING, K. L. 2015. Xpert MTB/RIF versus sputum microscopy as the initial diagnostic test for tuberculosis: a cluster-randomised trial embedded in South African roll-out of Xpert MTB/RIF. *Lancet Glob Health,* 3**,** e450-57.

CLAASSENS, M. M., JACOBS, E., CYSTER, E., JENNINGS, K., JAMES, A., DUNBAR, R., ENARSON, D. A., BORGDORFF, M. W. & BEYERS, N. 2013. Tuberculosis cases missed in primary health care facilities: should we redefine case finding? *Int J Tuberc Lung Dis,* 17**,** 608-614.

CLEARY, S., MOONEY, G. & MCINTYRE, D. 2010. Equity and efficiency in HIV-treatment in South Africa: the contribution of mathematical programming to priority setting. *Health Econ,* 19**,** 1166-1180.

CUNNAMA, L., SINANOVIC, E., RAMMA, L., FOSTER, N., BERRIE, L., STEVENS, W., MOLAPO, S., MAROKANE, P., MCCARTHY, K., CHURCHYARD, G. & VASSALL, A. 2016. Using top-down and bottom-up costing approaches in LMICs: The case for using both to assess the incremental costs of new technologies at scale. *Health Econ,* 25**,** 53-66.

ECONEX 2010. The human resource supply constraint: The case of nurses. Health reform note 9.

EPSTEIN, D., CHALABI, Z., CLAXTON, K. & SCULPHER, M. 2007. Efficiency, equity and budgetary policies: informing decisions using mathematical programming. *Med Decis Making,* 27**,** 128-137.

GERICKE, C. A., KUROWSKI, C., RANSON, M. K. & MILLS, A. 2005. Intervention complexity - a conceptual framework to inform priority-setting in health. *Bull World Health Organ,* 83**,** 285-293.

HANSON, K., RANSON, M. K., OLIVEIRA-CRUZ, V. & MILLS, A. 2003. Expanding access to priority health interventions: a framework for understanding the constraints to scaling up. *J Int Dev,* 15**,** 1-14.

HAUCK, K., THOMAS, R. & SMITH, P. C. 2016. Departures from cost-effectiveness recommendations: The impact of health system constraints on priority setting. *Health Systems & Reform,* 2**,** 61-70.

HONTELEZ, J. A. C., CHANGE, A. Y., OGBUOJI, O., DE VLAS, S. J., BARNIGHAUSEN, T. & ATUN, R. 2016. Changing HIV treatment eligibility under health system constraints in sub-Saharan Africa: investment needs, population health gains, and cost-effectiveness. *AIDS,* 30**,** 2341-2350.

HOUBEN, R. M. G. J., LALLI, M., SUMNER, T., HAMILTON, M., PEDRAZZOLI, D., BONSU, F., HIPPNER, P., PILLAY, Y., KIMERLING, M., AHMEDOV, S., PRETORIUS, C. & WHITE, R. G. 2016. TIME Impact – a new user-friendly tuberculosis (TB) model to inform TB policy decisions. *BMC Medicine,* 14**,** 1-10. 10.1186/s12916-016-0608-4.

IHME 2013. Global Burden of Disease Study. Institute for Health Metrics and Evaluation.

KUFA, T., HIPPNER, P., CHARALAMBOUS, S., KIELMANN, K., VASSALL, A., CHURCHYARD, G. J., GRANT, A. D. & FIELDING, K. L. 2014. A cluster randomised trial to evaluate the effect of optimising TB/HIV integration on patient level outcomes: the "merge" trial protocol. *Contemp Clin Trials,* 39**,** 280-7. 10.1016/j.cct.2014.10.003.

LANGLEY, I., LIN, H., EGWAGA, S., DOULLA, B., KU, C., MURRAY, M., COHEN, T. & SQUIRE, S. B. 2014. Assessment of the patient, health system, and population effects of Xpert MTB/RIF and alternative diagnostics for tuberculosis in Tanzania: an integrated modelling approach. *Lancet Glob Health,* 2**,** e581-91.

LIN, H. H., LANGLEY, I., MWENDA, R., DOULLA, B., EGWAGA, S., MILLINGTON, K. A., MANN, G. H., MURRAY, M., SQUIRE, S. B. & COHEN, T. 2011. A modelling framework to support the selection and implementation of new tuberculosis diagnostic tools. *Int J Tuberc Lung Dis,* 15**,** 996-1004. 10.5588/ijtld.11.0062.

MCGILLEN, J. B., ANDERSON, S.-J., DYBUL, M. R. & HALLETT, T. B. 2016. Optimum resource allocation to reduce HIV incidence across sub-Saharan Africa: a mathematical modelling study. *Lancet HIV,* 3**,** e441-e448.

MENZIES, N. A., GOMEZ, G. B., BOZZANI, F., CHATTERJEE, S., FOSTER, N., GARCIA BAENA, I., LAURENCE, Y. & ET AL. 2016. Cost-effectiveness and resource implications of aggressive TB control in China, India and South Africa: a combined analysis of nine models. *Lancet Glob Health,* 4**,** e816–e826.

MIKKELSEN, E., HONTELEZ, J. A. C., JANSEN, M. P. M., BÄRNIGHAUSEN, T., HAUCK, K., JOHANSSON, K. A., MEYER-RATH G., OVER, M., DE VLAS, S. J., VAN DER WILT, G. J., TROMP, N., BIJLMAKERS, L. & BALTUSSEN, R. M. P. M. 2017. Evidence for scaling up HIV treatment in sub-Saharan Africa: A call for incorporating health systems constraints. *PLoS Med,* 14**,** e1002240.

NATIONAL DEPARTMENT OF HEALTH 2012. Human resources for health South Africa. HRH strategy for the health sector: 2012/13 - 2016/17.

NATIONAL DEPARTMENT OF HEALTH & SOUTH AFRICA NATIONAL AIDS COUNCIL 2016. South African HIV and TB Investment Case. Reference report. Phase 1.

PAYSCALE. 2017. *Registered Nurse Salary (South Africa)* [Online]. Available: https://www.payscale.com/research/ZA/Job=Registered_Nurse_(RN)/Salary [Accessed 27th October 2017].

REID, S. 2004. Monitoring the effect of the new rural allowance for health professionals. Durban: Health Systems Trust.

REMME, M., SIAPKA, M., STERCK, O., NCUBE, M., WATTS, C. & VASSALL, A. 2016. Financing the HIV response in sub-Saharan Africa from domestic sources: Moving beyond a normative approach. *Soc Sci Med,* 169**,** 66-67.

SINANOVIC, E., RAMMA, L., VASSALL, A., AZEVEDO, V., WILKINSON, L., NDJEKA, N., MCCARTHY, K., CHURCHYARD, G. & COX, H. 2015. Impact of reduced hospitalisation on the cost of treatment for drug-resistant tuberculosis in South Africa. *Int J Tuberc Lung Dis,* 19**,** 172-178.

SOUTH AFRICA NATIONAL AIDS COUNCIL 2017. South Africa's National Strategic Plan for HIV, TB and STIs 2017-2022.

SOUTH AFRICAN NURSING COUNCIL. *Regulations Index - Educations and Training* [Online]. Available: http://www.sanc.co.za/regulat/index.html#EandT [Accessed 26th October 2017].

SOUTH AFRICAN NURSING COUNCIL. *South African Nursing Council Statistics* [Online]. Available: http://www.sanc.co.za/stats_ts.htm [Accessed 26th October 2017].

SUMNER, T., BOZZANI, F., MUDZENGI, D., HIPPNER, P., HOUBEN, R. M., CARDENAS, V., VASSALL, A. & WHITE, R. G. 2019. Estimating the Impact of Tuberculosis Case Detection in Constrained Health Systems: An Example of Case-Finding in South Africa. *Am J Epidemiol,* 188**,** 1155-1164. 10.1093/aje/kwz038.

THE AURUM INSTITUTE 2016. Managing TB in a new era of diagnostics. Version 3. Johannesburg: The Aurum Institute.

UNITED NATIONS POPULATION DIVISION. 2015. *World population prospects, 2015 revision* [Online]. Geneva. Available: https://esa.un.org/unpd/wpp/Download/Standard/Population/ [Accessed].

VAN BAAL, P., THONGKONG N. & SEVERENS, J. L. 2016. Human resource constraints and the methods of economic evaluation of health care technologies. *iDSI Methods Working Group.* Rotterdam.

VASSALL, A., MANGHAM-JEFFERIES, L., GOMEZ, G. B., PITT, C. & FOSTER, N. 2016. Incorporating demand and supply constraints into economic evaluation in low-income and middle-income countries. *Health Econ,* 25**,** 95-115. 10.1002/hec.3306.

WHITE, R. G., CHARALAMBOUS, S., CARDENAS, V., HIPPNER, P., SUMNER, T., BOZZANI, F., MUDZENGI, D., HOUBEN, R. M. G. J., COLLIER, D., KIMERLING, M. E., VASSALL, A., PILLAY, Y. & CHURCHYARD, G. 2018. Evidence-informed policymaking at country level: Lessons learned from the South African Tuberculosis Think Tank. *Int J Tuberc Lung Dis,* 22**,** 606-613.

WHO 2013. Systematic screening for active tuberculosis: principles and recommendations. Geneva: World Health Organization.

WHO 2015. WHO Global TB report. Geneva: World Health Organization.

WORLD BANK. *Official exchange rate (LCU per US$, period average)* [Online]. Available: http://data.worldbank.org/indicator/PA.NUS.FCRF [Accessed 28 April 2017].

CHAPTER 5: INFORMING BALANCED INVESTMENT IN SERVICES AND HEALTH SYSTEMS: A CASE STUDY OF PRIORITY SETTING FOR TUBERCULOSIS INTERVENTIONS IN SOUTH AFRICA

Citation

BOZZANI, F. M., SUMNER, T., MUDZENGI, D., GOMEZ, G. B., WHITE, R. & VASSALL, A. 2020. Informing balanced investment in services and health systems: A case study of priority setting for tuberculosis interventions in South Africa. *Value in Health*.

Paper 3 cover sheet

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

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

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	232851	**Title**	Ms
First Name(s)	Fiammetta Maria		
Surname/Family Name	Bozzani		
Thesis Title	Incorporating feasibility in priority setting: A case study of tuberculosis control in South Africa		
Primary Supervisor	Prof. 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

Where was the work published?	Value in Health		
When was the work published?	20/09/2020		
If the work was published prior to registration for your research degreem give a brief rationale for its inclusion	n/a		
Have you retained copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the lead author of this paper, which describes a cost-effectiveness analysis based on a tuberculosis transmission model built by Dr Tom Sumner. I built the cost-effectiveness model, ran the analysis and interpreted the results. I drafted the manuscript, incorporated feedback from co-authors and was responsible for submission to the journal and for carrying out the revisions recommended during the peer review process.

SECTION E

Student Signature	[redacted]
Date	14/03/2021

Supervisor Signature	[redacted]
Date	01/06/2021

5.1 ABSTRACT

Objectives: Health systems face non-financial constraints, which can influence the opportunity cost of interventions. However, empirical methods to explore their impact are under-developed. We develop a conceptual framework for defining health system constraints and empirical estimation methods that rely on routine data. We then present an empirical approach for incorporating non-financial constraints in cost-effectiveness models of health benefit packages for the health sector.

Methods: We illustrate the application of this approach through a case study of defining a package of services for tuberculosis case-finding in South Africa. An economic model combining transmission model outputs with unit costs was developed to examine the cost-effectiveness of alternative screening and diagnostic algorithms. Constraints were operationalised as restrictions on achievable coverage based on: (1) financial resources; (2) human resources; (3) policy constraints around diagnostics purchasing. Cost-effectiveness of the interventions was assessed under one 'unconstrained' and several 'constrained' scenarios. For the 'unconstrained' scenario, incremental cost-effectiveness ratios were estimated with and without the costs of 'relaxing' constraints.

Results: We find substantial differences in incremental cost-effectiveness ratios across scenarios, leading to variations in the decision rules for prioritising interventions. In constrained scenarios, the limiting factor for most interventions was not financial but rather the availability of human resources.

Conclusions: We find that optimal prioritisation amongst different tuberculosis control strategies in South Africa is influenced by whether and how constraints are taken into consideration. We thus demonstrate both the importance and feasibility of considering non-financial constraints in health sector resource allocation models.

5.2 INTRODUCTION

Health sectors face non-financial constraints that prevent the efficient allocation of resources. Non-financial constraints have consequences for the assessment of cost-effectiveness, as they can influence the opportunity cost of new interventions and technologies (van Baal et al., 2018, Vassall et al., 2016). Supply-side (or health systems) non-financial constraints occur when factors of production (inputs) are 'fixed' in the short run, either due to physical/external barriers (for example, it may take five years to train health professionals, there may be political barriers to immigration, or ' sunk' costs in operating theatres which prevent use of funds to expand outpatient facilities), or due to health sector actors deliberately constraining resource availability/flexibility through policy decisions (for example, accreditation systems restricting the supply of clinical labour, or budgeting and procurement practices). Whatever their nature, non-financial constraints ultimately impact the health sector's ability to react to technological change by 'fixing' the levels and use of specific sets of inputs and consequently, in the short run, new technologies dependent on these inputs may have higher opportunity costs than they would if all inputs were variable.

Van Baal and colleagues have previously presented both a theoretical and empirical approach for estimating the extent to which non-financial constraints affect opportunity costs (van Baal et al., 2018). They characterise the decision under two separate constraints, one for the general budget and one for the constrained input, recognising that the constrained input has a lower cost-effectiveness threshold (k_1) than the unconstrained input (k_0), which reflects its higher opportunity cost, so that $k_1 < k_0$. The traditional decision rule, comparing the incremental cost per unit of health produced by the intervention to the general opportunity cost threshold can thus be modified, by adjusting the opportunity cost of the constrained input by the ratio $\frac{\mathrm{k}_0}{k_1}$.

Empirically, van Baal and colleagues posit that the relative costs of constrained to non-constrained inputs per unit of outcome in the current standard of care reflect their relative current opportunity cost. Assuming constant returns to scale and perfectly divisible inputs, they provide a two-intervention, two-input model:

$$\frac{k_0}{k_1} = \frac{s-t}{q-p} \quad (1)$$

where *s* and *t* denote the unit costs of interventions *i* and *j*, while *q* and *p* denote the costs of the constrained inputs for the same interventions, respectively (van Baal et al., 2018).

This approach can be used to empirically correct for downward bias in incremental cost-effectiveness ratios (ICERs) of new technologies implemented in health systems where specific inputs are constrained (or upward bias in rarer cases of existing spare capacity in the system), and where data is available on both the cost of the intervention and standard of care divided into constrained and unconstrained inputs. In principle this approach could also be extended to within health sector budget constraints, for example when dealing with fixed budgets for different disease programmes. In this case, groups of disease-specific inputs have a higher opportunity cost than spending on other areas of the health system. Potentially, once the comparative cost per health outcome is known for each programme, the incremental cost-effectiveness of the programme may be adjusted using the same approach.

Based on an application by Revill and colleagues, this approach appears empirically feasible (Revill et al., 2018). However, it has several limitations that can be grouped into two sets, one that restricts its applicability to certain settings and another that questions its underlying assumptions. Firstly, in many low- and middle-income countries (LMICs) there remains a substantial empirical challenge in deriving cost estimates. Given data scarcity on the relationship between costs, outputs and outcomes it is unlikely that decision-makers are sufficiently informed for costs to represent current relative opportunity costs of inputs. Another setting-specific limitation is that the approach relies on the estimation of health sector opportunity cost-based thresholds, which add substantial uncertainty. With regards to the more general limitations, the assumption of constant returns to scale for inputs is only likely to hold for some inputs. Moreover, as it stands, the approach proposed by van Baal and colleagues and its subsequent application do not present the decision maker with a choice set that includes relaxing non-financial constraints.

5.2.1 Empirical approaches

Decision makers prioritising new technologies (or packages of interventions across specific disease areas) often do not have control over decisions made around the wider health system constraints. For example, the manager of an HIV programme may be able to decide to invest in a new HIV treatment but may not be able to determine the overall level of nurses available in the health sector. Ideally, when the supply of nurses is constrained, the HIV programme would prioritise interventions with a lower demand on nurses than it would in the absence of constraints. Alternatively, programme managers may consider co-financing interventions that relax the overall nursing constraints, although this rarely happens in practice (Remme et al., 2016).

Methods to support priority setting for investment in infectious disease programmes are evolving and receiving increased academic attention. The widespread use of mathematical modelling in economic evaluation for infectious disease interventions has enabled optimisation among multiple interacting intervention options under a disease-specific budget constraint (Kelly et al., 2018, McGillen et al., 2016). Currently, these models estimate the costs of interventions and comparators by multiplying services produced by their average cost or, in some cases, employing a cost function (Hontelez et al., 2016, Turner et al., 2016). We present an empirical method that builds on the strengths of these models. Our approach has four stages: a) consulting decision makers to elicit non-financial constraints applicable to the specific setting and interventions of interest; b) quantifying the constraints and their impact; c) employing economic evaluation models (in this case mathematical models) to estimate costs and quantities of constrained inputs; d) producing ICERs both with and without constraints. We illustrate the importance and feasibility of our method through a case study, conducted using secondary and routine data within a policy-led (national strategic planning) timeframe.

5.3 METHODS

5.3.1 Case study setting and interventions

Tuberculosis (TB) control is a major concern for the South African health system (Churchyard et al., 2014). In 2015, plans were announced for a comprehensive TB screening programme, one component of which involves using intensified case-finding (ICF) to screen every person attending a public health facility for any reason. Initial (conventional) mathematical modelling of potential impact found that scale-up of ICF to all health facility attendees is the single most effective intervention for reaching the post-2015 global TB targets (Houben et al., 2016), but also the costliest screening option (Menzies et al., 2016). Policy makers in South Africa, however, were concerned about the feasibility of implementing such a complex intervention at full scale in a health system that they felt was ‘over-stretched’. As part of the National Strategic Plan (2017-2022) priority setting process, we therefore re-assessed ICF policy options incorporating supply-side health system constraints, adding a measure of the feasibility of these options in terms of the costs of relieving the constraints.

Strategies to identify and treat people with TB, especially those who have not sought diagnostic services on their own initiative, have the potential to become an integral part of TB control in LMICs, where access to health services is poor even among symptomatic patients and there is limited capacity among health providers to recognise symptoms

(Vassall, 2014). ICF, or facility-based screening, was adopted in South Africa for detecting TB cases among HIV clinic attendees, who are screened for TB at each visit. However, the TB programme still relies on 'passive case-finding', screening only those individuals presenting with symptoms suggestive of TB for identifying cases among those who are HIV uninfected. This method was shown to miss a large proportion of facility-based TB cases presenting at health facilities for reasons other than respiratory symptoms (Claassens et al., 2013). TB symptoms screening traditionally relies on triaging patients based on the presence of prolonged cough. The World Health Organization (WHO) recently developed a more sensitive but less specific screening tool based on the presence of any of four symptoms (current cough, fever, weight loss or night sweats) for use among HIV patients in LMICs, which showed potential as part of a clinical scoring system for prioritising TB investigation among symptomatic individuals in South Africa (Hanifa et al., 2017).

Once referred for TB testing, suspects should go on to be tested with Xpert MTB/RIF, which was rolled out in South Africa to replace sputum smear microscopy in 2012 and reached an estimated coverage of 80% in 2016 (South Africa National Department of Health, 2017). Those patients who are HIV infected (or whose HIV status is unknown) and who receive a negative Xpert result should then have a second sputum sample investigated using TB culture, although adherence to the follow-up test is poor (McCarthy et al., 2016).

The sensitivity and specificity of the chosen screening and diagnostic algorithm determine the consequential costs of diagnosis and treatment along the TB care cascade and are therefore a crucial consideration for priority setting in a resource constrained health system. For this reason, the South African TB Think Tank, which supports TB policymaking, was tasked with carrying out a model-based economic evaluation to prioritise among the alternative algorithms considered for inclusion in the latest National Tuberculosis Plan (NTP). The status quo and intervention scenarios considered in the analysis and the respective policy-defined coverage targets are described in Figure 6 (Chapter 4).

5.3.2 Identifying constraints scenarios

Our approach was embedded within the strategic planning cycle through the South African TB Think Tank, a body that reviews evidence on TB interventions and was responsible for recommending those to be considered in the NTP (White et al., 2018). The TB Think Tank were asked to identify the main constraints on TB case detection. The process of elicitation and quantification of the constraints is described in detail elsewhere (Bozzani et al., 2018). The selection process relied on a published framework (Vassall et al., 2016) and aimed to illustrate the different forms that constraints might take in influencing the priority setting process for infectious disease control.

Three supply-side constraints on health system resources that apply to TB service provision in the public sector in South Africa were defined for incorporation in the model: (1) a *financial* constraint, characterised as the size of the available TB budget; (2) a *(non-financial) exogenous human resources* (HR) constraint, characterised as the maximum full time equivalent of nursing staff that can be employed nationally in the provision of TB services (registered, enrolled and specialised TB nurses supply virtually all TB services in the government sector in the country); (3) a *diagnostics* purchasing constraint, characterised as the maximum number of Xpert tests purchased annually by the TB programme. The latter was considered as a policy constraint internal to the vertical TB budget, which is restricted by an arbitrary, *a priori* belief held by policymakers on the viable number of tests per TB case detected (NDoH, personal communication).

For the budget and HR constraints, three possible scenarios were considered: a *more restrictive* scenario, where resources over time are assumed to be virtually 'static', their increase uniquely driven by the underlying growth rate of gross domestic product (GDP) and population, respectively; a *medium* scenario, where 'static' health resources are reallocated to TB services for the period covered by the 2017-2022 NTP to match the share of disease burden caused by TB, reported at 15% by NDoH; a *least restrictive* scenario, where 15% of 'dynamic' health resources, that realise their full growth potential, is reallocated to TB over the same period. The maximum potential growth in the TB budget was informed by a fiscal space analysis, while the availability of nurse time for TB was estimated from routine data on historical workforce growth (Bozzani et al., 2018). One single scenario was considered for the diagnostics constraint, setting the limit to a ratio of 20 Xpert tests purchased for every TB case diagnosed in the previous budgeting period. Details on how all constraints were parameterised are published in Bozzani et *al*. (2018) (Bozzani et al., 2018).

5.3.3 Cost-effectiveness model

We used a mathematical model of TB transmission to estimate the number of TB cases, TB mortality and the use of TB services under each of the intervention scenarios (intervention 1 being the base case and interventions 2-10 exploring different combinations of screening and diagnostic algorithms, see Figure 6) (Sumner et al., 2019). The model was calibrated for the year 2015 and cost projections were generated for a 20-year period up to 2035 by attaching unit costs to model outputs. Unit costs for the TB case-finding and diagnostic interventions as well as for the routine TB services affected by the policy changes were constructed using ingredients costing from ongoing studies as well as from published sources (Table 13). Only costs incurred by health service providers were considered. All costs are presented in 2016 US$ and a discount rate of 3% was applied to future costs.

Health benefits of the interventions were measured in terms of the Disability-Adjusted Life-Years (DALYs) averted by each intervention compared to the base case. DALYs were calculated using transmission model outputs including deaths by age and year and the annual population distribution across TB- and HIV-related health states. Disability weights were derived from a multi-country valuation (Salomon et al., 2012), assuming (i) asymptomatic HIV (CD4>350) equal to 'generic uncomplicated disease' (0.054); (ii) those with active TB and either asymptomatic HIV or on ART experience the same disability as those who are HIV uninfected (0.331); and (iii) those with Acquired Immunodeficiency Syndrome (AIDS, CD4<200) experience the same disability whether or not they have active TB (0.547). Remaining life expectancy was estimated throughout the period considered in the analysis from the South African life tables (WHO, 2015).

5.3.4 Estimating ICERs

The model was first run to estimate costs and effects of scaling up the interventions in the absence of constraints. The individual constraints scenarios were then applied independently to the model by reducing the intervention coverage such that the projected resource requirements remained below the constraint over the entire analytic horizon. The cost-effectiveness of the interventions was then assessed at the coverage that could be achieved within the available resources. If target coverage was not achieved, then a real constraint was identified and the model was re-run at a reduced coverage, such that the projected resource requirements remained below the constraint over the entire analytic horizon. Budget requirements were estimated by the standard economic model attaching unit costs to TB transmission model outputs. HR requirements were similarly calculated by attaching to model outputs an estimate of the nurse minutes required to deliver the TB screening and diagnostic interventions as well as the routine services along the TB care cascade (Bozzani et al., 2018). The diagnostics constraint was incorporated as a multiplier in the model, which limited intervention coverage once the set ratio of Xpert tests to TB notifications was exceeded.

For those interventions that had to be delivered at a reduced coverage under any of the HR constraint scenarios, the costs of 'relaxing' the constraint by adding extra nurses to the workforce to achieve full coverage were calculated (Bozzani et al., 2018), to produce a third set of ICERs alongside the ‘unconstrained’ and ‘constrained’ ICERs. These represent the true opportunity cost of delivering the interventions. We assumed no additional health system investment would be necessary for relaxing the financial and diagnostics constraints (besides increasing the TB budget and purchasing additional Xpert tests, respectively), so that the costs of achieving full coverage would be equal to those predicted by the model under the ‘unconstrained’ scenario.

5.4 RESULTS

The incremental costs, DALYs averted and ICERs compared to base case for all the interventions under the unconstrained and constrained scenarios (only for scenarios that had a realistic impact on feasibility of one or more interventions) are presented in Table 14. Detailed results on cost estimation and the effects of the constraints on intervention impact are presented elsewhere (Bozzani et al., 2018, Sumner et al., 2019).

Table 14. Incremental costs, DALYs averted and incremental cost-effectiveness ratios† for interventions 2-10 compared to intervention 1 (base case) under selected constraint scenarios

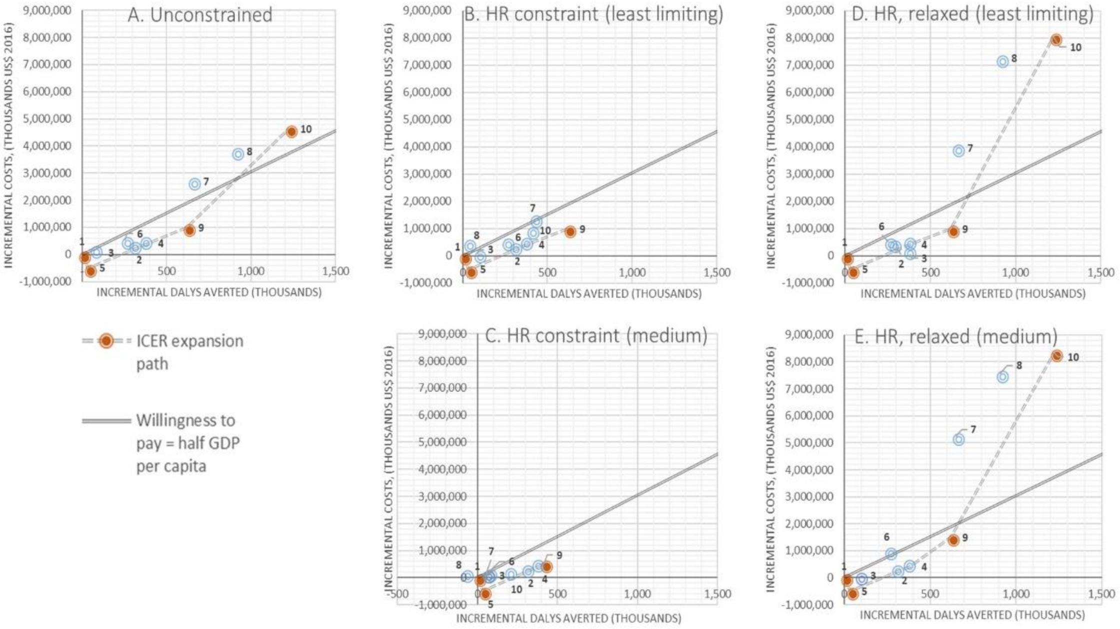
Intervention (target coverage*)	Constraint scenario	Incremental costs (US$,000)	DALYs averted (,000)	Incremental cost per DALY averted (US$)
2 (100% Xpert coverage)	Unconstrained	334,654	299	1,121
	HR (least limiting)	334,654	299	1,121
	HR (medium)	334,654	299	1,121
	Financial (medium)	334,654	290	1,153
	Diagnostics	189,237	234	809
3 (90% follow-up of Xpert negatives)	Unconstrained	73,201	86	847
	HR (least limiting)	73,201	86	847
	HR (medium)	73,201	86	847
	Financial (medium)	73,201	86	847
	Diagnostics	68,411	85	806
4 (2 + 3)	Unconstrained	417,027	381	1,093
	HR (least limiting)	417,027	381	1,093
	HR (medium)	417,027	381	1,093
	Financial (medium)	417,027	381	1,093
	Diagnostics	268,375	318	844

5 (cough triage in 100% HIV patients)	Unconstrained	-496,799	34	-14,588
	HR (least limiting)	-496,799	34	-14,588
	HR (medium)	-496,799	34	-14,588
	Financial (medium)	-496,799	34	-14,588
	Diagnostics	-395,416	89	-4,425
6 (cough triage in 90% PHC patients)	Unconstrained	525,977	255	2,061
	HR (least limiting)	525,514	255	2,060
	HR (medium)	126,528	56	2,248
	Financial (medium)	525,977	255	2,061
	Diagnostics	91,886	46	1,989
7 (WHO screener in 100% HIV patients)	Unconstrained	2,693,662	649	4,148
	HR (least limiting)	1,359,565	420	3,241
	HR (medium)	130,455	52	2,489
	Financial (medium)	2,693,662	649	4,148
	Diagnostics	128,738	56	2,303
8 (WHO screener in 90% PHC patients)	Unconstrained	3,800,388	907	4,190
	HR (least limiting)	463,344	27	17,201
	HR (medium)	170,109	-78	-2,193
	Financial (medium)	3,800,388	907	4,190
	Diagnostics	-31,106	-102	304‡
9 (4 + 6)	Unconstrained	988,363	620	1,595
	HR (least limiting)	987,853	619	1,595
	HR (medium)	512,389	414	1,237
	Financial (medium)	988,363	620	1,595
	Diagnostics	335,806	345	972
10 (4 + 8)	Unconstrained	4,631,162	1,222	3,789
	HR (least limiting)	932,298	401	2,327
	HR (medium)	606,355	303	2,004
	Financial (medium)	4,606,292	1,220	3,776
	Diagnostics	123,317	212	582

5.4.1 Cost-effectiveness ranking without constraints

Figure 9 presents the ICER ranking of intervention options on the cost-effectiveness plane. Dominant options are shown on the expansion path from intervention 1 (the base case) at the origin. Interventions that are strongly (more costly and less effective than an individual intervention) or weakly dominated (more costly and less effective than a combination of non-mutually exclusive interventions) are shown outside the expansion path. When supply-side constraints are not taken into consideration (Figure 9, panel A), the option with the highest costs and the most DALYs averted compared to base case was intervention 10, the combination of strengthening the diagnostic algorithm and screening 90% of all patients in primary health care (PHC) using the WHO tool. Assuming an indicative willingness-to-pay (WTP) threshold equal to half the GDP per capita per DALY averted (US$ 3,044), South Africa would adopt intervention 9 under this scenario, combining the strengthening of the Xpert algorithm with use of the less sensitive cough triage in the PHC population. This intervention would require a two-fold increase in the total TB budget for South Africa for 2015.

Figure 9. Cost-effectiveness planes for selected constraints scenarios



HR: Human Resources; DALYs: Disability-Adjusted Life-Years; ICER: Incremental Cost-effectiveness Ratio; GDP: Gross Domestic Product

Note: Dominant interventions shown on expansion path. Strongly (more costly, less effective than another individual intervention) and weakly (more costly, less effective than a combination of non-mutually exclusive interventions) dominated interventions shown in lighter shade.

5.4.2 Cost-effectiveness ranking with constraints

The least limiting financial constraint was not exceeded by any of the interventions, while the most limiting financial and HR constraints were exceeded by almost all interventions at some point during the analytical time horizon, indicating that any TB case-finding policy change would not be feasible in South Africa without some reprioritisation of funds. The medium financial constraint would cause a shortfall of approximately US$ 25 million over the period 2016-2035 and thus reduce overall intervention effectiveness (Table 14).

Incorporating non-financial constraints influences the ranking of interventions under the least restrictive and medium HR constraints (Figure 9, panels B-C), as well as under the diagnostic constraint. In these three scenarios, intervention 10 was (weakly) dominated by intervention 9 (combination of strengthened diagnostic algorithm and cough triage for screening PHC patients), which became more effective than option 10 at reduced coverage and had a lower ICER. The least restrictive and medium HR constraints had a substantial impact on the coverage of all ICF interventions (6-10) except for the use of cough-based screening in HIV clinics (5), which constitutes a reversal of the current guidelines recommending use of the WHO tool among HIV patients, adhered to in approximately 40% of cases (World Health Organisation, 2016). Overall, the diagnostics constraint caused the greatest reductions in the impact of all intervention options involving the strengthening of the diagnostic algorithm (interventions 2-4) as well as the expansion of ICF to all PHC patients using any screening tool (interventions 6, 8, 9 and 10), due to the limit it placed on the consequential scaling-up of Xpert.

5.4.3 Cost-effectiveness of relaxing human resource constraints

Figure 9, Panels B2-C2 show the ICERs considering the health system investment for training, hiring and deploying the additional nurses required to deliver the interventions at the target coverage. Once the constraints were relaxed, option 10 once again displayed the highest ICER, as in the unconstrained scenario (Figure 9, Panel A). However, investing in the generation of extra HR capacity to deliver the strengthened diagnostic and WHO screening algorithm intervention at the desired coverage requires an increase of approximately 60% in the TB service delivery budget during the 2016-2035 period compared to the current expenditure level (from about US$ 6.3 billion to US$ 10 billion), and these additional costs substantially decrease cost-effectiveness compared to the threshold.

5.5 DISCUSSION

We demonstrate an empirical approach to incorporating non-financial constraints into cost-effectiveness analysis that can inform investment decisions where health sectors face resource limitations and/or policy restrictions. In our case study, we illustrated to decision-makers the consequences of not addressing constraints (reduced intervention impact) and the returns on investment in removing them (costs of relaxing HR constraints). As such, we present an approach that reflects an understanding of health sectors facing complex short-run constraints and that allows policymakers to explore combinations of investments and to optimise between the short- and long-run.

The prior beliefs of policy makers around the potential lack of feasibility of expanding HR-intensive ICF strategies that generate high volumes of Xpert diagnostic tests further down the TB cascade in an over-stretched health system were reinforced by our analysis. Critically, we find that, in the presence of HR constraints, expanding the TB budget is not enough to achieve the desired coverage target of ICF interventions. This highlights the importance of long-term investments in training and hiring more nurses as well as the presence of a time lag for deploying this extra workforce, which in turn may impact intervention effect. Our findings are in line with van Baal and colleagues, whose theoretical model illustrated that, in the short term, choosing interventions whose feasibility is more dependent on the availability of physical inputs such as HR has a higher opportunity cost than choosing less resource-intensive options (van Baal et al., 2018).

Adding to van Baal's approach, the present work presents a possibility for dealing with available routine data that is also independent of specific opportunity cost thresholds. Moreover, it expands the choice set by presenting the option of relaxing health system constraints and, although not shown in the case study presented, could accommodate an analysis of returns to scale for physical inputs.

Despite being feasible, our approach has some potential limitations and requires further development. Firstly, even though we completed the analysis within a policy-defined timeframe, it required considerable additional effort compared to conventional approaches. In particular, we had to obtain high quality published and unpublished cost data from previous studies in South Africa, we gained access to and collated detailed data on HR supply and we spent considerable time defining constraints as well as discussing and deliberating with decision-makers (TB Think Tank) on how to represent them in the model. Our approach may thus be less feasible where data availability and formal planning structures are more limited. Secondly, our conclusions rely on the assumption that, in the presence of constraints, existing TB services would not be scaled back to accommodate new screening interventions. Although rare in practice, decision-makers might be willing to consider divesting from existing activities to increase coverage of desirable new interventions. Moreover, we have assumed that there would be no interactions between the constraints, as they applied to different types of resources. However, since constrained inputs are all funded from the health budget, interactions might occur and thus the analysis would need to apply the constraints to the model simultaneously and quantify the extent of the interactions. Finally, we have considered a single change in ICF coverage of screening in each scenario over time, without acknowledging that policies are dynamic and responsive to system changes.

Despite these limitations, the approach presented above emphasises the importance and feasibility of supplying decision-makers with information on the ‘real-world’ cost-effectiveness and performance of intervention options under different types of health system constraints. In many LMICs, decisions on the adoption of new technologies are coupled with scale-up decisions and not seen as separate processes. The further testing of approaches such as the one presented here is required to ensure that health sector decision-makers can explore the optimal balance between short-run purchasing of new technologies and long-term investment to reduce non-financial health systems constraints.

REFERENCES

BOZZANI, F. M., MUDZENGI, D., SUMNER, T., GOMEZ, G. B., HIPPNER, P., CARDENAS, V., CHARALAMBOUS, S., WHITE, R. & VASSALL, A. 2018. Empirical estimation of resource constraints for use in model-based economic evaluation: an example of TB services in South Africa. *Cost Eff Resour Alloc,* 16**,** 27. https://doi.org/10.1186/s12962-018-0113-z.

CHURCHYARD, G. J., MAMETJA, L. D., MVUSI, L., NDJEKA, N., HESSELING, A. C., REID, A., BABATUNDE, S. & PILLAY, Y. 2014. Tuberculosis control in South Africa: Successes, challenges and recommendations. *S Afr Med J,* 104**,** 244-248.

CLAASSENS, M. M., JACOBS, E., CYSTER, E., JENNINGS, K., JAMES, A., DUNBAR, R., ENARSON, D. A., BORGDORFF, M. W. & BEYERS, N. 2013. Tuberculosis cases missed in primary health care facilities: should we redefine case finding? *Int J Tuberc Lung Dis,* 17**,** 608-614.

HANIFA, Y., FIELDING, K. L., CHIHOTA, V. N., ADONIS, L., CHARALAMBOUS, S., FOSTER, N., KARSTAEDT, A., MCCARTHY, K., NICOL, M. P., NDLOVU, N., SINANOVIC, E., SAHID, F., STEVENS, W., VASSALL, A., CHURCHYARD, G. & GRANT, A. D. 2017. A clinical scoring system to prioritise investigation for tuberculosis among adults attending HIV clinics in South Africa. *PLoS One,* 12**,** e0181519.

HONTELEZ, J. A. C., CHANGE, A. Y., OGBUOJI, O., DE VLAS, S. J., BARNIGHAUSEN, T. & ATUN, R. 2016. Changing HIV treatment eligibility under health system constraints in sub-Saharan Africa: investment needs, population health gains, and cost-effectiveness. *AIDS,* 30**,** 2341-2350.

HOUBEN, R., MENZIES, N. A., SUMNER, T., HUYNH, G. H., ARINAMINAPATHY, N., GOLDHABER-FIEBERT, J. D., LIN, H., WU, C., MANDAL, S., PANDEY, S., SUEN, S., BENDAVID, E., AZMAN, A. S., DOWDY, D. W., BACAËR, N., RHINES, A. S., FELDMAN, M. W., HANDEL, A., WHALEN, C. C., CHANG, S. T., WAGNER, B. G., ECKHOFF, P. A., TRAUER, J. M., DENHOLM, J. T., MCBRYDE, E. S., COHEN, T., SALOMON, J., PRETORIUS, C., LALLI, M., EATON, J. W., BOCCIA, D., HOSSEINI, M., GOMEZ, G. B., SAHU, S., DANIELS, C., DITIU, L., CHIN, D. P., WANG, L., CHADHA, V. K., RADE, K., DEWAN, P., HIPPNER, P., CHARALAMBOUS, S., GRANT, A. D., CHURCHYARD, G., PILLAY, Y., MAMETJA, L. D., KIMERLING, M. E., VASSALL, A. & WHITE, R. G. 2016. Feasibility of achieving the 2025 WHO global tuberculosis targets in South Africa, China, and India: a combined analysis of 11 mathematical models. *Lancet Glob Health,* 4**,** e806-e815.

KELLY, S. L., MARTIN-HUGHES, R., STUART, R. M., YAP, X. F., KEDZIORA, D. J., GRANTHAM, K. L., HUSSAIN, S. A., REPORTER, I., SHATTOCK, A. J., GROBICKI, L., HAGHPARAST-BIDGOLI, H., SKORDIS-WORRALL, J., BARANCZUK, Z., KEISER, O., ESTILL, J., PETRAVIC, J., GRAY, R. T., BENEDIKT, C. J., FRASER, N., GORGENS, M., WILSON, D., KERR, C. C. & WILSON, D. P. 2018. The global Optima HIV allocative efficiency model: targeting resources in efforts to end AIDS. *Lancet HIV,* 5**,** e190-e198. 10.1016/S2352-3018(18)30024-9.

MCCARTHY, K. M., GRANT, A. D., CHIHOTA, V., GININDZA, S., MVUSI, L., CHURCHYARD, G. J. & FIELDING, K. L. 2016. What happens after a negative test for tuberculosis? Evaluating adherence to TB diagnostic algorithms in South African primary health clinics. *J Acquir Immune Defic Syndr,* 71**,** e119-e126.

MCGILLEN, J. B., ANDERSON, S.-J., DYBUL, M. R. & HALLETT, T. B. 2016. Optimum resource allocation to reduce HIV incidence across sub-Saharan Africa: a mathematical modelling study. *Lancet HIV,* 3**,** e441-e448.

MENZIES, N. A., GOMEZ, G. B., BOZZANI, F., CHATTERJEE, S., FOSTER, N., GARCIA BAENA, I., LAURENCE, Y. & ET AL. 2016. Cost-effectiveness and resource implications of aggressive TB control in China, India and South Africa: a combined analysis of nine models. *Lancet Glob Health,* 4**,** e816–e826.

REMME, M., SIAPKA, M., STERCK, O., NCUBE, M., WATTS, C. & VASSALL, A. 2016. Financing the HIV response in sub-Saharan Africa from domestic sources: Moving beyond a normative approach. *Soc Sci Med,* 169**,** 66-67.

REVILL, P., WALKER, S., CAMBIANO, V., PHILLIPS, A. & SCULPHER, M. J. 2018. Reflecting the real value of health care resources in modelling and cost-effectiveness studies - The example of viral load informed differentiated care. *PLoS One,* 13**,** e0190283.

SALOMON, J. A., VOS, T., HOGAN, D. R., GAGNON, M., NAGHAVI, M., MOKDAD, A., BEGUM, N., SHAH, R., KARYANA, M., KOSEN, S., FARJE, M. R. & ET AL. 2012. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet,* 15**,** 2129-43. 10.1016/S0140-6736(12)61680-8.

SOUTH AFRICA NATIONAL DEPARTMENT OF HEALTH 2017. National Tuberculosis Programme Strategic Plan: 2017-2021.

SUMNER, T., BOZZANI, F., MUDZENGI, D., HIPPNER, P., HOUBEN, R. M., CARDENAS, V., VASSALL, A. & WHITE, R. G. 2019. Estimating the Impact of Tuberculosis Case Detection in Constrained Health Systems: An Example of Case-Finding in South Africa. *Am J Epidemiol,* 188**,** 1155-1164. 10.1093/aje/kwz038.

TURNER, H. C., TRUSCOTT, J. E., FLEMING, F. M., HOLLINGSWORTH, T. D., BROOKER, S. J. & ANDERSON, R. M. 2016. Cost-effectiveness of scaling up mass drug administration for the control of soil-transmitted helminths: a comparison of cost function and constant costs analyses. *Lancet Infect Dis,* 16**,** 838-846. 10.1016/S1473-3099(15)00268-6.

VAN BAAL, P., MORTON, A. & SEVERENS, J. L. 2018. Health care input constraints and cost effectiveness analysis decision rules. *Soc Sci Med,* 200**,** 59-64. 10.1016/j.socscimed.2018.01.026.

VASSALL, A. 2014. Benefits and costs of the tuberculosis targets for the post-2015 development agenda. Copenhagen Consensus Center.

VASSALL, A., MANGHAM-JEFFERIES, L., GOMEZ, G. B., PITT, C. & FOSTER, N. 2016. Incorporating demand and supply constraints into economic evaluation in low-income and middle-income countries. *Health Econ,* 25**,** 95-115. 10.1002/hec.3306.

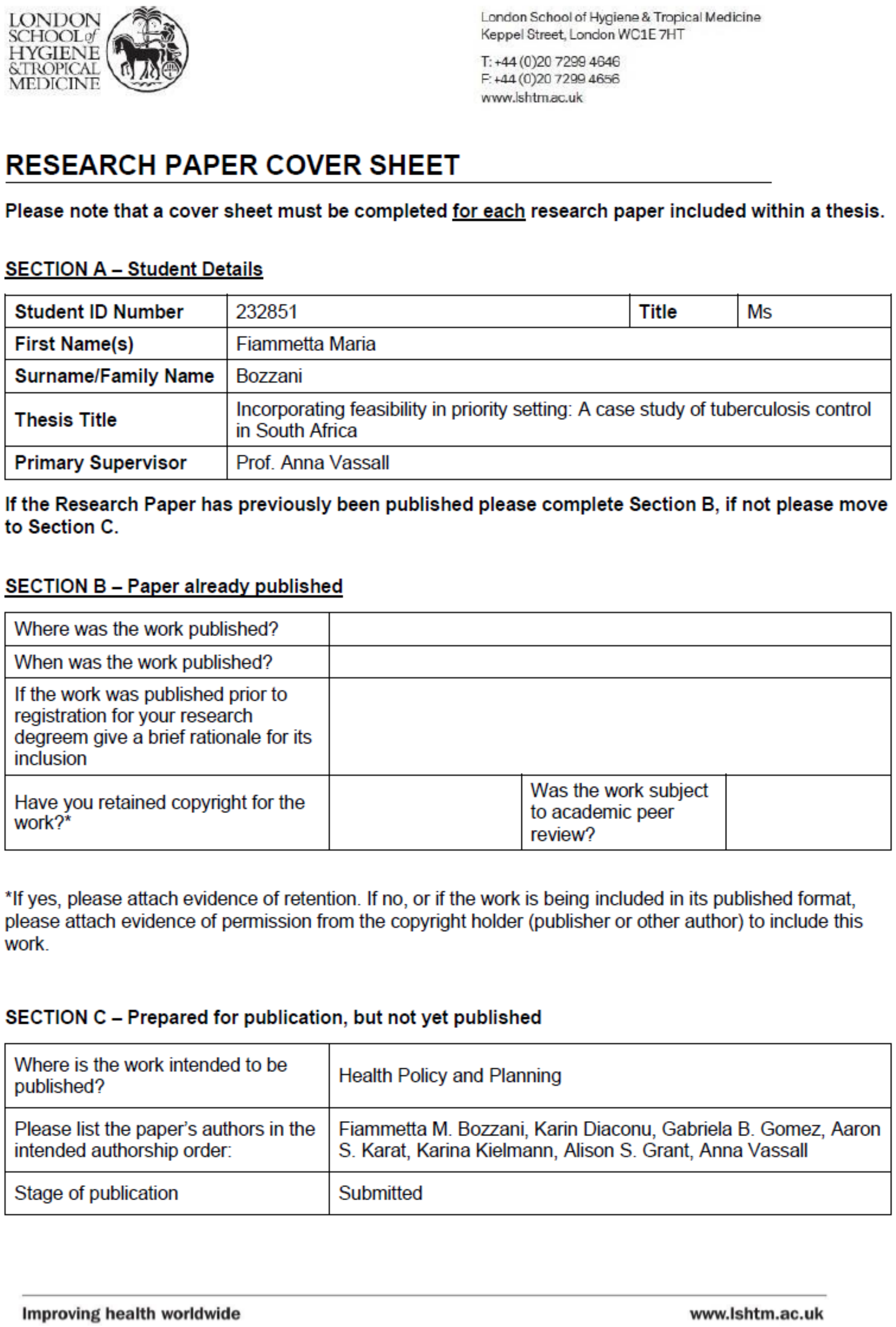
WHITE, R. G., CHARALAMBOUS, S., CARDENAS, V., HIPPNER, P., SUMNER, T., BOZZANI, F., MUDZENGI, D., HOUBEN, R. M. G. J., COLLIER, D., KIMERLING, M. E., VASSALL, A., PILLAY, Y. & CHURCHYARD, G. 2018. Evidence-informed policymaking at country level: Lessons learned from the South African Tuberculosis Think Tank. *Int J Tuberc Lung Dis,* 22**,** 606-613.

WHO. 2015. *Life tables by country, South Africa* [Online]. Available: http://apps.who.int/gho/data/?theme=main&vid=61540 [Accessed 2015].

WORLD HEALTH ORGANISATION 2016. WHO Treatment Notifications Database. Geneva.

CHAPTER 6: USING SYSTEM DYNAMICS MODELLING TO ESTIMATE THE COSTS OF RELAXING HEALTH SYSTEM CONSTRAINTS: A CASE STUDY OF TUBERCULOSIS INFECTION PREVENTION AND CONTROL INTERVENTIONS IN SOUTH AFRICAN HEALTH FACILITIES

Paper 4 cover sheet



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

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	232851	**Title**	Ms
First Name(s)	Fiammetta Maria		
Surname/Family Name	Bozzani		
Thesis Title	Incorporating feasibility in priority setting: A case study of tuberculosis control in South Africa		
Primary Supervisor	Prof. 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

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degreem give a brief rationale for its inclusion			
Have you retained copyright for the work?*		Was the work subject to academic peer review?	

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Health Policy and Planning
Please list the paper's authors in the intended authorship order:	Fiammetta M. Bozzani, Karin Diaconu, Gabriela B. Gomez, Aaron S. Karat, Karina Kielmann, Alison S. Grant, Anna Vassall
Stage of publication	Submitted

Improving health worldwide **www.lshtm.ac.uk**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the lead author of this paper, which builds on a group model building exercise led by Dr Karin Diaconu. I collected all cost data, analysed it and interpreted the results, drafted the manuscript incorporating feedback from co-authors and submitted it to the journal.

SECTION E

Student Signature	[redacted]
Date	31/05/2021

Supervisor Signature	[redacted]
Date	01/06/2021

Update: as of December 2021, the final version of this article appears as

Bozzani FM, Diaconu K, Gomez GB, Karat AS, Kielmann K, Grant AD, Vassall A. Using system dynamics modelling to estimate the costs of relaxing health system constraints: a case study of tuberculosis prevention and control interventions in South Africa. 2021. Health Policy and Planning, 37, 2022, 369–375. DOI: https://doi.org/10.1093/heapol/czab155

6.1 ABSTRACT

Health system constraints are increasingly recognised as an important addition to model-based analyses of disease control interventions, as they affect achievable impact and scale. Enabling activities implemented alongside interventions to relax constraints and reach the intended coverage may incur additional costs, which should be considered in priority setting decisions. We explore the use of group model building, a participatory system dynamics modelling technique, for eliciting information from key stakeholders on the constraints that apply to tuberculosis infection prevention and control processes within primary healthcare clinics in South Africa. This information was used to design feasible interventions, including the necessary enablers to relax existing constraints. Intervention and enabler costs were then calculated at two clinics in KwaZulu-Natal using input prices and quantities from the published literature and local suppliers. Among the proposed interventions, the most inexpensive were retrofitting buildings to improve ventilation (US$ 1,644 per year), followed by maximising the use of community sites for medication collection among stable patients on antiretroviral therapy (US$ 3,753) and introducing appointments systems to reduce crowding (US$ 9,302). Enablers identified included enhanced staff training, supervision and patient engagement activities to support behaviour change and local ownership. Several of the enablers identified by the stakeholders, such as obtaining building permissions or improving information flows between levels of the health systems, were not amenable to costing. Despite this limitation, an approach to costing rooted in system dynamics modelling can be successfully applied in economic evaluations to more accurately estimate the 'real world' opportunity cost of intervention options. Further empirical research applying this approach to different intervention types (e.g. new preventive technologies or diagnostics) may identify interventions that are not cost-effective in specific contexts based on the size of the required investment in enablers.

6.2 INTRODUCTION

Reducing transmission of *Mycobacterium tuberculosis* (*Mtb*) in primary care clinics and other health care settings is a priority on the tuberculosis (TB) infection prevention and control (IPC) agenda in South Africa. Transmission of drug-resistant (DR) *Mtb* is documented within health facilities (O'Donnell et al., 2010, World Health Organization, 2019). Moreover, recent mathematical modelling evidence generated using data from KwaZulu-Natal implies that the risk of *Mtb* transmission in clinics in high human immunodeficiency virus (HIV) burden settings may be higher than contact data would suggest for both health care workers and patient (McCreesh et al., 2020). Guidelines for airborne IPC in health facilities are widely available (National Department of Health, 2015, World Health Organization, 2019), but numerous implementation challenges are documented (Barrera-Cancedda et al., 2019). These are linked to a range of contributing factors including clinic design, climatic conditions, work practices and the organization of care, risk perceptions, competing priorities, organizational culture and concerns about stigma (Claassens et al., 2013, Farley et al., 2012, WHO, 2014). As constraints to IPC implementation arise at different levels of the health system (facility or service level, provincial and national), strategies for tackling nosocomial *Mtb* transmission require complex, multi-layered interventions that are best designed using a whole systems approach. This is defined as an interdisciplinary approach that (1) contextualises clinic-level TB IPC processes within the structure of the broader health system; and (2) analyses interactions across health system components (Kielmann et al., 2020).

Mathematical models of disease transmission are increasingly recognised as a vital tool for understanding health system functioning and optimisation, given their capability to simulate the behaviour of complex adaptive systems (Cassidy et al., 2019). Mathematical models allow for the use of locally relevant epidemiological parameters, and model outputs can be combined with local unit costs (or cost functions). In this way, models enable analysts to explore the efficiency of investments in infection control in specific settings, and can assist with priority setting and resource allocation at the country level. Most recently, studies have begun exploring possibilities for parameterising models with data on the health system constraints affecting real-world intervention implementation (Bozzani et al., 2021, Vassall et al., 2016). Constraints can operate through elements of the health system's 'hardware', for example in the form of physical inputs shortages (human resources, diagnostic equipment and consumables, drugs), or through its 'software', as factors influencing the decision-making process (such as equity and other political and social considerations) (Sheikh et al., 2011). Both types of constraints might impact on *feasibility*, through the pace of scale-up, and *effectiveness* of interventions, by reducing achievable coverage. Their impact can be particularly severe in low- and middle-income countries, where budgets are limited and new interventions often represent a large proportion of the available funds (Mills, 2014). For this reason, it is vital to produce estimates of opportunity costs that are accurate and complete, including the costs of any additional activities alongside intervention implementation ('enablers') that may be necessary to overcome the constraints.

While it is possible to use routine data for this purpose, building cost parameters that account for the additional expenses incurred to relieve the constraints and achieve the intended intervention targets in a 'real-world' setting poses novel difficulties for analysts (Bozzani et al., 2018). In particular, there is no consensus currently on the best way to elicit comprehensive information on the constraints that apply to a specific setting and intervention (i.e. on the dynamic interactions between the intervention and specific elements of the health system) and their impact on successful implementation and scale-up. In this paper, we use TB IPC interventions as a case study to illustrate how system dynamics modelling (SDM) techniques can be used to take a whole systems approach to costing, that includes information on health system constraints and on the actions required to relax them at different levels of the health system.

6.3 MATERIALS AND METHODS

Ethics approval for the study was granted by the research ethics committees of the University of KwaZulu-Natal (BE662/17) the University of Cape Town (165/2018) and the London School of Hygiene and Tropical Medicine (14872/3).

6.3.1 Study setting

The costing exercise presented in this case study was undertaken at two clinics in rural KwaZulu-Natal, South Africa, as part of *Umoya omuhle*, a multidisciplinary project aimed at understanding the drivers of nosocomial transmission of *Mtb* in primary healthcare facilities (Kielmann et al., 2020). *Umoya omuhle* collected a wealth of information on the policies, norms and values governing TB-IPC processes for clinic staff and patients, as well as on the infrastructure and resources for TB-IPC, implementation challenges, and on existing levels of indoor ventilation and congregation to parametrise a model of *Mtb* transmission in the clinics and surrounding communities (Colvin et al., 2020, McCreesh et al., 2020, Voce, 2020).

6.3.2 System dynamics modelling

The TB IPC interventions investigated in the *Umoya omuhle* study were identified and designed using a SDM approach described in detail elsewhere (Diaconu et al., 2021). The approach was selected due to its focus on health systems as complex adaptive systems, which allows for the translation of this complexity in intervention design (Paina and Peters, 2012). Group model building, a participatory method used for qualitative SDM elaboration of causal loop diagrams, was used in *Umoya omuhle* to learn about the feedback loops and non-linear effects that are present in the TB IPC system in South Africa and that might cause unexpected or unintended outcomes in response to interventions and policy changes (Iwelunmor et al., 2015, Northridge and Metcalf, 2016). The group model building exercise consisted of two one-day workshops, the first with national- and provincial-level policymakers and the second with district- and facility-level health professionals, patient advocates and public health practitioners in a range of specialties, including managers, researchers and architects. During the workshops, participants were guided to develop causal loop diagrams which identify the current dynamics shaping nosocomial *Mtb* transmission at clinic level, including points of fragility within the TB IPC system and, among those, points where interventions would be feasible.

This information then fed into the design of interventions that would be effective at reducing nosocomial *Mtb* transmission and that would take existing constraints into account, incorporating to the extent feasible the necessary enablers to overcome these constraints. Pathwys of action of the identified interventions and enablers were described through a process of iterative review and revision of the causal loop diagrams and free lists generated by stakeholders during the workshops, integrated with the qualitative evidence gathered by the wider *Umoya Omuhle* project.

6.3.3 Interventions costing

Unit costs for core intervention activities and enablers were estimated using price and quantity data from the published literature and quotes from local suppliers. Unit costs captured the incremental economic costs of all core activities, including the opportunity cost of staff time, recognising that even activities that are not time-consuming and that are already implemented to some degree, such as opening windows and doors to improve ventilation or directing queuing patients, will need dedicated staff to increase their feasibility and impact compared to current levels (Islam et al., 2021). Quantity assumptions were supplemented with data from interviews with facility managers, IPC managers and nurses at the *Umoya omuhle* study facilities, who were asked about input requirements, including staff time, for carrying out hypothetical tasks. Capital investments and other start-up costs were annualised using a 3% discount rate for future costs. All costs are presented in 2019 US$.

All core activities and enablers that emerged from the group model building sessions as desirable to improve the feasibility and impact of the proposed interventions were considered for inclusion in the cost model. However, reliable data sources could not be identified for some of the proposed activities that were entirely novel (e.g. electronic health records linkage to appointment systems), above service-level (e.g. redesigning training materials using routine monitoring and evaluation data), or outside the remit of the Department of Health (e.g. improving transport links to clinics to ensure the viability of appointment systems). Other activities were acknowledged as central to the intervention but excluded from the costing exercise, as they did not represent an actual cost, i.e. they referred to barriers that could not be overcome through financial investments (for example, having to obtain permission from the district to carry out clinic building modifications).

The final list of interventions included in the cost model is presented in Table 15, which details the core activities and enablers costed as well as those enablers indicated as desirable by the SDM participants that could not be costed. A full list of price and quantity assumptions is presented in the Supplementary Material. Unit costs and underlying assumptions were checked and validated with SDM participants multiple times during model development, first through monthly drop-in virtual meetings and finally during a second SDM workshop, where preliminary costing results were presented to participants. Their feedback was then incorporated in the analysis to produce the final estimates.

Table 15. Description of interventions costed

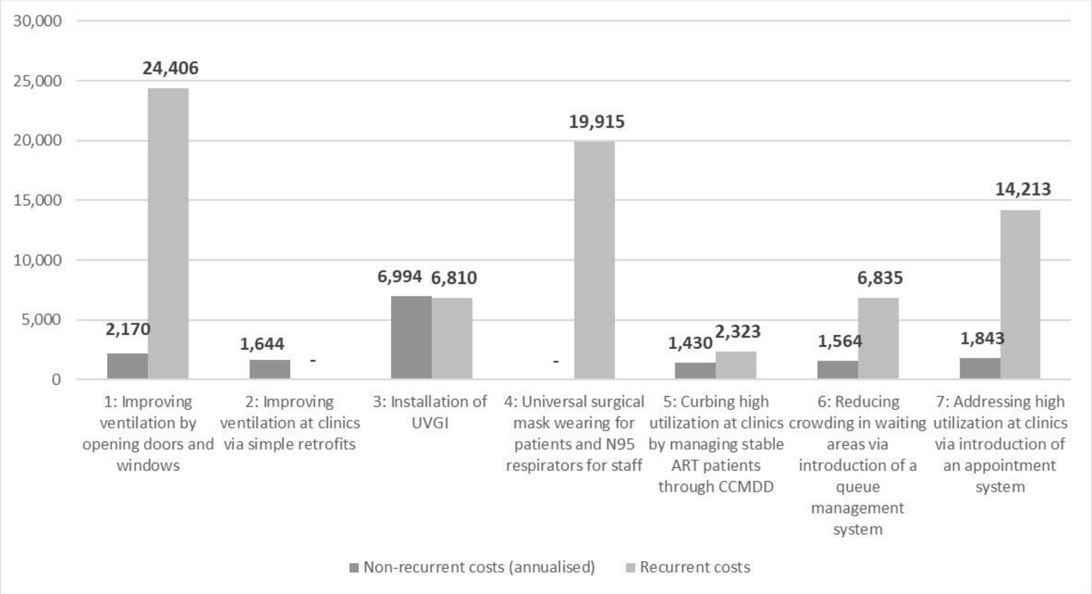
Intervention	Core activities modelled	Enablers modelled	Enabler as % of unit cost	Enablers not modelled
1: Improving ventilation by opening doors and windows	One clinical staff doing a round of the clinic every hour	One-day training for all clinical staff every three years and intensified supervision from district. Electric heaters/fans to ensure thermal comfort.	23%	Other communication materials and training formats re-designed based on M&E data
2: Building retrofits	Raising roof of waiting area, installing turbine ventilators and lattice brickwork	None	0%	Obtaining permissions from district, community workshop to decide which retrofits
3: UVGI	UV lights installation, maintenance, calibration and electricity	One-day training for all clinical staff every three years	11%	National level processes for lifting existing moratorium and launching new tender
4: Surgical mask wearing for patients and N95 respirators for staff	One N95 respirator per staff every 5 shifts, fitted annually (50% coverage). One surgical mask per patient per visit (70% coverage)	One-day training for all clinical staff every three years. Free leaflet for one in ten patients disseminated around clinic	25%	Other communication materials, training formats or community events redesigned based on M&E data
5: Maximising use of existing CCMDD facilities	None	Half-day training for staff involved in implementation every three years. Once-off community workshops	100%	Providing additional CCMMD pick-up points outside of clinics, particularly where no private pharmacies available within catchment area
6: Queue management system	One nurse triaging patients and one lay staff directing queues	Half-day training for staff involved in implementation every three years and intensified supervision from district. Once-off community workshops. Covered outdoor waiting area	46%	Other ways of addressing 'queue anxiety' such as numbered tickets, re-designing training formats and materials incorporating M&E data
7: Appointments system	One hour per day for clerk to pre-retrieve files and record appointments. One hour for public awareness messaging in waiting area	Half-day training for staff involved in implementation every three years. Once-off community workshops.	54%	Addressing issues with transportation availability throughout the day, redesigning training formats and materials incorporating M&E data

CCMDD: Central Chronic Medicines Dispensing and Distribution. UVGI: Ultraviolet Germicidal Irradiation. M&E: Monitoring and Evaluation

6.4 RESULTS

Incremental annual costs of each intervention option, including upfront capital investment and recurrent costs of all intervention activities and enablers, are reported in Figure 10. The least expensive interventions considered were the retrofitting of buildings to improve ventilation, which consisted of relatively cheap and long-lasting building modifications such as installing turbine ventilators, substituting portions of walls and windows with lattice brickwork and raising waiting area roofs; and expanding the decentralised treatment management of stable antiretroviral therapy (ART) patients through the Central Chronic Medicines Dispensing and Distribution (CCMDD) system (Dorward et al., 2020). The switch from more frequent monitoring at ART clinics to 6-monthly repeat prescriptions and drug dispensing through CCMDD might ultimately be cost-saving for the health system, as it promotes task shifting from nurses, who write prescriptions during routine ART clinic visits, to lay workers staffing the external CCMDD pick up points.

Figure 10. Annual incremental costs at two clinics in KwaZulu-Natal, 2019 US$



The most expensive input to intervention implementation was the time of clinic staff. For this reason, relatively simple but human resource intensive interventions, such as ensuring the regular opening of windows and doors or implementing a queuing system that allows for coughing patients to be rapidly triaged and for other patients to wait in a sheltered area outdoors, were found to be more expensive than those interventions relying on capital investments and technology, such as installing ultraviolet germicidal irradiation (UVGI) systems.

Enablers identified ranged from relatively inexpensive capital investments, such as electric heaters to ensure thermal comfort in winter when windows are kept open, to more costly enhancements to training programmes for clinic staff and consultations with community representatives, to ensure lasting changes in work culture and local ownership of the interventions. Overall, the proportion of total intervention costs represented by the enablers was inversely proportional to the size of capital investment required by the intervention; and directly proportional to the intervention’s reliance on changes in the behaviour of patients and/or staff (Table 15). Correspondingly, the share of total costs represented by the enablers ranged from 0 for the retrofitting of buildings to 54% for introducing appointment systems and 100% for expanding the use of community sites for ART collection.

6.5 DISCUSSION

This analysis applied group model building, an established SDM approach, to elicit information on the health system constraints that operate in TB IPC in South Africa. This information was then used in a novel way to build a model of the local incremental costs of a set of TB IPC interventions implemented at two clinics in KwaZulu-Natal. The interventions were designed bearing in mind potential barriers to implementation and necessary investments to overcome these; then costed iteratively, based on feedback given by SDM participants. The resulting unit costs thus reflect information linking the implementation process to outcomes, and are a closer representation of the full opportunity costs of these interventions compared to those generated with standard costing methods, as they include the costs of relaxing health system constraints.

Despite the addition of enabling costs, the TB IPC interventions considered are substantially less expensive than other interventions for preventing TB transmission currently included in the South African National Strategic Plan for HIV and TB as well as in the Investment Case for TB, such as improving the timeliness and yield of facility-based TB screening by using more sensitive algorithms and contact tracing (National Department of Health and South Africa National AIDS Council, 2016, South Africa National AIDS Council, 2017). Intensified facility-based TB case-finding was found to be the most effective intervention at reducing TB incidence in model-based analyses, but it is also extremely costly in the short and medium term, as it generates an increase in diagnosis and treatment costs further along the TB care cascade (Menzies et al., 2016). In addition, its feasibility was found to be low in an empirical proof of concept analysis quantifying the constraints around TB diagnosis and treatment in South Africa, and the costs of relaxing these constraints were substantial (Bozzani et al., 2018). If proved to be at least as effective as the measures currently funded, TB IPC interventions could shift the balance of resource allocation within the South African TB programme.

Further cost savings could be realised by considering the proposed TB IPC interventions as a package, thus allowing the costs of those enablers that are shared by more than one intervention to be spread across them. An example would be the costs of enhancing routine staff training and supervision, which is shared by all the interventions analysed with the exception of building retrofits. Similarly, gains in efficiency could be realised from scaling up the interventions to the regional and/or national level (Gomez et al., 2020). In this application, the SDM approach was used to identify intervention designs that build on current practice uniquely specific to the two study clinics. SDM could in principle be used to assist with designing more universally scalable interventions. However, there is substantial variation in the implementation of TB IPC measures across provinces and regions in South Africa. This made it difficult to estimate the national level costs of such context-specific interventions as retrofitting buildings or establishing appointments and queuing systems, all of which are dependent on clinic characteristics and on processes that were not uniformly established in the past and are currently used with varying rates of success (Voce, 2020, Zwama et al., 2020).

Another potential limitation of applying the SDM approach to a costing exercise is that its focus on the broader health system characteristics and pathways of action may lead to the identification of certain constraints that cannot be relaxed through financial investments (e.g. lifting the moratorium on UVGI) or that are otherwise ‘uncostable’. This may be because the interventions and enablers consist of novel activities for which sources of price and quantity data cannot be readily identified, such as setting up new CCMDD pick up points; or they may consist of high-level activities, such as redesigning training formats and materials based on data collected from routine monitoring and evaluation, the costs of which are above-site and difficult to allocate to specific interventions; or they may consist of activities that fall outside the remit of the health sector, such as improving public transportation links to health facilities to support the implementation of a clinic appointment system that spaces patient visits throughout the day. While activities that do not incur a cost and those that fall outside the health sector might be excluded from an economic evaluation (depending on the perspective taken), additional data collection is needed for costing novel activities and for allocating and scaling the costs of shared above-site enablers, for example from pilot/demonstration projects or feasibility studies.

6.6 CONCLUSIONS

SDM-informed costing allows for a comprehensive view of the health system influences on intervention impact and feasibility, in a way that may be superior to other, less participatory stakeholder consultation methods. By providing several occasions for interaction between different TB IPC stakeholders at national and decentralised level, as well as between stakeholders and researchers, the group model building exercise presented in this analysis enabled a thorough process for validating and refining costing assumptions, including on the details of intervention and enabler design. For successful application of this approach in economic evaluation, further research is needed into ways of integrating insights from SDM, that are well suited to identifying above-service level costs, with more traditional costing methods, which usually focus more on service-level inputs. Such a combination can, for example, smooth the process of linking costs into transmission model outputs, which are usually service-level units, as well as potentially inform the choice of a functional form for modelling costs at scale. SDM can also be useful for identifying intervention types that might not be cost-effective based on the share of total costs represented by the required enablers. Further analyses of interventions that are more or less reliant on capital investments or on behaviour change, such as new preventive or diagnostic technologies, are needed to fully assess its potential applications in economic evaluation and priority setting.

SUPPLEMENTARY MATERIAL

S.1 PRICE ASSUMPTIONS

Ingredients prices used in the estimation of unit costs are summarised in Table 16.

Table 16. Price data summary

	Ingredient	Unit price (2019 US$)	Unit	Source
Intervention specific costs				
Staff time	Nurse minute	0.36	per minute	(1)
	Outpatient visit - Nurse Cost	1.45	per visit	(1)
	Outpatient visit - Other Cost	4.32	per visit	(1)
	General worker minute	0.03	per minute	(1)
	Administrator/data clerk minute	0.10	per minute	(1)
Building retrofits	Lattice brickwork installation	187	1x1.5 m	(2)
	Raising roof	1,000	per item	(3)
	Turbine ventilators installation	350	per item	(4)
Personal protective equipment	N95 respirator	2.50	per item	(5)
	N95 respirator fit testing	6.12	per event	(6)
	Surgical mask	0.37	per item	South African retail price
UVGI	Clinic 1 UV lamps and installation	47,672	per event	Local supplier quote
	Clinic 2 UV lamps and installation	22,677	per event	Local supplier quote
	Life-cycle maintenance	766	per unit	(7)
	Air mixing system	1,500	per clinic	(7)
	Acceptance testing	75	per clinic	(7)
	GUV meter	2,000	per clinic	(7)
ART	Antiretroviral therapy	60	per patient month	(8)
Enabler costs				
Training and public health messaging	one-day stand-alone nurse training	372	per person	Local supplier quote
	one-day stand-alone lay worker training	102	per person	Local supplier quote
	one-day add-on nurse training	223	per person	(9)
	one-day add-on lay worker training	69	per person	(9)
	IEC materials/job aids	0.18	per person	(9)
Thermal comfort	Electric heater	51	per unit	South African retail price
	Electric fan	20	per unit	South African retail price

ART: Antiretroviral Therapy. IEC: Information, Education and Communications materials. UVGI: Ultraviolet Germicidal Irradiation.

(1) Bozzani FM, Mudzengi D, Sumner T, Gomez GB, Hippner P, Cardenas V, et al. Empirical estimation of resource constraints for use in model-based economic evaluation: an example of TB services in South Africa. Cost effectiveness and resource allocation: C/E. 2018;16:27.

(2) Taylor JG, Yates TA, Mthethwa M, Tanser F, Abubakar I, Altamirano H. Measuring ventilation and modelling M. tuberculosis transmission in indoor congregate settings, rural KwaZulu-Natal. Int J Tuberc Lung Dis. 2016;20(9):1155-61.
(3) Escombe AR, Ticona E, Chavez-Perez V, Espinoza M, Moore DAJ. Improving natural ventilation in hospital waiting and consulting rooms to reduce nosocomial tuberculosis transmission risk in a low resource setting. BMC Infect Dis. 2019;19(1):88.
(4) Cox H, Escombe R, McDermid C, Mtshemla Y, Spelman T, Azevedo V, et al. Wind-driven roof turbines: a novel way to improve ventilation for TB infection control in health facilities. PLoS One. 2012;7(1):e29589.
(5) End Tuberculosis Transmission Initiative (ETTI). Technical information sheet. Personal respiratory protection. Available from: http://www.stoptb.org/wg/ett/assets/documents/ETTI_InfoSheet_Respirators_Final.pdf
(6) End Tuberculosis Transmission Initiative (ETTI). Technical information sheet. Respirator fit testing. Available from: http://www.stoptb.org/wg/ett/assets/documents/ETTI_InfoSheet_FitTesting_Final.pdf
(7) End Tuberculosis Transmission Initiative (ETTI). Technical information sheet. Disinfecting room air with upper-room (UR) germicidal UV (GUV) systems. Available from: http://www.stoptb.org/wg/ett/assets/documents/ETTI_TechSheet_GUV_final%20version.pdf.
(8) Tagar E, Sundaram M, Condliffe K, Matatiyo B, Chimbwandira F, Chilima B, et al., Multi-country analysis of treatment costs for HIV/AIDS (MATCH): Facility-level ART unit cost analysis in Ethiopia, Malawi, South Africa and Zambia. PloS ONE. 2014;9(11)
(9) Jamieson L, Gomez GB, Rebe K, Brown B, Subedar H, Jenkins S, et al. The impact of self-selection based on HIV risk on the cost-effectiveness of preexposure prophylaxis in South Africa. AIDS. 2020;34(6):883-91.

S.2 QUANTITIES AND OTHER COST CALCULATION PARAMETER ASSUMPTIONS

Annual ingredients quantities and other assumptions made in the calculation of interventions and enablers unit costs are summarised in Table 17 and Table 18, respectively.

Table 17. Annual quantities and other intervention parameter assumptions

Interventions	**Ingredients**	**Quantity**		**Assumptions**
		Clinic 1	**Clinic 2**	
1. Improving ventilation by opening windows and doors	Nurse minutes	40,320	16,128	One clinical member of staff doing a round of the clinic every working hour (n=8) for every working day (n=252). Rounds take 20 minutes per hour at Clinic 1 and 8 minutes per hour at Clinic 2.
2. Building retrofits	Lattice brickwork, 1x1.5m unit	8	3	Clinic 1: lattice brickwork along 1/5 of main corridor length and 1/7 of secondary corridor. Raise roof of secondary waiting area. Install 14 turbine ventilators in park homes. Clinic 2: lattice brickwork along 2/3 of width and 1/15 of length of main waiting area. Raise roof of main waiting area. Install 4 turbine ventilators in central area of main building
	Roof raising	1	1	
	Turbine ventilators	14	4	
3. UVGI	GUV R30	6	2	Clinic 1: 25 UVGI lamps in main building, 31 lamps in chronics building. Clinic 2: 26 UVGI lamps in clinic building. Count based on assessment by local supplier
	GUV R31	14	10	
	GUV R32	36	14	
4. Surgical mask wearing for patients and N95 respirators for staff	N95 respirators	2,608	782	One N95 respirator per clinical member of staff every 5 shifts (50% coverage), fit-tested annually. One surgical mask per patient per visit (70% coverage)
	N95 fit testing	103	32	
	Surgical masks	10,749	5,374	
5. Maximising use of existing CCMDD facilities	ART nurse visits per year, ineligible patients	12	12	CCMDD intervention ensures all stable patients (92%) receive 6-months repeat prescriptions so nurse visits reduced to two per year. Ten remaining visits occur at CCMDD point staffed by lay worker. From *Umoya omuhle* social contacts survey data, it is estimated that maximising use of the CCMDD system will lead to a 31% reduction in clinic visits costs (1).
	ART nurse visits, eligible patients	2	2	
	ART lay worker visit	10	10	
6. Queue management system	General worker minutes	7,678	3,839	One designated nurses triaging coughing patients and one lay queue marshal directing the queue at each clinic (half a minute per visit).
	Nurse minutes	7,678	3,839	
7. Appointments system	Administrator/data clerk minutes	45,360	30,240	One extra hour per day for clerk to pre-retrieve files and record appointments (two clerks at Clinic1). One hour for public awareness messaging in waiting area

ART: Antiretroviral Therapy. CCMDD: Central Chronic Medicines Dispensing and Distribution. UVGI: Ultraviolet Germicidal Irradiation

(1) McCreesh N, Karat AS, Baisley K, Diaconu K, Bozzani F, Beckwith P, Yates T, Deol A, White RG, Grant A. Effect of infection prevention and control measures on rate of *Mycobacterium tuberculosis* transmission in primary health clinics in South Africa. Forthcoming

Table 18. Annual quantities and other enabler parameter assumptions

Enablers	**Interventions enabled**	**Quantity**		**Assumptions**
		Clinic 1	**Clinic 2**	
Electric heaters	Opening windows and doors	7	3	Heaters positioned in waiting areas to ensure thermal comfort
Electric fans	Opening windows and doors	30	8	Fans positioned in consultation rooms to ensure thermal comfort
Onsite stand-alone staff training, people trained	UVGI Opening windows and doors N95 for staff and surgical masks for patients	45	14	One day training for each intervention, repeated every 3 years
Onsite add-on staff training, people trained	Appointments system Queuing system Maximising use of CCMDD	45	14	Half-day add-on training for each intervention, delivered in combination with other routine training, repeated every 3 years
Increased supervision from District Health Manager, days	Opening windows and doors Appointments system	54	54	At introduction: daily facility visits for one month, weekly for another 2 months Post-introduction: monthly visits
Offsite community workshops	Appointments system Queuing system Maximising use of CCMDD	120	120	Four sessions with 30 attendees each, once-off. Equivalent to stand-alone lay worker training
Information, education and communication materials	N95 for staff and surgical masks for patients	1,536	768	Information leaflets on surgical mask use disseminated around clinic for one in every ten patients

CCMDD: Central Chronic Medicines Dispensing and Distribution. UVGI: Ultraviolet Germicidal Irradiation

REFERENCES

BARRERA-CANCEDDA, A. E., RIMAN, K. A., SHINNICK, J. E. & BUTTENHEIM, A. M. 2019. Implementation strategies for infection prevention and control promotion for nurses in Sub-Saharan Africa: a systematic review. *Implement Sci,* 14**,** 111. 10.1186/s13012-019-0958-3.

BOZZANI, F. M., MUDZENGI, D., SUMNER, T., GOMEZ, G. B., HIPPNER, P., CARDENAS, V., CHARALAMBOUS, S., WHITE, R. & VASSALL, A. 2018. Empirical estimation of resource constraints for use in model-based economic evaluation: an example of TB services in South Africa. *Cost Eff Resour Alloc,* 16**,** 27. https://doi.org/10.1186/s12962-018-0113-z.

BOZZANI, F. M., VASSALL, A. & GOMEZ, G. B. 2021. Building resource constraints and feasibility considerations in mathematical models for infectious disease: A systematic literature review. *Epidemics,* In press.

CASSIDY, R., SINGH, N. S., SCHIRATTI, P. R., SEMWANGA, A., BINYARUKA, P., SACHINGONGU, N., CHAMA-CHILIBA, C. M., CHALABI, Z., BORGHI, J. & BLANCHET, K. 2019. Mathematical modelling for health systems research: a systematic review of system dynamics and agent-based models. *BMC Health Serv Res,* 19**,** 845. 10.1186/s12913-019-4627-7.

CLAASSENS, M. M., VAN SCHALKWYK, C., DU TOIT, E., ROEST, E., LOMBARD, C. J., ENARSON, D. A. & ET AL. 2013. Tuberculosis in Healthcare Workers and Infection Control Measures at Primary Healthcare Facilities in South Africa. *PLoS One,* 8. doi: 10.1371/journal.pone.0076272.

COLVIN, C. J., KALLON, I. I., SWARTZ, A., MACGREGOR, H., KIELMANN, K. & GRANT, A. D. 2020. 'It has become everybody's business and nobody's business': Policy actor perspectives on the implementation of TB infection prevention and control (IPC) policies in South African public sector primary care health facilities. *Global Public Health*. https://doi.org/10.1080/17441692.2020.1839932.

DIACONU, K., KARAT, A., BOZZANI, F., FALCONER, J., MCCREESH, N., VOCE, A., VASSALL, A., GRANT, A. & KIELMANN, K. 2021. Systems interventions for improving TB infection prevention and control in South African primary care facilities. *Under review*.

DORWARD, J., MSIMANGO, L., GIBBS, A., SHOZI, H., TONKIN-CRINE, S., HAYWARD, G., BUTLER, C. C., NGOBESE, H., DRAIN, P. K. & GARRETT, N. 2020. Understanding how community antiretroviral delivery influences engagement in HIV care: a qualitative assessment of the Centralised Chronic Medication Dispensing and Distribution programme in South Africa. *BMJ Open,* 10**,** e035412.

FARLEY, J. E., TUDOR, C., MPHAHLELE, M., FRANZ, K., PERRIN, N. A., DORMAN, S. & VAN DER WALT, M. 2012. A national infection control evaluation of drug-resistant tuberculosis hospitals in South Africa. *Int J Tuberc Lung Dis,* 16**,** 82-9. 10.5588/ijtld.10.0791.

GOMEZ, G. B., MUDZENGI, D. L., BOZZANI, F., MENZIES, N. A. & VASSALL, A. 2020. Estimating Cost Functions for Resource Allocation Using Transmission Models: A Case Study of Tuberculosis Case Finding in South Africa. *Value in Health*. https://doi.org/10.1016/j.jval.2020.08.2096.

ISLAM, M. S., CHUGHTAI, A. A., BANU, S. & SEALE, H. 2021. Context matters: Examining the factors impacting the implementation of tuberculosis infection prevention and control guidelines in health settings in seven high tuberculosis burden countries. *J Infect Public Health,* 14**,** 588-597. 10.1016/j.jiph.2021.01.014.

IWELUNMOR, J., BLACKSTONE, S., VEIRA, D., NWAOZURU, U., AIRHIHENBUWA, C., MUNODAWAFA, D. & ET AL. 2015. Toward the sustainability of health interventions implemented in sub-Saharan Africa: a systematic review and conceptual framework. *Implement Sci,* 11**,** 43. doi:10.1186/s13012-016-0392-8.

KIELMANN, K., KARAT, A. S., ZWAMA, G., COLVIN, C., SWARTZ, A., VOCE, A. S., YATES, T. A., MACGREGOR, H., MCCREESH, N., KALLON, I., VASSALL, A., GOVENDER, I., SEELEY, J. & GRANT, A. D. 2020. Tuberculosis infection prevention and control: why we need a whole systems approach. *Infect Dis Poverty,* 9. https://doi.org/10.1186/s40249-020-00667-6.

MCCREESH, N., GRANT, A. D., YATES, T. A., KARAT, A. S. & WHITE, R. G. 2020. Tuberculosis from transmission in clinics in high HIV settings may be far higher than contact data suggest *International Journal of Tuberculosis and Lung Disease,* 24**,** 403-408. https://doi.org/10.5588/ijtld.19.0410.

MENZIES, N. A., GOMEZ, G. B., BOZZANI, F., CHATTERJEE, S., FOSTER, N., GARCIA BAENA, I., LAURENCE, Y. & ET AL. 2016. Cost-effectiveness and resource implications of aggressive TB control in China, India and South Africa: a combined analysis of nine models. *Lancet Glob Health,* 4**,** e816–e826.

MILLS, A. 2014. Health care systems in low- and middle-income countries. *N Engl J Med,* 370**,** 552-7. 10.1056/NEJMra1110897.

NATIONAL DEPARTMENT OF HEALTH 2015. National Infection Prevention and Control Guidelines for TB, MDR-TB and XDR-TB. Pretoria, South Africa.

NATIONAL DEPARTMENT OF HEALTH & SOUTH AFRICA NATIONAL AIDS COUNCIL 2016. South African HIV and TB Investment Case. Reference report. Phase 1.

NORTHRIDGE, M. E. & METCALF, S. S. 2016. Enhancing implementation science by applying best principles of systems science. *Health Res Policy Syst,* 14**,** 74. doi:10.1186/s12961-016-0146-8.

O'DONNELL, M. R., JARAND, J., LOVEDAY, M., PADAYATCHI, N., ZELNICK, J., WERNER, L., NAIDOO, K., MATER, I., OSBURN, G., KVASNOVSKY, C., SHEAN, K., PAI, M., VAN DER WALT, M., HORSBURGH, C. R. & DHEDA, K. 2010. High Incidence of Hospital Admissions With Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis Among South African Health Care Workers. *Ann. Intern. Med,* 153**,** 516-22. doi: 10.7326/0003-4819-153-8-201010190-00008.

PAINA, L. & PETERS, D. H. 2012. Understanding pathways for scaling up health services through the lens of complex adaptive systems. *Health Policy Plan,* 27**,** 365-373. https://doi.org/10.1093/heapol/czr054.

SHEIKH, K., GILSON, L., AGYEPONG, I. A., HANSON, K., SSENGOOBA, F. & BENNETT, S. 2011. Building the field of health policy and systems research: framing the questions. *PLoS Med,* 8**,** e1001073. 10.1371/journal.pmed.1001073.

SOUTH AFRICA NATIONAL AIDS COUNCIL 2017. South Africa's National Strategic Plan for HIV, TB and STIs 2017-2022.

VASSALL, A., MANGHAM-JEFFERIES, L., GOMEZ, G. B., PITT, C. & FOSTER, N. 2016. Incorporating demand and supply constraints into economic evaluation in low-income and middle-income countries. *Health Econ,* 25**,** 95-115. 10.1002/hec.3306.

VOCE, A. 2020. Health systems strengthening: 'One size does not fit all'. *6th Global Symposium on Health Systems Research.*

WHO. 2014. *The End TB Strategy. Global strategy and targets fro tuberculosis prevention, care and control after 2015* [Online]. Available: http://who.int/tb/post2015_TBstrategy.pdf?ua=1 [Accessed].

WORLD HEALTH ORGANIZATION 2019. WHO Guidelines on tuberculosis infection prevention and control, 2019 update. Geneva: World Health Organisation.

ZWAMA, G., COLVIN, C., SWARTZ, A., MACGREGOR, H., KIELMANN, K. & VOCE, A. 2020. Interacting policy imperatives: Is the clinic a safe space for its workers and users? *6th Global Symposium on Health Systems Research.*

CHAPTER 7: DISCUSSION

This thesis aims to inform priority setting for infectious disease control by reviewing and expanding on methods for considering the *feasibility* of intervention implementation within the decision-making process. The **areas for methodological and empirical advancement** identified at the outset, each addressed by a **thesis objective** and a corresponding paper, were:

1. Lack of (1) a precise analytical definition of *feasibility* for inclusion in health care priority setting, and (2) standard methods for incorporating feasibility considerations in model-based economic evaluations (**Chapter 3**);
2. Lack of established empirical methods for characterising and quantifying non-financial health system constraints in a given setting and intervention scenario, within the policy timeframe and preferably using routine health system data (**Chapter 4**);
3. Lack of applied examples of the effect of including non-financial health system constraints algorithmically within the cost-effectiveness framework on the resulting decision rules, in a real-world setting (**Chapter 5**);
4. Lack of guidance on selecting stakeholder elicitation methods to inform costing exercises that take health system constraints and the costs of relaxing them into account, to calculate the full opportunity cost of intervention options (**Chapter 6**).

7.1 MAIN FINDINGS

7.1.1 Analytical definition and inclusion of feasibility in priority setting models

The scoping review of the literature presented in Chapter 1 highlighted an increasing recognition that recommendations from economic evaluations which ignore feasibility might end up being disregarded by decisionmakers, and ultimately lead to inefficient outcomes (Hauck et al., 2016, Mikkelsen et al., 2017). Empirical evidence shows that non-financial constraints and decision criteria other than cost-effectiveness are often at the forefront in priority setting, especially in overstretched health systems. For example, a systematic review of procurement and prioritisation decisions on medical devices in LMICs observed that these are more often dictated by the local availability of necessary supply chains, cultural acceptability, efficacy and safety of the devices as well as advocacy by strong political groups, rather than efficiency considerations (Diaconu et al., 2017).

To overcome barriers to evidence-informed decision-making and ensure local relevance, the literature calls for stakeholder involvement in the evidence generation process (Baltussen et al., 2016, Daniels and Sabin, 2008). Moreover, policymakers should be routinely presented with evidence on: (i) the optimal allocation of the available budget across new interventions/technologies and health systems strengthening interventions (Hauck et al., 2019, Morton et al., 2016, Vassall et al., 2019); and (ii) the trade-offs involved in pursuing objectives other than health maximisation, such as equity or financial protection (Karsu and Morton, 2021).

Despite mounting evidence and recommendations, the theoretical frameworks reviewed in Chapter 2 revealed a general lack of consistency in (1) providing an operational definition of feasibility and (2) standardising approaches for considering feasibility in economic evaluations.

Providing an analytical definition of feasibility

The systematic review presented in Chapter 3, as well as the group model building exercise described in Chapter 6, uncovered several meanings of ‘feasibility’ for different people and in different contexts. This thesis defined feasibility as the product of the dynamic interplay between the intervention and the context, which sets boundaries around the decision-making process. It further proposed the following operational classification of feasibility for use in priority setting:

- Demand and supply constraints that affect the interventions’ *feasibility of implementation*. These constraints may limit the pace of intervention scale-up (e.g. human resources scarcity in the short run); or may be insurmountable even with increased resourcing (e.g. an ethical obligation to provide treatment to all those in need); or may incur costs that are not observable when interventions are tested in research settings.
- Policy objectives that restrict the *political feasibility* of interventions. These encompass the prevailing norms and values that determine policy priorities, as well as the structure of health systems and institutions.

This classification is useful for guiding applications in economic evaluations as it distinguishes between constraints that result in higher (short run) opportunity costs than predicted by standard cost-effectiveness analyses as opposed to criteria that modify the cost-effectiveness decision rule and/or that are traded off against cost-effectiveness.

Building feasibility into priority setting models

In Chapter 3, the thesis presented a systematic review of practical methods used to date for incorporating non-financial health system constraints in mathematical model-based priority setting for infectious disease control. The review identified three main approaches, all potentially amenable to accommodating economic analyses: (i) estimation of constraints within the disease transmission model by restricting outputs (and costs); (ii) linking disease transmission and health system models; (iii) optimising under constraints (other than the budget). Models were then used to estimate the resulting reductions in intervention coverage and/or to estimate the additional resources needed to 'relax' the constraints and successfully implement the interventions at scale.

All of these approaches can be used in transmission model-based economic evaluations for estimating the impact of interactions between the intervention and the health system on ICERs for different coverage scenarios. The review found that linking transmission and health system models to generate estimates of non-financial constraints impact is currently the least used approach, potentially because of its more data-intensive nature. In fact, health system modelling is, by design, the only approach in the literature that requires analysts to define and characterise health system constraints and decision-making objectives in detail and in a form that is analytically viable. In contrast, transmission model-based estimation and optimisation analyses often explore stylised scenarios (e.g. severe vs mild constraints) without specifying what the constraints and the actions needed to relax them are (e.g. identifying the maximum HSS investment that allows the intervention to remain cost-effective, without defining the nature of the investment).

Using 'exemplary' rather than 'real-world' scenarios not only allows modellers to bypass the uncertainty around how to elicit and operationalise constraints, but also avoids any inconsistencies between the structure of the disease transmission model and the mechanism of action of interventions and enablers. In fact, an insight gained from the literature review and the application of a health system model (SDM) to an economic analysis presented in Chapter 6 is that interventions and enablers affect not only the economic but also the disease transmission modelling frame. In simple terms, mathematical models of disease transmission can be classified as either frequency-dependent, where transmission rates are driven by the frequency of contacts between individuals in the population (for example, most models of sexually-transmissible infections), and density-dependent models, where transmission rates are driven by the density of individuals in the population (for example, influenza models) (Begon et al., 2002). TB transmission models are usually frequency-dependent: the force of infection in the general population is a function of the number of individuals with active TB and the number of contacts among individuals (Trauer et al., 2014). However, interventions to prevent nosocomial TB transmission such as queuing or appointment systems and enablers such as providing covered waiting areas outside clinic buildings have an effect on TB transmission mainly by reducing the density of the population at risk rather than by changing the frequency of contacts. In this sense, then, considering ‘real-world’ interventions and constraints adds an additional layer of complexity to both the disease transmission and economic modelling frames.

7.1.2 Testing an empirical method for characterising and quantifying constraints

Chapter 4 set out to test an empirical approach for systematically building constraints parameters into priority setting models in a real-world setting. The approach was designed for use within the policy timeframe, and thus aimed to minimise primary data collection requirements by making use of routine health system data sources. Decision-makers’ involvement was ensured by carrying out this work as part of the South African TB Think Tank, although for this proof of concept no systematic stakeholder elicitation method was used and only supply-side constraints were considered.

This analysis demonstrated pragmatically that, as theorised by van Baal and colleagues, human resource constraints should be considered in economic evaluation to avoid producing biased cost-effectiveness estimates (van Baal et al., 2018), as their impact on service outputs is substantial and so are the costs of relieving these constraint by training and deploying additional human resources. Based on the data presented in Chapter 4, South Africa would have to employ between 15% and 25% of its existing nursing workforce on TB to achieve the coverage of intensified TB case-finding required to meet its post-2015 TB targets, an unfeasible ask for an overstretched health system at current staffing levels (Bärnighausen et al., 2016). The costs of hiring and training an equivalent number of nurses to expand the workforce corresponds to 60% of all financial resources currently allocated to TB care.

The approach presented proved feasible within the policy context and timeline and using routinely collected data on human resources, service volumes, financial allocation to infectious disease programmes and coverage of diagnostic services. However, its applicability to different contexts and wider adoption are highly dependent on both local data sources and policy processes. In LMICs that adopted the District Health Information System (DHIS), for example, data on the levels of staffing by facility type and role (e.g. TB nurse) are routinely collected and available upon request for estimating the human resource constraint. These data, however, are not updated every year to reflect staff movements between the public and private sectors or in and out of the workforce. Adjustments have to be made by triangulating with other routine (e.g. annual number of nursing graduates joining the public sector from training institutions or professional councils) and non-routine data sources (e.g. published literature on immigration and on health workforce in the private sector) that might be available in different formats and of varying quality and accessibility in different settings. Applicability and feasibility of the approach is thus positively related to the existence of established planning processes which, in turn, determine availability of relevant, accurate and complete data for priority setting.

7.1.3 Assessing the impact of constraints on cost-effectiveness decision rules

Further expanding on the theoretical framework put forward by van Baal and colleagues (van Baal et al., 2018), Chapter 5 built the constraints estimates developed in the previous chapter into a model-based economic evaluation of TB control interventions, to assess their impact on the ranking of interventions on the cost-effectiveness plane.

The analysis found that, as expected given the magnitude of the constraint's impact and of the costs of relaxing them, there is a substantial difference between the ranking of TB control interventions from an 'unconstrained' analysis and the rankings generated when constraints are included in the model and then relaxed by adding in the costs of specific health system enablers (e.g. training and hiring additional human resources or expanding rules for the procurement of diagnostics).

These results are in line with recommendations by Revill and colleagues (Revill et al., 2018), who applied van Baal's method of adjusting ICERs to reflect the true value of fixed health care inputs to the cost-effectiveness estimation of differentiated ART care in Zimbabwe. The method presented in this thesis builds on the same theoretical framework and expands on its output, by producing information on the full opportunity costs of the constrained inputs (i.e. the costs of relaxing the constraints) in addition to a set of adjusted ICERs. The type of information presented to policymakers is similar to that generated by value of information analyses: ICERs from the 'unconstrained' scenario are equivalent to the expected value of perfect implementation; ICERs from the constrained scenarios are equivalent to the expected value of actual implementation; and ICERs from the 'relaxed' scenario are equivalent to the value of implementation in terms of their significance and value for decision-making (Walker et al., 2014). However, one fundamental difference between the two approaches is that the value of implementation framework is tailored to incremental investment decisions and only considers the implementation activities (enablers) necessary to the specific health technologies under consideration (Faria et al., 2014, Ochalek et al., 2018). The approach presented in Chapter 5, on the other hand, was shown to accommodate enablers that may affect entire platforms (that are, in other words, more than 'implementation activities'), such as increasing the supply of human resources. This approach is thus, in principle, suitable not only for incremental decision-making but also for answering priority setting questions at the sectoral level, on how to balance investment across interventions and enablers. A requirement for this further application of the approach is information on the specific constraints acting at the wider health system level (including those driven by 'software' components) and their dynamic interaction with any new interventions being considered.

7.1.4 Group model building to elicit information on constraints for economic analyses

Chapter 6 explores the use of group model building, a participatory SDM technique, for eliciting information on the dynamic interactions between the health system and interventions from relevant stakeholders, to complement the methods presented in the previous chapters. The technique is successfully used in this application to iteratively cost a set of TB IPC interventions and their enablers, identified by policymakers, health practitioners and patient advocates as the necessary activities to overcome existing constraints to the successful implementation of the core interventions. The cost model built in this way, through repeated engagement with SDM participants to validate assumptions on activity design, input prices and quantities, reflects the true opportunity cost of the interventions by recognising that some of the interventions place higher demands on constrained resources such as nurses' time (including for training and for activities aimed at embedding behaviour change in the work culture and in the modes of care-seeking during interactions with clients).

This development is in line with recent calls not only to develop sounder methods for real-world economic evaluation, as extensively presented in this thesis, but also to consider complexity, a feature both of health care and multi-sectoral interventions and of the health system that delivers them (Greenhalgh and Abimbola, 2019), as an essential feature of evidence generation for public health policy (Chang et al., 2017, Rutter et al., 2017). The pragmatic SDM technique was deemed an appropriate choice for this work, as it allows to explore the linkages and feedback loops between the elements of the system and the interventions that cause the constraints, the possible pathways for acting to relieve the constraints, as well as the role of different actors at the various levels of the health system, who may make decisions at each level based on different criteria (Diaconu et al., 2017). The facilitated inclusion of different categories of stakeholders covering various areas and levels of technical expertise, aimed at building consensus and validating assumptions at multiple stages, may also overcome some of the challenges with interpreting and operationalising findings described with other structured elicitation techniques (Granger Morgan, 2014, Soares et al., 2018). Another advantage of such a locally grounded participatory approach is its ability to maximise local accountability and ownership of the process, as well as accuracy and applicability of the findings, all of which increase the chances that the knowledge generated can be used to improve health (Menzies et al., 2019, Pisani and Kok, 2017, Rehfuess et al., 2016).

Like all constraints elicitation methods, group model building is based on a precise concept of how constraints arise and operate within the health system. As opposed to other elicitation methods such as theories of change or the informal expert consultations used in the approach presented in Chapters 4 and 5, which are based on a static frame of the health system that is affected by incremental change, qualitative system dynamics elicitation intrinsically focuses stakeholders' attention beyond individual constraints to look at complexity and dynamic interactions. This work explores approaches that aim to inform priority setting prospectively, before the constraints 'happen'. By identifying a broader range of constrains and enablers, group model building is unlikely to underestimate the need and magnitude of investments in HSS, as might instead be the case with elicitation methods based on static frames. However, compared to less comprehensive elicitation methods that tend to focus on incremental changes at service level, the work presented in Chapter 6 has shown how qualitative SDM is also more likely to identify enablers that cannot easily be incorporated in quantitative analyses. For example, it may be difficult to accurately measure the costs and effects of above-service level enablers such as improving routine use of information systems, particularly if prospectively, and to correctly allocate these across multiple interventions relying on the platform being strengthened.

7.2 LIMITATIONS AND AREAS FOR FUTURE RESEARCH

Two key areas for further exploration have emerged during the course of this research, that are not addressed within the scope of the thesis.

Firstly, the empirical method for health system constraints estimation presented in Chapter 4 relies on the availability of relevant, accurate, complete and accessible local data sources, a requirement that might not be met in many settings. It is, in fact, more likely that researchers will have access to data of different nature (e.g. from different years or expressed in different units) and of varying quality. In many LMICs, it might be the case that certain data types are not available at all and must be extrapolated from neighbouring countries. While guidance on synthesising knowledge from different sources for health policy decision-making exists, this has historically been fragmentary (Tricco et al., 2016) and does not cover the needs of model-based priority setting and economic analyses parameterisation (Langlois et al., 2018).

Secondly, the focus on complex, multi-layered and multi-level interventions and, particularly, their associated constraints and enablers, highlight the importance of developing methods for collecting and analysing above service-level costs. These costs are often ignored in economic evaluations although their importance for establishing the full opportunity cost of health interventions is increasingly recognised. For example, Sohn and colleagues, who recently developed a conceptual framework for costing intervention implementation in LMICs (Sohn et al., 2020), point out that above-service level costs can account for up to two thirds of the total costs of intervention scale-up, as confirmed by empirical research (Chandrashekar et al., 2014). Aside from issues with cost data availability and with allocating shared HSS costs prospectively across new interventions and existing services, above-service level costs have implications for the choice of analytic time horizon for economic evaluations and for the affordability of interventions requiring a large initial investment in HSS. Even though they might prove cost-effective in the long run, these interventions might be deprioritised by decision-makers.

The inclusion of above service-level costs might also present problems for transmission model-based analyses, as model outputs are usually in the form of service-level units. Lastly, defining the relationship between above service-level costs and intervention scale-up, i.e. the intervention's cost function, is another crucial aspect for model-based priority setting, as it also impacts resource allocation decisions based on the cost-effectiveness and affordability criteria.

7.3 CONCLUSIONS

In conclusion, the analytic frame and empirical proof of concept tested in Chapters 4 and 5 prove that it is possible to incorporate feasibility, defined as the dynamic interaction between the intervention and the context, within the economic evaluation framework. This approach is preferable to the adjustment proposed by van Baal and colleagues in that it provides decision makers with additional information on the costs of relaxing existing constraints. It is also preferable to the value of information framework for considering constraints and enablers that have a sectoral impact rather than only an incremental impact on individual intervention effects. Qualitative SDM is the elicitation method that is best suited to complement the proposed approach for considering feasibility in economic analysis, as it allows for the identification and operationalisation of dynamic interactions. However, it is also likely to identify high level health system constraints that are difficult to incorporate in quantitative analyses. Information on these constraints might be best presented to decisionmakers (a) alongside, but externally to cost-effectiveness analysis results, as in more standard qualitative MCDA applications; or (b) in the form of disease transmission model 'exemplary' scenarios where intervention effects (but not costs) are restricted, as was often done in the model-based priority setting exercises reviewed in Chapter 3.

REFERENCES

BALTUSSEN, R., JANSEN, M. P., MIKKELSEN, E., TROMP, N., HONTELEZ, J., BIJLMAKERS, L. & VAN DER WILT, G. J. 2016. Priority setting for Universal Health Coverage: We need evidence-informed deliberative processes, not just more evidence on cost-effectiveness. *Int J Health Policy Manag,* 5**,** 615-618.

BÄRNIGHAUSEN, T., BLOOM, D. E. & HUMAIR, S. 2016. Human resources for treating HIV/AIDS: Are the preventive effects of antiretroviral treatment a game changer? *PLoS ONE,* 11 (10) (no pagination). http://dx.doi.org/10.1371/journal.pone.0163960.

BEGON, M., BENNETT, M., BOWERS, R. G., FRENCH, N. P., HAZEL, S. M. & TURNER, J. 2002. A clarification of transmission terms in host-microparasite models: numbers, densities and areas. *Epidemiol Infect,* 129**,** 147-53. 10.1017/s0950268802007148.

CHANDRASHEKAR, S., GUINNESS, L., PICKLES, M., SHETTY, G. Y., ALARY, M., VICKERMAN, P., GROUP, C.-E. & VASSALL, A. 2014. The costs of scaling up HIV prevention for high risk groups: lessons learned from the Avahan Programme in India. *PLoS One,* 9**,** e106582. 10.1371/journal.pone.0106582.

CHANG, A. Y., OGBUOJI, O., ATUN, R. & VERGUET, S. 2017. Dynamic modeling approaches to characterize the functioning of health systems: A systematic review of the literature. *Soc Sci Med,* 194**,** 160-167. 10.1016/j.socscimed.2017.09.005.

DANIELS, N. & SABIN, J. E. 2008. Accountability for reasonableness: an update. *BMJ,* 337**,** a1850. 10.1136/bmj.a1850.

DIACONU, K., CHEN, Y.-F., CUMMINS, C., JIMENEZ MOYAO, G., MANASEKI-HOLLAND, S. & LILFORD, P. 2017. Methods for medical device and equipment procurement and prioritization within low- and middle-income countries: findings of a systematic review. *Globalization and Health,* 13.

FARIA, R., WALKER, S., WHYTE, S., DIXON, S., PALMER, S. & SCULPHER, M. 2014. Getting cost-effective technologies into practice: the value of implementation. An application to novel anticoagulants in the prevention of stroke and systemic embolism. Policy Research Unit in Economic Evaluation of Health & Care Interventions (EEPRU).

GRANGER MORGAN, M. 2014. Use (and abuse) of expert elicitation in support of decision making for public policy. *PNAS,* 111**,** 7176-7184. 10.1073/pnas.1319946111/-/DCSupplemental.

GREENHALGH, T. & ABIMBOLA, S. 2019. The NASSS Framework - A Synthesis of Multiple Theories of Technology Implementation. *Stud Health Technol Inform,* 263**,** 193-204. 10.3233/SHTI190123.

HAUCK, K., MORTON, A., CHALKIDOU, K., CHI, Y. L., CULYER, A., LEVIN, C., MEACOCK, R., OVER, M., THOMAS, R., VASSALL, A., VERGUET, S. & SMITH, P. C. 2019. How can we evaluate the cost-effectiveness of health system strengthening? A typology and illustrations. *Soc Sci Med,* 220**,** 141-149.

HAUCK, K., THOMAS, R. & SMITH, P. C. 2016. Departures from cost-effectiveness recommendations: The impact of health system constraints on priority setting. *Health Systems & Reform,* 2**,** 61-70.

KARSU, O. & MORTON, A. 2021. Trading off health and financial protection benefits with multiobjective optimization. *Health Econ,* 30**,** 55-69. 10.1002/hec.4176.

LANGLOIS, E. V., DANIELS, K. & AKL, E. A. (eds.) 2018. *Evidence synthesis for health policy and systems: a methods guide,* World Health Organization.

MENZIES, N. A., MCQUAID, C. F., GOMEZ, G. B., SIROKA, A., GLAZIOU, P., FLOYD, K., WHITE, R. G. & HOUBEN, R. M. G. J. 2019. Improving the quality of modelling evidence used for tuberculosis policy evaluation. *Int J Tuberc Lung Dis,* 23**,** 387-395.

MIKKELSEN, E., HONTELEZ, J. A. C., JANSEN, M. P. M., BÄRNIGHAUSEN, T., HAUCK, K., JOHANSSON, K. A., MEYER-RATH G., OVER, M., DE VLAS, S. J., VAN DER WILT, G. J., TROMP, N., BIJLMAKERS, L. & BALTUSSEN, R. M. P. M. 2017. Evidence for scaling up HIV treatment in sub-Saharan Africa: A call for incorporating health systems constraints. *PLoS Med,* 14**,** e1002240.

MORTON, A., THOMAS, R. & SMITH, P. C. 2016. Decision rules for allocation of finances to health systems strengthening. *J Health Econ,* 49**,** 97-108.

OCHALEK, J., REVILL, P., MANTHALU, G., MCGUIRE, F., NKHOMA, D., ROLLINGER, A., SCULPHER, M. & CLAXTON, K. 2018. Supporting the development of a health benefits package in Malawi. *BMJ Glob Health,* 3**,** e000607. 10.1136/bmjgh-2017-000607.

PISANI, E. & KOK, M. 2017. In the eye of the beholder: to make global health estimates useful, make them more socially robust. *Glob Health Action,* 10.

REHFUESS, E. A., DURAO, S., KYAMANYWA, P., MEERPOHL, J. J., YOUNG, T., ROHWER, A. & CONSORTIUM, C. 2016. An approach for setting evidence-based and stakeholder-informed research priorities in low- and middle-income countries. *Bull World Health Organ,* 94**,** 297-305. 10.2471/BLT.15.162966.

REVILL, P., WALKER, S., CAMBIANO, V., PHILLIPS, A. & SCULPHER, M. J. 2018. Reflecting the real value of health care resources in modelling and cost-effectiveness studies - The example of viral load informed differentiated care. *PLoS One,* 13**,** e0190283.

RUTTER, H., SAVONA, N., GLONTI, K., BIBBY, J., CUMMINS, S., FINEGOOD, D. T., GREAVES, F., HARPER, L., HAWE, P., MOORE, L., PETTICREW, M., REHFUESS, E., SHIELL, A., THOMAS, J. & WHITE, M. 2017. The need for a complex systems model of evidence for public health. *Lancet,* 390**,** 2602-2604. 10.1016/S0140-6736(17)31267-9.

SOARES, M. O., SHARPLES, L., MORTON, A., CLAXTON, K. & BOJKE, L. 2018. Experiences of Structured Elicitation for Model-Based Cost-Effectiveness Analyses. *Value Health,* 21**,** 715-723. 10.1016/j.jval.2018.01.019.

SOHN, H., TUCKER, A., FERGUSON, O., GOMES, I. & DOWDY, D. 2020. Costing the implementation of public health interventions in resource-limited settings: a conceptual framework. *Implement Sci,* 15**,** 86. 10.1186/s13012-020-01047-2.

TRAUER, J. M., DENHOLM, J. T. & MCBRYDE, E. S. 2014. Construction of a mathematical model for tuberculosis transmission in highly endemic regions of the Asia-pacific. *J Theor Biol,* 358**,** 78-84.

TRICCO, A. C., SOOBIAH, C., ANTONY, J., COGO, E., MACDONALD, H., LILLIE, E., TRAN, J., D'SOUZA, J., HUI, W., PERRIER, L., WELCH, V., HORSLEY, T., STRAUS, S. E. & KASTNER, M. 2016. A scoping review identifies multiple emerging knowledge synthesis methods, but few studies operationalize the method. *J Clin Epidemiol,* 73**,** 19-28. 10.1016/j.jclinepi.2015.08.030.

VAN BAAL, P., MORTON, A. & SEVERENS, J. L. 2018. Health care input constraints and cost effectiveness analysis decision rules. *Soc Sci Med,* 200**,** 59-64. 10.1016/j.socscimed.2018.01.026.

VASSALL, A., BOZZANI, F. & HANSON, K. 2019. Considering Health-Systems Constraints in Economic Evaluation in Low- and Middle-Income Settings. *Oxford Research Encyclopaedias*

WALKER, S., FARIA, R., WHYTE, S., DIXON, S., PALMER, S. & SCULPHER, M. 2014. Getting cost-effective technologies into practice: the value of implementation. Report on framework for valuing implementation initiatives. Policy Research Unit in Economic Evaluation of Health & Care Interventions (EEPRU).