Impact assessment of new tuberculosis diagnostic tools and algorithms to support policy makers in low and middle income countries:

An innovative modelling approach

by

Ivor Langley

Submitted for consideration for the degree of
Doctor of Philosophy by published work

Health Sciences
Warwick Medical School
University of Warwick

June 2016

CONTENTS

List of illustrations and tables

Figures

Tables

Acknowledgements

I would like to thank all those who have supported me during the studies described in this document. In particular the TREAT TB initiative that has funded this research through the United States Agency for International Development (USAID) and led by the International Union Against Tuberculosis and Lung Disease. Especially I express my gratitude to Professor Bertie Squire of the Liverpool School of Tropical Medicine who had the amazing foresight to see how someone who has worked most of their career in manufacturing, retail and financial services could contribute to tuberculosis research in sub-Saharan Africa. None of this would have been possible without his imaginative and generous support. Thank you to all the co-authors of the publications submitted here, in particular Dr Hsien-Ho Lin of the National University of Taiwan who took the lead role in the transmission modelling components of these studies. I thank the National TB programme in Tanzania for their unstinting support and hospitality on my many trips to Dar es Salaam – in particular Basra Doulla the head of the Central TB reference Laboratory. I thank Dr Jason Madan of the University of Warwick for his insightful guidance and support as supervisor of my PhD studies. I also thank my wife, Liz, for being prepared to back me in what seemed 5 years ago an amazing leap into the unknown. Finally I thank God who has been, and continues to be, my constant provider and inspiration – "***It's in Christ that we find out who we are and what we are living for. Long before we first heard of Christ and got our hopes up, he had his eye on us, had designs on us for glorious living, part of the overall purpose he is working out in everything and everyone***" [Pauls letter to the Ephesians, Chapter 1, Verses 11-12 in The Message version of the Bible, NavPress Publishing Group].

Submission declaration

I declare that the submitted material as a whole is not substantially the same as published or unpublished material that I have previously submitted, or am currently submitting, for a degree, diploma, or similar qualification at any university or similar institution. No parts of the works have been submitted previously for any aforementioned qualification.

List of publications

A list of the 5 papers submitted are shown below alongside a brief description.

Title of Paper	First Author	Co-authors	Publication and Date	Description
A modelling framework to support the selection and implementation of new tuberculosis diagnostic tools [1]	Hsien-Ho Lin **Ivor Langley** (N.B. HHL and IL contributed equally in the writing of this article)	R. Mwenda B. Doulla S. Egwaga K.A. Millington G.H. Mann M. Murray S.B. Squire T. Cohen	International Journal Against Lung Diseases and Tuberculosis August 2011	Explores the feasibility of linked operational and transmission modelling for the impact assessment of new tuberculosis diagnostic algorithms in the developing world
Modelling the impacts of new diagnostic tools for tuberculosis in developing countries to enhance policy decisions [2]	**Ivor Langley**	B. Doulla H-H Lin K.A. Millington S.B Squire	Health Care Management Science September 2012	Demonstrates how an operational model of tuberculosis diagnostics could assist in policy development in the developing world.
Assessment of the patient, health system, and population effects of Xpert MTB/RIF and alternative diagnostics for tuberculosis in Tanzania: an integrated modelling approach [3]	**Ivor Langley**	H-H. Lin S. Egwaga B. Doulla C-C Ku M. Murray T. Cohen S.B. Squire	Lancet – Global Health October 2014	Uses a linked operational and transmission model to evaluate alternative new tuberculosis diagnostic algorithms in Tanzania and identifies cost-effective options for scale-up.
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 [4]	**Ivor Langley**	E. Adams B. Doulla S.B. Squire	Parasitology December 2014	Reviews the operational modelling approach used for impact assessment in tuberculosis and how it might be used in other disease areas such as human parasitic diseases.
Developments in Impact Assessment of New Diagnostic Algorithms for Tuberculosis Control [5]	**Ivor Langley**	S. B Squire R. Dacombe J. Madan J.R. Lapa eSilva D. Barreira R. Galliez M.M. Oliveira P.I. Fujiwara A. Kritski	Clinical Infectious Diseases October 2015	Reviews experiences from using the Impact Assessment Framework[6] and linked modelling to assess and revise the framework for tuberculosis diagnostics.

The contribution of the author of this thesis (Ivor Langley) to each of these studies is detailed in Appendix A. The way the five publications are linked to each other and to two earlier publications[6, 7] is detailed in the SUMMARY OF STUDIES section.

Word Count

Summary:	566
Background:	2,365
Summary of the publications:	3,178
Discussion:	3,441
Conclusion:	218
Total:	9,768

List of Abbreviations and Definitions

95% CrI	95% Credible Interval
ACER	Average Cost-Effectiveness Ratio, a comparison of cost per DALY averted compared to the base case.
aNAAT	Automated Nucleic Acid Amplification Test, such as Xpert
ART	Antiretroviral Therapy for HIV
Bacteriologically confirmed TB case	A TB case from whom a biological specimen is positive by smear microscopy, culture or WRD (such as Xpert MTB/RIF).
Catastrophic costs	Healthcare and related costs incurred by patients that place excessive burdens on the patient households.
Clinically diagnosed TB case	A TB case that does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner for TB treatment.
DALY	Disability Adjusted Life Year (number of years lost due to ill-health, disability or early death)
DES	Discrete Event Simulation (Note: WITNESS software can be used to build DES models)
Defaulters	See LTFU
DOT	Directly Observed Treatment
End TB Strategy	WHO's global strategy and targets for TB prevention, care and control after 2015
HAT	Human African Trypanosomiasis
HIV	Human Immune-deficiency Virus
IAF	Impact Assessment Framework
ICER	Incremental Cost-Effectiveness Ratio (incremental costs divided by incremental DALYs averted) to compare one option with the next less-effective option
LAMP	Loop-mediated isothermal AMPlification
LED	Light Emitting Diode fluorescence microscopy
LMIC	Low and Middle Income Countries

LTFU	Lost to follow up – patients who do not complete diagnosis (diagnostic LTFU) or treatment (treatment LTFU) – sometimes referred to as defaulters
MDR-TB	Multi-Drug Resistant TB (resistance to at least isoniazid and rifampicin).
NTP	National TB Programme
NTLP	National TB and Leprosy Programme (Tanzania)
Presumptive TB case	A patient who presents with symptoms or signs suggestive of TB (synonym – TB suspect)
Pulmonary TB	Any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree
RDT	Rapid Diagnostic Test
Same-day LED	LED fluorescence microscopy with two samples collected on the same day
Sensitivity of a diagnostic test	Proportion of people who test positive for the disease (e.g. TB) among those who have the disease
Specificity of a diagnostic test	Proportion of patients who do not have the disease (e.g. TB) that test negative
Smear-negative TB case	Individuals who are tested negative for TB by sputum smear microscopy
Smear-positive TB case	Individuals who are tested positive for TB by sputum smear microscopy
STH	Soil Transmitted Helminths
TB	Tuberculosis
TB case	Individual diagnosed to receive TB treatment
TB suspects	See Presumptive TB case
US$	Financial values are given in United States of America dollars
WHO	World Health Organization
WRD	WHO-approved Rapid Diagnostic
Xpert	The Xpert® MTB/RIF test for TB and rifampicin resistance - Cepheid, Sunnyvale, CA, USA
ZN	Ziehl Neelsen Microscopy

SUMMARY

Background - In many low and middle income countries the infectious disease tuberculosis is a leading and persistent cause of death, sickness and hardship. This is despite an effective and readily available treatment regimen. Better diagnostics and more rapid initiation of patients onto treatment is essential if the high burden of tuberculosis in these settings is to be substantially reduced, as there is currently no effective vaccine. There is an encouraging pipeline of improved diagnostic tools and algorithms being developed, some of which have been endorsed by the World Health Organization (e.g. Xpert MTB/RIF). These new diagnostic tools have the potential to overcome many of the weaknesses of the present processes, however they might substantially increase the demands on scarce resources and funds. In addition, whether these new diagnostics should replace existing methods or be used in combination with them is unclear. Before national tuberculosis programmes can scale-up new diagnostics, policy makers need to understand the effects on patients, the health system, and the wider population. Failure to do so could lead to poor performance outcomes, unsustainable implementation, and wasted resources.

Methods - An innovative linked modelling approach is proposed that brings together detailed operational models of patient pathways with transmission models to provide the comprehensive projections required. The studies that make up this research first explore the concept of linked modelling, then in the second study develop a detailed operational model incorporating cost-effectiveness analysis. The third study uses the linked modelling approach to explore eight alternative diagnostic algorithms in Tanzania. It provides comprehensive projections of patient, health system and community impacts including cost-effectiveness analysis, from which the national tuberculosis programme can develop a strategy for scale-up of new diagnostics across the country. Having shown how the approach of linked operational and transmission modelling can assist policy makers, the fourth and fifth studies review the process of impact assessment and recommend how it

can be improved, and how the lessons from this research in tuberculosis diagnostics might apply to other health decisions in low and middle income countries.

Findings - The linked modelling approach is feasible and relevant in supporting rational decision making for tuberculosis diagnostics in low and middle income countries. The results from using the approach in Tanzania show that full scale-up of Xpert MTB/RIF is a cost-effective option with an incremental cost-effectiveness ratio of US$169 per DALY averted (95% credible interval, 104–265), and has the potential to significantly reduce the national tuberculosis burden. Substantial levels of funding would need to be mobilised to translate this into clinical practice. In the context of Tanzania, targeting Xpert MTB/RIF to HIV-positive patients only, was not cost-effective compared to rollout of LED fluorescence microscopy with two samples collected on the same day. Review of the Impact Assessment Framework and operational modelling used in these studies found the approaches had many other potential applications, for example for decisions around human parasitic disease diagnostics and tuberculosis treatment.

Interpretation - In Tanzania full scale-up of Xpert MTB/RIF should be progressed in districts where resources and funding are available. LED fluorescence microscopy using two samples collected on the same day should be considered in other districts. Tuberculosis programmes should use the operational modelling approach to prioritise the implementation of new diagnostics by district. The operational and linked operational and transmission modelling approaches have many other potential applications in other contexts and disease areas and these should be further researched.

BACKGROUND

Overview of Tuberculosis Worldwide in 2014

The World Health Organization (WHO) estimates 1.5 million people died in 2014 as a result of Tuberculosis (TB), meaning that TB now ranks alongside human immune-deficiency virus (HIV) as the world's leading cause of death from an infectious disease. 9.6 million individuals became sick with TB in 2014, of these 1.2 million were co-infected with HIV. The majority (85%) of TB cases reported are pulmonary TB.[8]

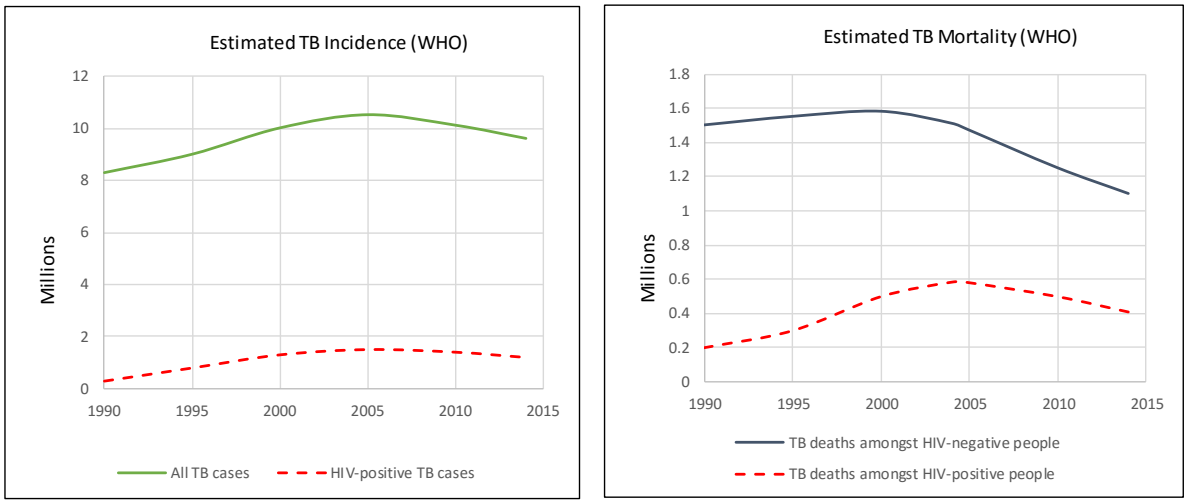


Figure 1 – Trends in estimated global TB incidence and mortality 1990-2015[8]

Some improvements in TB incidence and mortality levels as a result of TB have been observed over the last 10 years (Figure 1), however the levels remain very high particularly in sub-Saharan Africa, the Indian sub-continent and some parts of Asia (Figure 2). In addition there has been a rise of drug resistant TB, in particular resistance to both isoniazid and rifampicin (known as multi-drug resistant TB (MDR-TB)) which is a growing concern in many parts of the world.

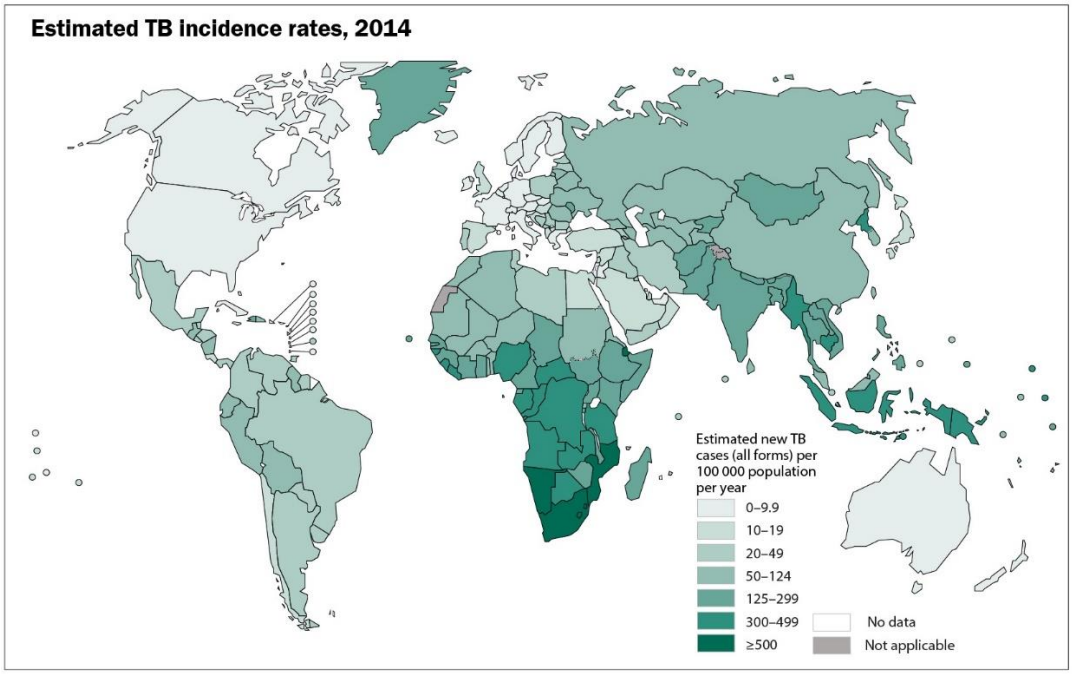


Figure 2 – Estimated TB incidence in 2014[8]

It is essential that the barriers to prevention of infection, rapid case detection and initiation and completion of appropriate treatment are addressed if the global goals of reducing incidence and death rates from TB by 90% and 95% respectively are to be achieved by 2035, as targeted by the WHO in the End TB strategy[9]. Critical to this is the availability and use of accurate and rapid diagnostics for TB and MDR-TB[10]; this is the focus and context of this body of research.

TB Diagnosis and the patient pathway

The most frequently used diagnostic tool in the developing world, where the burden of TB is highest, is sputum smear microscopy. A typical diagnostic pathway for an individual who becomes sick with symptoms consistent with TB is shown in Figure 3[2]. Once an individual has been identified as someone who may have TB and requires diagnostic testing (known as a presumptive TB case)[11], they will be directed to a health facility where sputum will be collected. If smear microscopy is to be used as the diagnostic test, the individual will typically be asked to return the next day to provide a second sputum sample (in some countries a third sample may be required)[12]. The individual will then generally go home and

return at a later date to receive diagnosis. The sputum will be tested in a laboratory at the diagnostic facility where the turnaround time for tests is likely to be 1 to 3 days.

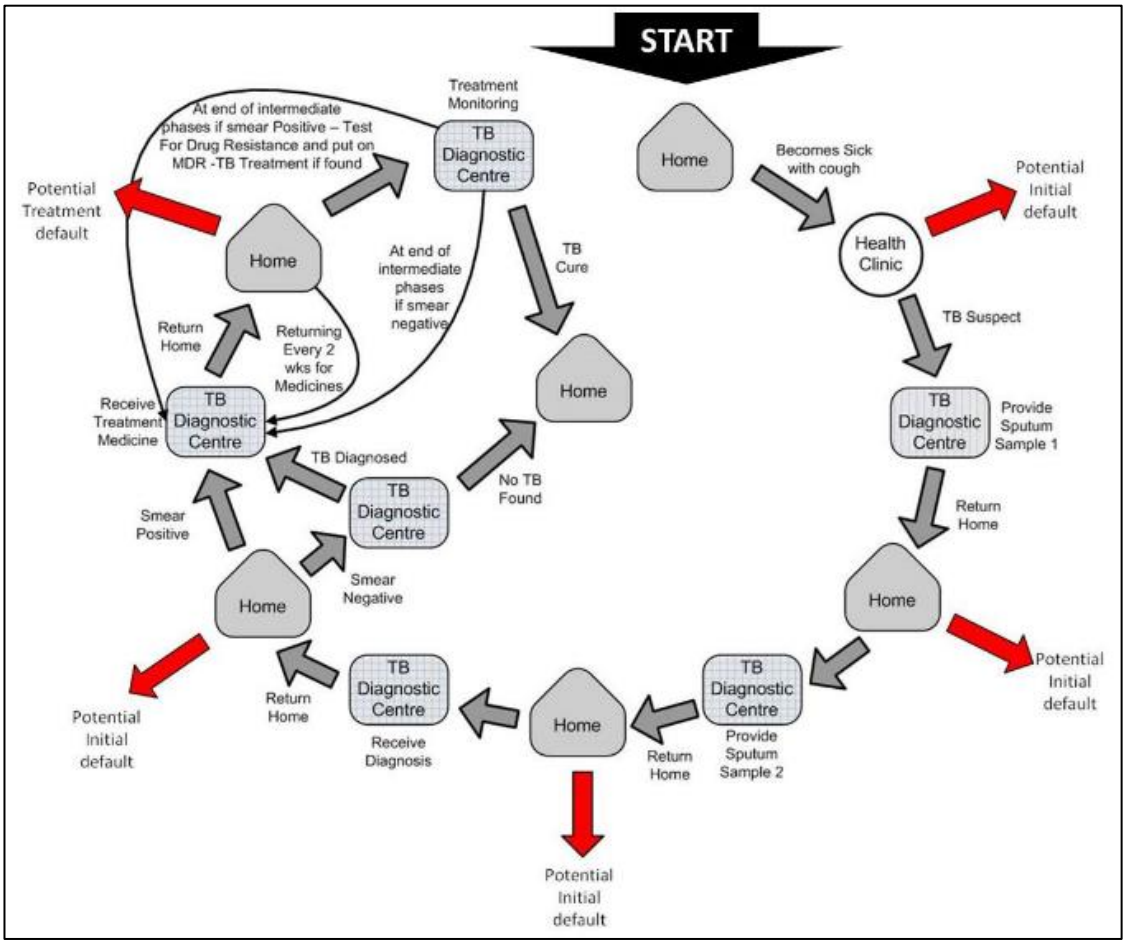


Figure 3 Typical diagnostic pathway for an individual with pulmonary TB symptoms (e.g. Tanzania) [2]

A positive test will mean the individual is identified as a smear-positive (or bacteriologically confirmed) TB case. Treatment may be initiated immediately after a positive test, or the individual may be required to return another day (or to another facility) so that they, along with a supporter, can receive guidance on the importance of treatment adherence and monitoring. The supporter may be a member of the family or a community health worker whose role is to improve treatment adherence by observing the patient taking their medication daily. This process is known as Directly Observed Treatment (DOT)[13] and helps to ensure patients complete the full course of treatment.

Some microscopy tests will be negative, but the individual will still exhibit TB symptoms. In these cases the individual will be asked to visit a facility that can conduct an X-ray and potentially will also be prescribed a short course of broad spectrum antibiotics. If symptoms persist and the X-ray is consistent with TB, the individual may be diagnosed by the clinician and initiated onto TB treatment – these are smear-negative (or clinically diagnosed) TB cases and represent around 42% of pulmonary TB cases worldwide[8].

TB cases typically return to the diagnostic centre or health clinic every 2 weeks for more drugs and treatment monitoring. At key intervals the monitoring will also involve sputum smear microscopy to assess treatment effectiveness (typically at 2 months, 5 months and 6 months)[14].

For MDR-TB the diagnostic and treatment process is much longer. Diagnosis is likely to involve culture and drug sensitivity testing typically taking 6-12 weeks and if drug resistance is diagnosed the duration of treatment will extend to 18-24 months[14].

Issues associated with the diagnostic tools and the patient pathway for TB

In the developing world individuals can often find it difficult and expensive to access diagnosis for TB[15, 16]. This results in delayed diagnosis and treatment initiation which risks transmission of TB to a larger circle of contacts[17]. Figure 3 illustrates where some patients drop out of the diagnostic or treatment process and become lost to follow up (LTFU). LTFU during the diagnostic process is critical as it results in many individuals with TB symptoms not starting on TB treatment and continuing to transmit the disease. Despite TB diagnosis and drug treatment usually being provided free (even in the poorest countries), the need for repeated visits to a diagnostic facility, hospital, or health clinic which may be many miles from home can result in significant and sometimes catastrophic costs for the individual[18, 19]. In this environment high levels of LTFU are common and account for 10-20% of the presumptive TB cases[20].

There are principally two barriers associated with the most frequently used diagnostic tools and algorithms in high burden developing countries, such as those in sub-Saharan Africa. These are the accuracy of diagnosis and the time (and related patient cost) associated with completing the diagnostic process and starting treatment.

Accuracy - Boehme *et al.*[21] observed in a study from 6 countries (Peru, Azerbaijan, Uganda, South Africa, India, and Philippines) that sputum smear microscopy had a sensitivity of 72.3% (69.2, 75.2) in HIV-negative individuals or when HIV status was unknown. This fell to 44.6% (37.7, 51.6) in HIV-positive individuals. Specificity was high at 100% (99.4, 100) for HIV-negative and unknown status, and 99.4% (99.1, 99.6) for HIV-positive status. These figures are consistent with systematic reviews[22, 23]. The low sensitivity of smear microscopy, particularly for HIV-positive individuals, leads to the high levels of clinically diagnosed TB. Without clinical diagnosis many individuals with active TB would not receive treatment. There is little published evidence on the accuracy of clinical diagnosis for TB, but where it does exist the evidence suggests that there are many cases where patients without TB are placed on TB treatment (false positive)[24]. This is partly due to the relatively low specificity of X-ray for TB. A culture of the sputum is usually only ordered in sub-Saharan Africa if there is a high risk of MDR-TB.

Time - The time from sputum collection to initiation of TB treatment for smear-positive cases will vary with individual and context. Boehme *et al*[21] found a mean time of 6.6 days with a median of 4 days. This time is in addition to the time an individual spends getting to the point where a TB test is ordered, which could be many weeks[15]. For smear-negative TB the delay in starting treatment is likely to be even longer, and in the Boehme *et al*[21] study the mean time was 67 days and

the median 56 days. This delay and the frequent visits required to health facilities results in increased LTFU, continued transmission, extended morbidity and potentially high costs to patients[15, 16, 20].

TB diagnosis research

Investment in research has resulted in promising new tools and modifications of existing algorithms for the diagnosis of TB and MDR-TB which could address the barriers of low accuracy and delays to diagnosis. For example, the WHO have endorsed in recent years the use of LED fluorescence microscopy[25], same day sputum collection[26], Xpert MTB/RIF (Xpert)[27], Line Probe Assay (LPA) [28], liquid culture approaches (e.g. MGIT 960)[29] and most recently in very restricted cases a lateral flow urine lipoarabinomannan assay (LF-LAM)[30]. Xpert in particular has had a big influence on TB control programmes since first being endorsed by the WHO in 2011[31], primarily for HIV-positive patients and those with suspected drug resistance. This endorsement has since been broadened and now includes all adults and children suspected of having pulmonary and extrapulmonary TB[27].

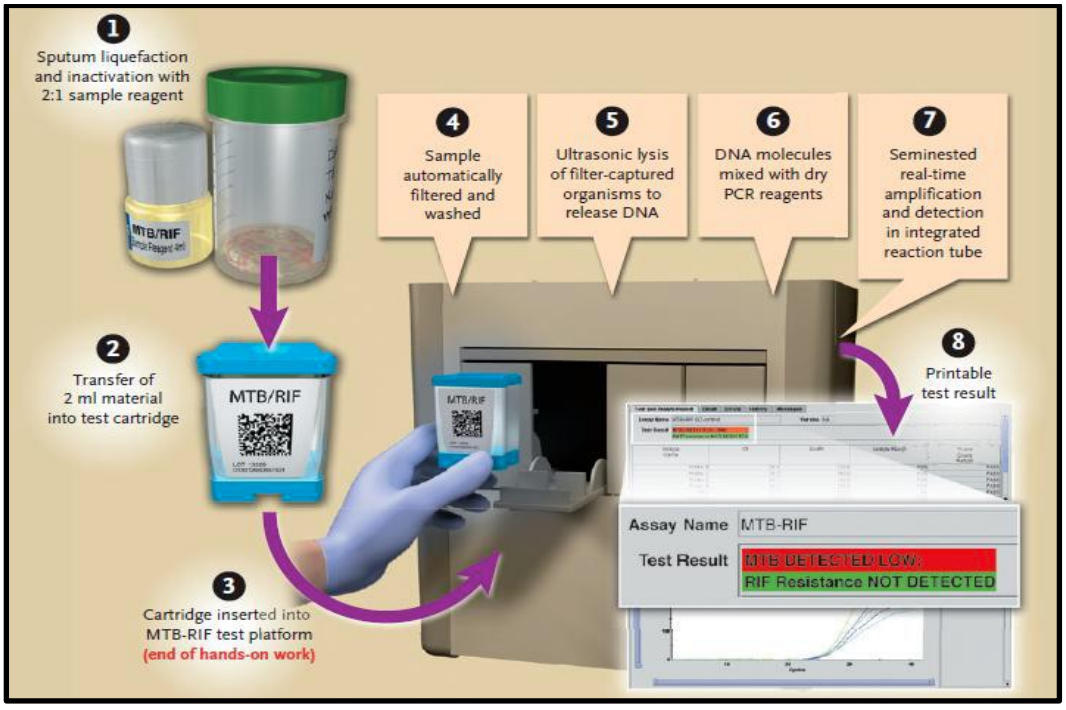


Figure 4: Assay Procedure for Xpert MTB/RIF[32]

Xpert is a molecular assay (see Figure 4) that can identify *Mycobacterium tuberculosis* and resistance to one of the key drugs used in standard treatment, rifampicin. Trials of Xpert have shown improved accuracy and accelerated time to appropriate diagnosis in comparison to smear microscopy[21]. Many countries are looking to rollout Xpert, and South Africa[33] in particular has achieved greatest coverage. However concerns about the cost of the device and test cartridges has been a barrier to wider implementation in some countries. In addition, there are other issues such as the need for a reliable power supply, questions on where to site the devices and which cases to target, that have delayed scale-up. There are improvements to Xpert and many other new diagnostic tools that are currently under development and testing, for example the Xpert Ultra cartridge, Genedrive MTB/RIF, TBDx and TB LAMP[10].

Impact Assessment for new TB diagnostic tools and algorithms

The WHO has focused on obtaining robust data on test accuracy and using a systematic approach (GRADE)[34] to appraise and develop guidelines for implementation of new tools. However, many authors have indicated that more work is needed to go beyond test accuracy in order to promote rational, evidence-based decision-making on scale-up and implementation[35, 36].

An impact assessment framework (IAF)[6] (Table 1) to support decision making on new diagnostics by linking evidence on inputs to outcomes was proposed, followed by further calls for more work beyond accuracy[37]. This recognises that decision-makers need a lot more information than just the scientific performance of a test in idealistic conditions. They also need to understand the operational and pragmatic impacts of implementation in combination with existing and other new tests. There has also been recognition that new TB diagnostics are not implemented in isolation, but are always part of an algorithm that operates in conjunction with other diagnostic approaches, such as clinical judgement or

radiology[39]. Policy makers choosing between diagnostic strategies need evidence on what is the best combination of tools for their context, which tools should be used for which patients and whether the new tools replace or are used in combination with existing tools. A flexible, practical and rapidly implementable methodology is needed which is applicable to developing countries and usable by the TB control community within different health systems. This could then be used to evaluate impact on patients, health systems and the wider community in order to provide evidence to support national policy decisions. This is where computer based decision analytic modelling can assist, but the approach needed must take account of the local operational and epidemiological context to be most useful.

Table 1 – The Impact Assessment Framework (IAF)[6]

Layer of Assessment	**Example questions that need addressing in understanding impacts of new diagnostics for TB**
Layer 1: EFFECTIVENESS ANALYSIS	How well does the new tool work in terms of accuracy? How many additional cases will be identified? How many additional cases will actually start treatment? What will happen to the time from presentation to starting treatment?
Layer 2: EQUITY ANALYSIS	Who benefits from the new tool? (e.g. poor/less poor, adults/children) Why do these benefits accrue? (e.g. change time to issue of results)
Layer 3: HEALTH SYSTEM ANALYSIS	What are the human resource implications? What are the infrastructure implications?
Layer 4: SCALE-UP ANALYSIS	What are the projected impacts of going to scale with the new tool? e.g. a) cost savings to patients in relation to income b) cost savings to health providers / the health system c) effects on transmission
Layer 5: POLICY ANALYSIS	What other similar technologies are available or likely to become available? How do similar existing or emerging technologies compare?

Modelling TB diagnostic algorithms

Computer based decision analytic modelling is increasingly being used in the developed world to evaluate alternative health care technologies[40, 41]. Frequently this includes taking into account budget constraints alongside projecting resource needs and health outcomes.

The approach can bring together global experience of new technologies with detailed national or provincial data to provide policy makers with the evidence they need to support rational decisions.

Modelling of TB has in the past focused mainly on high level dynamic epidemiological models of disease transmission[42-45]. These models typically project incidence, prevalence and mortality outcomes of interventions, but do not take account of the local patient pathways and operational constraints that exist within all health systems and especially in developing countries. In order to promote rational, evidence-based decision-making on implementation it is vital for national policy makers to consider and evaluate the health system process in relation to TB diagnosis and to have projections on the performance of the health system, health system budgets and patient impacts. The operational modelling approach (discrete event simulation[46, 47] or DES) used extensively in the developed world to model proposed changes in health care facilities[48] and other environments such as manufacturing processes[49] and retail outlets[50], could potentially provide the missing level of detail required by national TB policy makers in developing countries. DES is a very flexible approach that could be used to address many policy related questions like those proposed by the IAF. It would enable patient pathways to be modelled in detail, including each significant event a patient experiences within the pathway. Interaction with staffing and other patients that result in queuing and potential bottlenecks[47]would be modelled. In DES there are five key elements that make up the model, these are:

1. **Entities** representing people or objects moving around a process (e.g. patients, samples)
2. **Attributes** associated with entities (e.g. age, gender, HIV status)
3. **Queues** representing waiting areas for entities (e.g. waiting rooms)
4. **Activities** where actions take place (e.g. sputum collection).
5. **Resources** required to complete an activity (e.g. laboratory technician)

If an operational DES model of the patient pathways to diagnosis and treatment could be linked with an epidemiological model of the transmission dynamics of TB, then all the key patient, health system and transmission impacts of changes in diagnostic technology and algorithms could potentially be projected. Data collated from the context of interest could be used to populate the model and would enable many of the questions posed in the IAF (Table 1) to be addressed to support policy decisions in the context of interest.

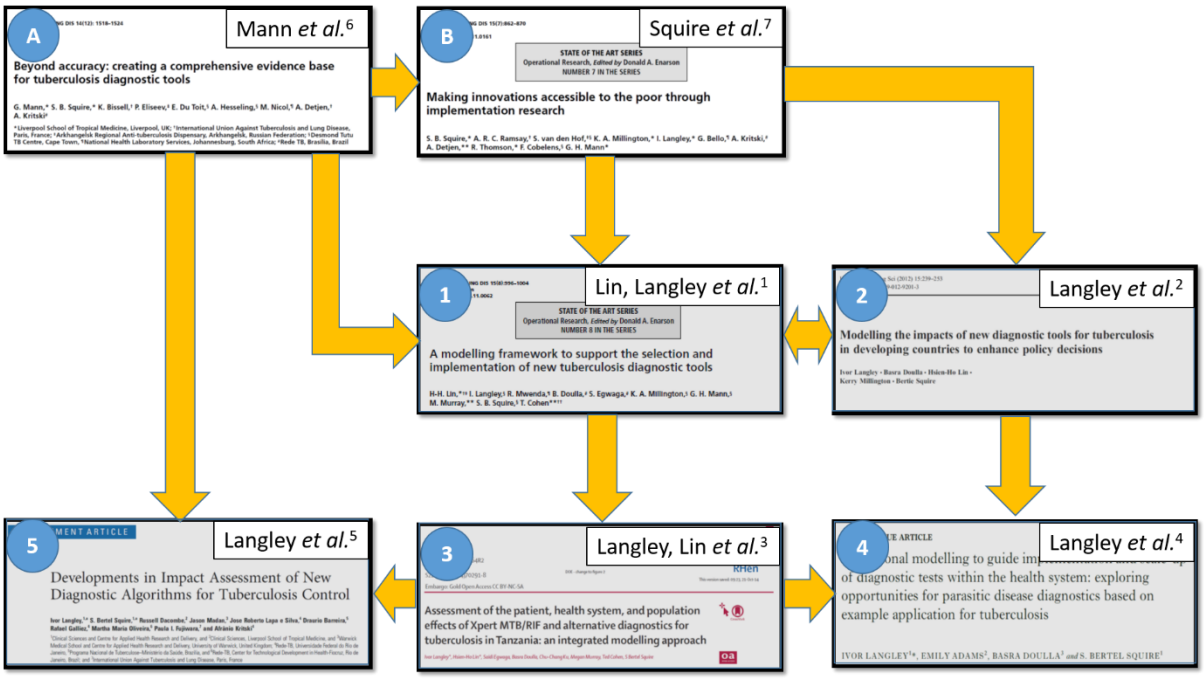
The research studies

This portfolio of research studies contributes to original knowledge by exploring the feasibility and use of the new and innovative approach of linked operational and transmission modelling to support the selection and implementation of new tuberculosis diagnostic tools in the developing world[1, 3]. For the first time, an operational model of patient pathways incorporating cost-effectiveness analysis is used to study alternative TB diagnostics in sub-Saharan Africa[2]. The linked modelling approach is used to evaluate the scale-up of new diagnostic algorithms in Tanzania providing a methodology and the information required by the national TB programme to develop a comprehensive strategy for new TB diagnostics[3]. The modelling approach is reviewed to see if it might be used in other disease areas such as human parasitic diseases[4]. Finally, alongside additional studies carried out by the author in Brazil and Ethiopia, the Impact Assessment Framework is reviewed[5].

SUMMARY OF STUDIES

Linking the Publications

The five studies in this body of research are linked to each other and two earlier studies as shown in Figure 5. The two earlier publications by Mann *et al.* [6] (Paper A) and Squire *et al*.[7] (Paper B), in part inspired the five publications described (Papers 1 to 5). Paper A[6] proposed an Impact Assessment Framework (IAF) for tuberculosis diagnostics as a tool to generate the questions that policy makers need to consider about which new diagnostic algorithms to implement. Paper B[7] identified the need for a new approach to address many of these questions.



N.B. Grey boxes refer to the publications for the studies submitted in this thesis. The white boxes refer to two publications that in part inspired this overall body of work.

Figure 5 – Linking the publications

Paper 1[1] develops the innovative concept of linked operational and transmission modelling of tuberculosis mentioned in paper B[7] to address many of the issues raised by the IAF for TB diagnostics described in paper A[6]. Paper 2[2] describes and uses an operational model of TB diagnostics for the first time in the developing world, to demonstrate that many of the

national policy issues for the Tanzanian context could be addressed by using such an approach. Paper 3[3] uses linked operational and transmission modelling with national and district TB data to assess the impacts of eight optional diagnostic algorithms in the Tanzanian context. It provides detailed patient, health system and community projections, including incremental cost-effectiveness measures, to draw conclusions on the scale-up of new diagnostic algorithms for TB in Tanzania. Paper 4[4] draws on the evidence from papers 2[2] and 3[3] to consider whether the operational modelling approach might be appropriate to guide scale-up and implementation of new diagnostics for human parasitic diseases. Paper 5[5] discusses how the IAF proposed in paper A[6] might be improved, based on the evidence in paper 3[3] and from other uses of the IAF by the author in Brazil and Ethiopia. Table 2 shows the main focus for each study and how they compare.

Table 2 – Main focus of the five studies

Study	Context focus	Disease Area	Operational Modelling	Linked Operational & Transmission Modelling	Type of paper
1	Developing world with data sourced from Tanzania and Malawi	TB and MDR-TB diagnostics	Yes	Yes	Conceptual
2	Dar es Salaam and Kilimanjaro in Tanzania	TB diagnostics	Yes – primary focus	Discussed	Technical – modelling paper
3	Tanzania scale-up	TB diagnostics	Yes	Yes	Policy development
4	Developing world	Diagnostics for Parasitic disease	Yes - Primary focus	Discussed	Review
5	Developing world with data from Tanzania, Ethiopia and Brazil	TB and MDR-TB diagnostics and treatment	Discussed	Discussed	Review

Each study is summarised individually below.

Study 1 - A modelling framework to support the selection and implementation of new tuberculosis diagnostic tools[1].

Primary Objective: To propose a new and effective modelling concept to support national policy decisions on TB diagnostics by providing comprehensive projections of impact for alternative tools and algorithms relevant to the national context.

Journal: Internal Journal of Tuberculosis and Lung Disease

Target Audience: Global and national TB programmes and those involved in TB research in developing countries

Method: Projecting the impact of new diagnostic tools and algorithms requires estimates of patient benefits, health system effects and impacts on disease transmission that are relevant to the context under consideration. Since these effects are all interrelated a model which could link detailed operational simulation of health systems with a transmission model of the national epidemiology was considered appropriate. This methodology is innovative and would potentially provide an approach that could inform national decision making. To test the concept, two independent model components were first developed and then linked as follows:-

Operational model – A detailed discrete event simulation (DES) was developed to reflect the diagnostic pathways for presumptive TB cases from sputum collection, through laboratory testing, and onto appropriate treatment based on the WHO guidelines[51]. Diagnostic algorithms for new and retreatment presumptive TB cases were represented in the model. Sample collection and sputum examination by microscopy at the diagnostic centre and in the reference laboratory were modelled in detail. The WITNESS modelling software (http://www.lanner.com/en/witness.cfm) for DES was used to develop the model and produce the projections.

Transmission model - The transmission modelling component for this study was based on a differential equation model that captured the most important features of the natural history of TB and was developed at the National Taiwan University by Dr Hsien-Ho Lin. As with many TB transmission models[52, 53] states for susceptible, latently infected, infectious, and recovered were included. To incorporate the health system context where the diagnostic tool would be employed, the usual active disease states of the model were extended to include details of the pathway from disease onset to TB diagnosis and initiation of treatment. The extended transmission model provided a platform to systematically understand how the improved test characteristics of new tools could be translated into population impact on transmission of TB.

Linked operational and transmission model - The operational and transmission model components were linked by using outputs of one model to serve as inputs into the other. For example, the incidence of TB is an output of the transmission model; this informs the input into the operational model through the number of TB presumptive cases coming for diagnosis in the health system. Similarly, the average time to receive diagnosis is an output of the operational model which effects the duration of infectiousness, which therefore becomes an input into the transmission model (Table 3). Information collected from Tanzania and Malawi was used to calibrate the linked model.

Table 3. List of inputs into and outputs from the operational and transmission models.

OPERATIONAL MODEL	
Input	**Output**
Average number of TB presumptive cases coming for diagnosis per diagnostic centre per day	Average time to receive diagnosis
Proportion of Tests Smear Positive	Lost to Follow-Up (Diagnostic default)
Treatment times	Number of visits to diagnostic centre
Number of microscopy staff at diagnostic centre	Diagnosis Outcomes
Lab time per sample	Treatment outcomes
Staff shift patterns	Time to complete treatment
Physician availability	Default in treatment
Probability of default during diagnostic and treatment pathways	Number of samples processed
Transport availability for samples	Health System Costs
Unit costs	Patient Costs
TRANSMISSION MODEL	
Output	**Input**
TB incidence	Transmission rate
TB prevalence	Primary progression rate
	Reactivation rate
	Natural cure rate
	TB-specific mortality
	Diagnostic Test Performance - Sensitivity
	Lost to Follow-Up (Diagnostic default)
	Duration parameters (e.g., from symptom onset to health center visit, from seeking diagnosis to reciving diagnosis)
	TB treatment parameters (e.g., fraction of initial defaulters, treatment success rate, treatment failure and death rate)

Results: The potential impact of a new generic diagnostic with improved sensitivity, a shorter laboratory processing time and reduced sample requirements was compared with standard smear microscopy using the linked model. The results of the linked model showed the alternative diagnostic strategy reduced the average time to diagnosis (~60%), nearly eliminated the fraction of presumptive TB cases lost to diagnostic follow-up, and increased the number of patients accessing treatment (~20%). The transmission model component projected that the alternative diagnostic scenario may result in a more rapid decline in TB incidence. The rate of reduction in incidence (compared to the base case) would increase over time (~1% in Year 1, ~3% in Year 5 and ~6% in Year 10). These results demonstrated some of the effects different diagnostic tools may have on key outcomes, and illustrated the feasibility of a linked modelling approach.

Study 2 - Modelling the impact of new diagnostic tools for tuberculosis in developing countries to enhance policy decisions[2].

Primary Objective: To describe and demonstrate how a discrete event simulation (DES) model of the detailed patient pathways to TB diagnosis could be integrated with a cost-effectiveness analysis to enhance policy decisions on new diagnostics in developing countries

Journal: Health Care Management Science

Target Audience: Management Science community involved in Health Care research

Method: The IAF was used to postulate the questions that policy makers in developing countries would need to address in order to decide which of the available diagnostic tools for TB were most appropriate for a given context. In order to address these questions an operational model linked to a transmission model (as described in study 1) would be required to address the patient, health system and community questions. This study was primarily focused on the operational model used to project patient and health system impacts. The study used data from two very different diagnostic centres in Tanzania (an urban centre in Dar es Salaam and a rural centre in Kilimanjaro). Patient pathways for presumptive TB cases and individuals being treated for TB were mapped based on these two centres. The sputum sample pathways were also mapped through the laboratory process. A DES of the health system was developed using the WITNESS modelling software encompassing these patient and sputum sample pathways. The visual WITNESS representation of these pathways is shown in Figure 6.

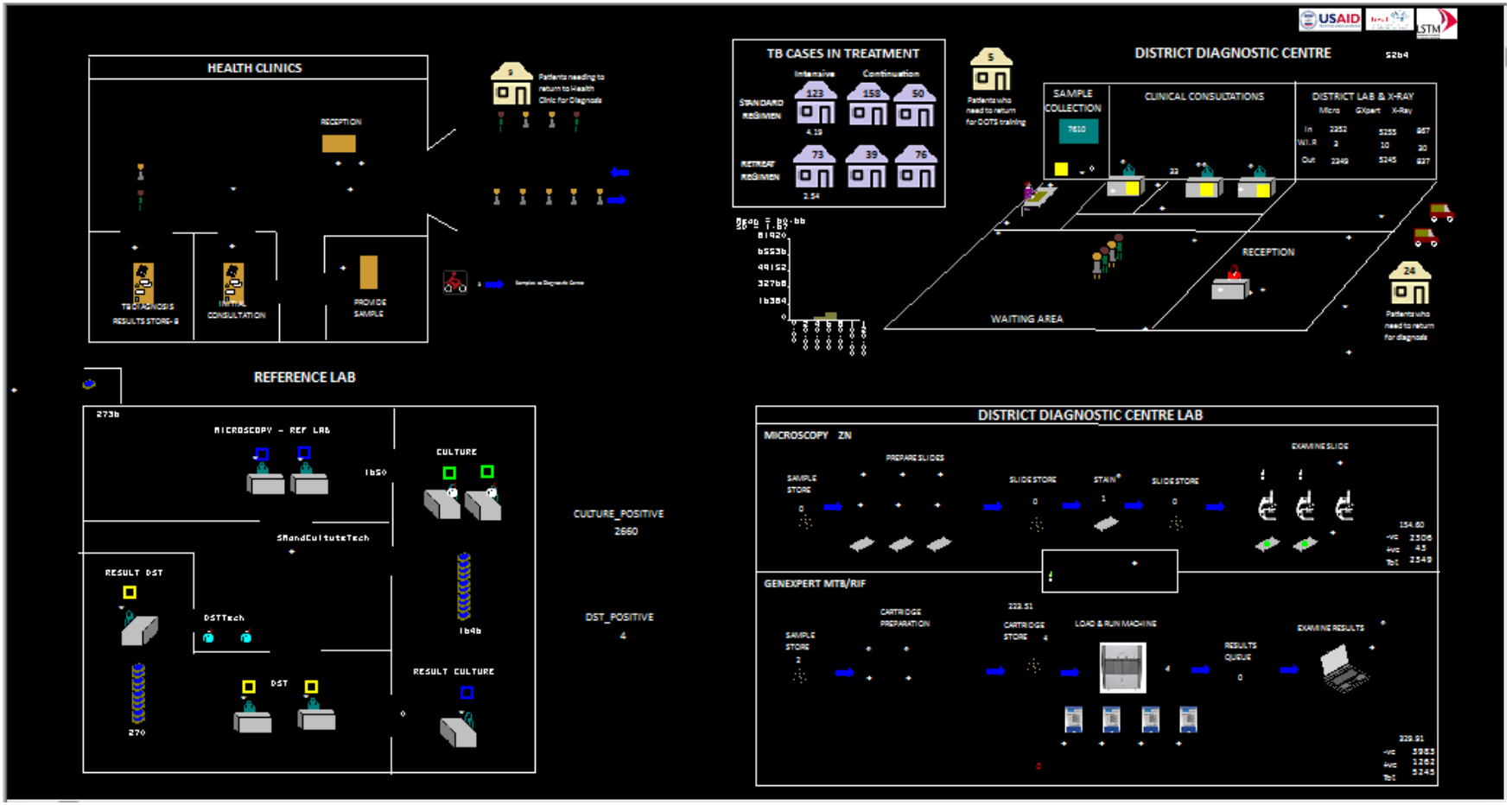


Figure 6 – Snapshot of the WITNESS operational model of TB diagnostics in Tanzania

(The four sections show patient pathways in the health clinic, the patient pathways at a diagnostic centre, sputum sample pathways at the central TB reference laboratory, and sputum sample pathways at the district diagnostic centre laboratory)

The developed model was used to project the impacts of three optional diagnostic algorithms compared to a base case of Ziehl Neelsen microscopy (ZN). The optional new algorithms were light emitting diode fluorescence microscopy (LED), and two alternative algorithms for placement and use of automated nucleic acid amplification tests (aNAAT) such as Xpert MTB/RIF[54]. The impact on health system costs was included in the analysis and an incremental cost-effectiveness ratio (ICER)[55] calculated to compare implementations of the alternative algorithms in the two districts in Tanzania.

Results: The results of the operational model demonstrated that in the urban centre in Dar es Salaam significant improvements in TB diagnosis could be delivered through optimising sputum smear microscopy by implementing LED. In this resource constrained setting, an estimated 5.0 % increase in TB cures could be delivered at very low investment. If more finance were available, implementation of aNAAT could be cost-effective in both Dar es Salaam and Kilimanjaro. The model demonstrated that the benefit of aNAAT in the number of patients cured would be up to 15.8 % in Dar es Salaam and 25.3 % in Kilimanjaro. These benefits would accrue not just from an increase in the number of patients started on TB treatment, but also from earlier case detection, reduced diagnostic LTFU and a reduction in false positive diagnoses by increasing the proportion of cases bacteriologically confirmed. Comparing results between the two diagnostic centres indicated that the benefits and cost-effectiveness vary between settings. Five cost-effective strategies were identified for the rollout of new diagnostics. These ranged from only implementing LED in Dar es Salaam (ICER - US$1 per disability adjusted life year (DALY) averted) at an incremental cost of less than US$1,000 per year, through to full rollout of aNAAT in both centres (ICER - US$65 per DALY averted at an incremental cost of nearly US$80,000 per year).

Study 3 – Assessment of the patient, health system, and population effects of Xpert MTB/RIF and alternative diagnostics for tuberculosis in Tanzania: an integrated modelling approach[3].

Primary Objective: To predict the impact and cost-effectiveness in Tanzania of the scale-up of Xpert as a diagnostic tool for TB under alternative targeting scenarios and in comparison to current practice and other microscopy based diagnostic algorithms.

Journal: The Lancet – Global Health

Target Audience: Health care researchers and TB programmes working in the developing world with particular interest in diagnostics.

Method: Following the methodologies described and tested in the first two studies, this study assessed the scale-up effects in Tanzania of different diagnostic algorithms for TB at the patient, health system, and population levels, using a modelling platform that integrated operational and transmission modelling components as shown in Figure 7.

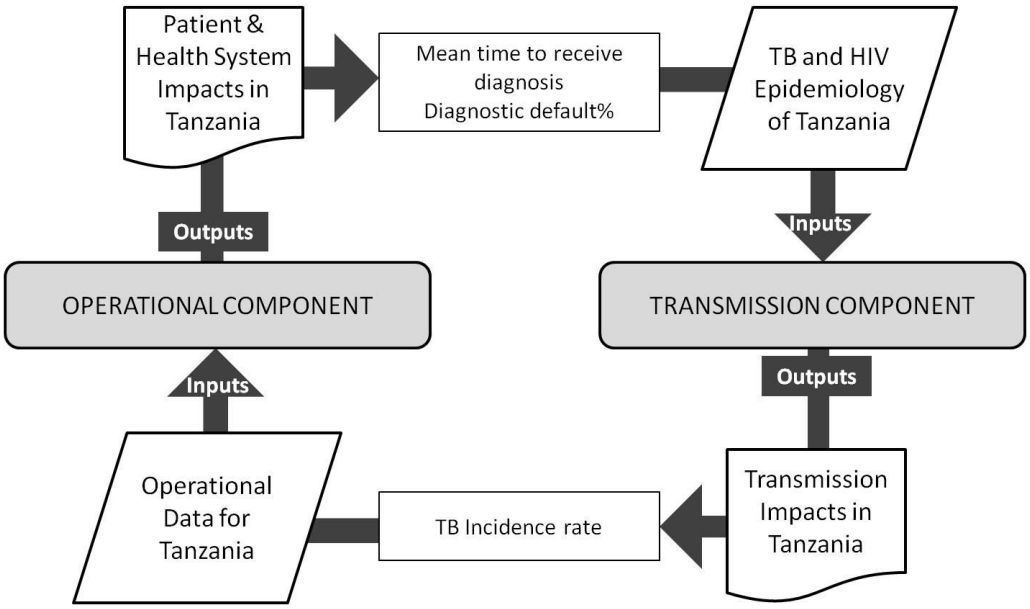
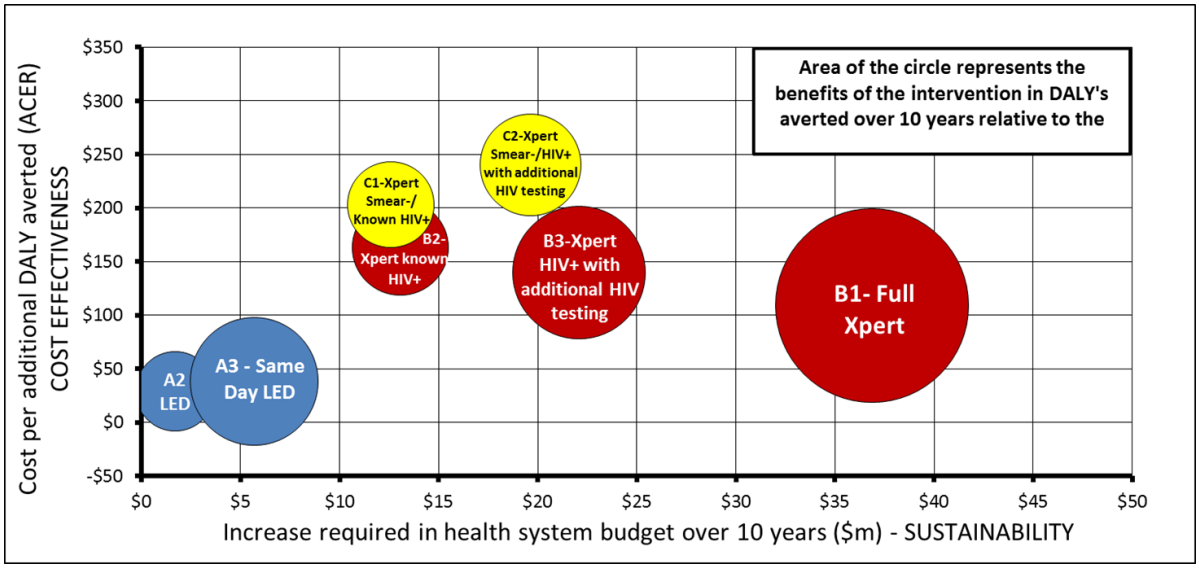


Figure 7: Linked operational and transmission modelling[3]

The operational component[2] used the DES approach and incorporated patient and sputum sample pathways based on WHO guidelines and the present diagnostic procedures in Tanzania. The model was calibrated using data from two diagnostic centres in Tanzania (Temeke and Kibong'oto). The transmission component followed previous dynamic epidemiological modelling approaches and incorporated the care seeking pathway of patients with TB[56]. The model was calibrated to the epidemiological situation of tuberculosis in Tanzania. Cost-effectiveness analyses were completed to compare eight different diagnostic options including ZN Microscopy, LED microscopy with two alternative sputum sample collection strategies, Xpert full scale-up and four alternative algorithms to target Xpert at HIV-positive and/or smear-negative presumptive TB cases. The incremental cost of implementing each alternative diagnostic option over the base case of ZN microscopy was derived from the Tanzanian health system perspective, and included the additional annual running costs (e.g. consumables, drugs, equipment maintenance, and laboratory personnel) and the investment costs (e.g., microscopes and the equipment related to Xpert implementation). The introduction of new tuberculosis diagnostics is expected to improve the survival of patients co-infected with HIV, therefore the incremental costs of additional antiretroviral therapy (ART) on the basis of the projected number of deaths from tuberculosis and HIV co-infection were estimated. The population effect on tuberculosis epidemiology was summarised using DALYs[57]. Uncertainty and sensitivity analysis was also performed.

Results: Comprehensive projections for all the major outcomes were produced at patient level (e.g. likelihood of treatment and cure, time to start treatment, and number of visits to diagnostic facilities), health system level (e.g. staffing requirements, number of tests, anti-retroviral treatments for HIV (ART) and additional costs) and community level (e.g. TB incidence, prevalence and mortality, and HIV prevalence). Three cost-effective strategies in the context of Tanzania were identified: full scale-up of Xpert at an ICER of US$169 per

DALY averted; followed by LED microscopy with two samples collected on the same day (Same-day LED) at US$45 per DALY averted; and LED fluorescence microscopy with two samples collected on different days at US$29 per DALY averted. Figure 8 shows for each diagnostic algorithm (represented by the circles), the projected additional costs to the health service (X-axis), and the average cost-effectiveness ratio (ACER) (Y-axis). The ACER is the cost-effectiveness ratio compared to ZN microscopy rather than the ICER which compares to the next best alternative strategy. The size of the circle is proportional to the benefits in DALYs averted for each option. This shows, for example that full Xpert scale-up (B1) has the greatest benefit in DALYs averted (largest circle), but also the highest additional cost. Same-day LED (A3) and targeted Xpert to HIV-positive cases with additional HIV testing (B3) have similar benefits in DALYs averted, but Same-day LED is significantly less costly and therefore more cost-effective (lower on the Y axis).



Note: The circles represent each diagnostic option. A2: LED microscopy with two samples on different days; A3: Same-day LED; B1: full scale-up of Xpert; B2: Xpert for known HIV-positive presumptive TB cases only; B3: as B2, but with additional HIV testing to increase proportion of presumptive TB cases that know their HIV status; C1: Xpert for smear-negative, HIV-positive presumptive TB cases only; C2: as C1, but with additional HIV testing to increase proportion of presumptive TB cases that know their HIV status.

Figure 8 – Intervention impact - Sustainability vs. Cost-Effectiveness vs. DALYs averted.

Study 4 – 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[4].

Primary Objective: To review the operational modelling approach used to support decisions on diagnostics for TB and consider whether the approach could provide useful insights to support implementation of new diagnostic innovations for human parasitic diseases.

Journal: Parasitology

Focus: Health care programmes and researchers working in the developing world with particular interest in diagnostics for human parasitic diseases.

Method: Decisions on new diagnostics for any disease require the comparison of different strategies that consider the technical characteristics of the tools, how these tools will be implemented within a health system, and the likely effects on outcomes and costs. Operational modelling to assess the potential impact of new diagnostic strategies on health system costs, infrastructure, patient access and outcomes has been used to assist in policy decisions on TB diagnostics[3]. Such an approach has not previously been deployed for parasitic diseases[58]. In Study 4 the approach used for TB modelling is described and then, with reference to the literature, the opportunities for use to assist in policy decisions on new diagnostics for human parasitic diseases such as malaria[59], schistosomiasis[60], and human African trypanosomiasis (HAT)[61] are considered.

Results: Operational modelling of TB diagnostics in Tanzania has provided valuable insight to help policymakers understand context-specific impacts of new tools and algorithms. The approach has been used to assist the TB programme in the development of a national

strategy on the use of a new molecular test (Xpert)[2, 3]. In addition, the approach has helped assist in important decisions concerning diagnosis of MDR-TB in Brazil[5] and South Africa[62].

These experiences from TB and a review of published material and comments from experts in parasitic disease diagnostics, suggest there are potential useful applications of operational modelling for policy decisions on diagnostics for human parasitic diseases. For example, the arrival of rapid diagnostic tests (RDTs) and molecular genotyping for diseases such as malaria[59], HAT[61] and schistosomiasis[60]. With the new diagnostic opportunities comes an ever increasing set of complex decisions on which diagnostic to use, in which context and how to incorporate them into the existing diagnostic algorithms. Modelling the potential impacts of these opportunities, including cost-effectiveness would provide a useful decision support tool. For example, fluorescent microscopy and molecular test loop-mediated isothermal amplification (LAMP) have been developed for HAT. There is the potential for a complicated diagnostic algorithm to ensue involving these new and existing tools. Modelling of the diagnostic pathway for each tool could help to identify how best to integrate diagnostics in the pathway, and increase effective uptake of these novel tests. It was concluded that operational modelling as used in assisting policymakers address the issues with new TB diagnostics, could usefully be applied to the diagnostic challenges of a number of human parasitic diseases.

Study 5 – Developments in Impact Assessment of New Diagnostic Algorithms for Tuberculosis Control[5].

Primary Objective: To review the Impact Assessment Framework (IAF) as a tool to support TB programmes and researchers based on experience of its use in Brazil and Ethiopia.

Journal: Clinical Infectious Diseases

Focus: Global and national infectious disease programmes and researchers working in the developing world with particular interest in TB and MDR-TB diagnosis and treatment.

Method: The IAF[6] was developed in 2010 by a multi-disciplinary team to provide a framework to indicate what information should ideally be collected, in a systematic manner, for new diagnostic tools and approaches for TB to assist in policy decisions. Study 5 reviewed the use of the IAF in Brazil where it had been used as an integral part of an implementation trial of new diagnostics[63], and in Ethiopia where it had been used conceptually as a training tool for staff in the TB programme. The experiences of using the IAF in these two different contexts was considered alongside experiences from modelling TB diagnostics in other low and middle income countries (LMIC) such as Tanzania[1,2,3] to discover what lessons could be learnt and how the IAF might be improved to enhance understanding and use.

Results: The IAF was found to be an effective tool in both the implementation trial in Brazil and in the Ethiopian training programme. In the implementation trial it assisted in the design phase to ensure that data collection covered all the areas required to assist in policy decisions. Members of the study team had their thinking challenged and this helped to avoid misperception and missing key information required for the analysis phase. For example, in collecting data on both health system and patient impacts (Layers 2 and 3). In the analysis phase, this comprehensive data collection enabled evidence for scale-up, and

policy analysis (Layers 4 and 5) to be performed. This went beyond what could purely be provided from a diagnostic accuracy trial, for example by enabling the impact of rollout of Xpert as a frontline tool for diagnosis to be considered, as well as for drug susceptibility testing as used in the trial.

The conceptual testing of the IAF in the Ethiopian training programme received positive feedback from attendees. The greatest benefits were in defining a comprehensive set of research questions needed to provide the evidence on impact to support policy decisions in Ethiopia. Having arrived at the questions, it was then possible to define how the data could be collected and the analysis tools required to address the questions (e.g. health economic tools, patient pathway mapping, and operational modelling). The main lessons from the review were:-

1. The IAF should be reconfigured to emphasise that equity should be at the centre of the evaluation and to show how data from the Effectiveness, Patient and Health System layers feed into Scale-up and Policy Analysis (renamed Horizon Scanning) (Figure 9).

2. A methodology to synthesize and present the broader evidence from an impact assessment study is required. Operational modelling as used in the study in Tanzania[3] would be an effective methodology that could enable projections and synthesis of results and outcomes.

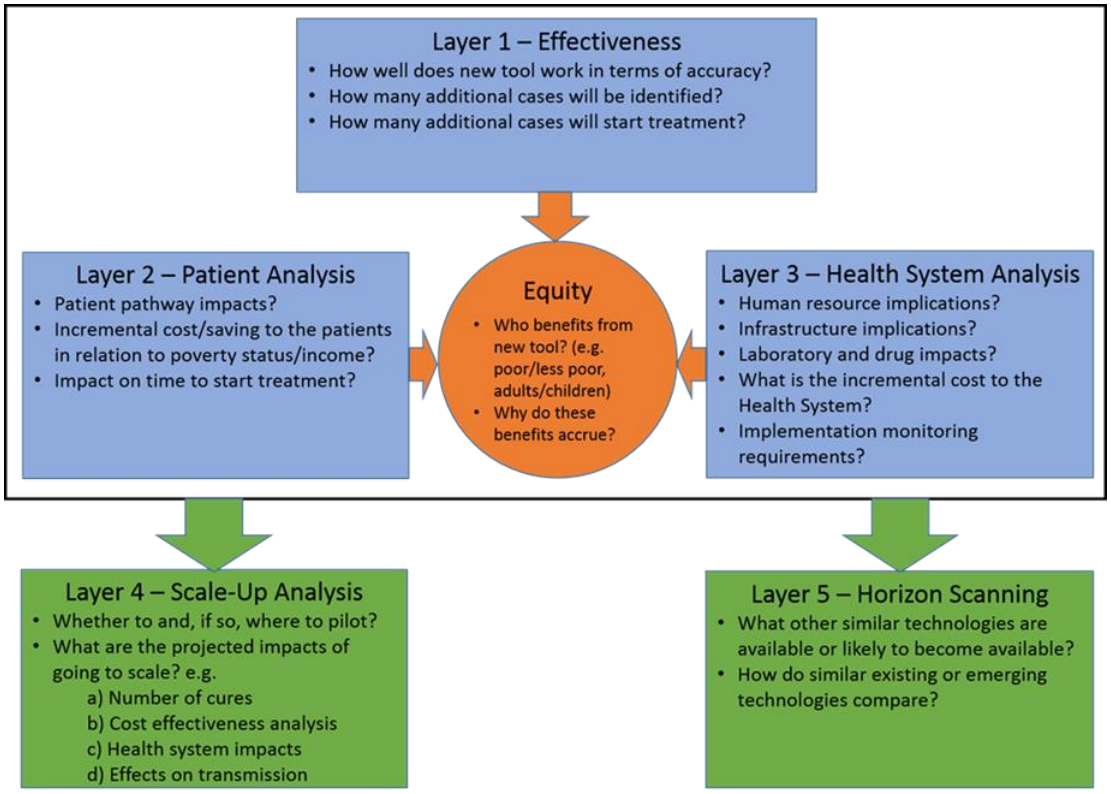


Figure 9 – Revised presentation of the Impact Assessment Framework[5]

DISCUSSION

Main findings

Prior to ***Study 1*** much of the research on TB diagnostics had focused on measures of the sensitivity and specificity of new tools[22, 64] and on demonstration projects of these tools[65]. These studies are essential to the evaluation of new tools, but do little to help understand impacts on the operation of the health system, patient effects and the knock on impacts on transmission of the disease from new diagnostic algorithms.

The concept of linked operational and transmission models to compare the potential overall effects of different tools and algorithms was first demonstrated in Study 1. The study showed, using two simple alternative diagnostic strategies, how the test characteristics of diagnostic tools (e.g., sensitivity and number of specimens required for diagnosis) have an effect on important epidemiological parameters (e.g., LTFU during diagnosis and thus the average duration of infectiousness). Similarly, changing epidemiological parameters (e.g., TB incidence) affects the demand on health systems (e.g., number of presumptive TB cases requiring diagnostic services). In many settings, detailed knowledge of patient, specimen and information flows, including bottlenecks, may not be well understood. Operational models demonstrate why these logistical issues are important for predicting the effectiveness of diagnostic tools. Sensitivity and uncertainty analysis can be used to identify which unknown operational components are most important to measure. In study 1 the feasibility of the linked modelling approach was demonstrated. The approach was found to be flexible and could be used to assess many different options (e.g., different tools and different ways of using those tools within the health system). The model could be adjusted to reflect specific epidemiological situations and health system infrastructures.

Policy makers need to simultaneously consider the existing infrastructure and capabilities, the local epidemiology and what future diagnostic tools may be in the pipeline, before committing to a particular decision. The linked modelling approach can assist in these decisions and could be particularly important as local policy makers grapple with the rapidly expanding list of diagnostic recommendations from the WHO[10].

Study 2 focused particularly on the operational component of the linked modelling approach and added a health economic assessment. The study used data from two diagnostic districts in Tanzania (Dar es Salaam and Kilimanjaro) with different HIV comorbidities, capacities, current diagnostic tools and population densities (urban and rural). The study found that operational modelling using DES could provide useful projections of the effects on the health system, running costs, and patient outcomes of alternative TB diagnostic strategies in the diagnostic centres of Tanzania. An incremental cost-effectiveness analysis using the outputs from the modelling approach found cost-effective implementation scenarios across the two districts for aNAAT based on Xpert. Depending on the available funds different implementation scenarios would be more effective. So the operational modelling approach allowed decision makers to understand the true opportunity cost of different options by reflecting on the budgetary constraints. For example, with unlimited funds full scale-up in both sites was cost-effective, but if funds were restricted to less than US$30,000 per year (either due to budgetary constraints or other health intervention opportunities being more cost-effective) then scale-up of aNAAT for all presumptive TB cases in Kilimanjaro and implementation of LED microscopy in Dar es Salaam would be the most effective use of funds. The flexibility of the DES modelling approach enabled policy makers in Tanzania to consider specific sites and algorithms for trialling the new aNAAT technology. This study proposed that using the same modelling approach, an overall assessment of the impacts of scale-up of alternative diagnostic

algorithms using aNAAT across the 168 diagnostic districts of Tanzania could be performed and linked to a disease transmission model (Study 3).

Policy advisers in Tanzania recognised the benefits of the modelling approach and requested to use the DES themselves to evaluate alternative diagnostic strategies in the future. This request led to a pilot study conducted in 2014. The visual and interactive capability of the operational modelling tool enabled national policy makers to assist in validation, identify new strategies to investigate, and engage with the modelling process and the outputs. As proposed in study 1, this study confirmed that where possible the DES should be linked to a disease transmission component to enhance predictions and to provide outputs on important factors such as TB incidence, which in turn impact health system and patient outcomes.

Study 3 built on the first two studies by taking the linked operational and transmission modelling approach proposed, developing a model to represent all districts in Tanzania, and using the linked model to deliver comprehensive projections of impact for eight alternative diagnostic algorithms for TB if scaled-up across the whole of Tanzania. No study had previously been so comprehensive and modelled so many outcomes including patient, health system, community and cost-effectiveness measures in a single study. Focussing on the cost-effectiveness outcomes which are derived from the projections at patient, health system and community levels, three alternative cost-effective scale-up strategies for the initial diagnosis of TB in the context of Tanzania were identified: -

1. Xpert as a replacement for microscopy at US$169 per DALY averted
2. Same-day LED microscopy at US$45 per DALY averted
3. LED microscopy with two samples on different days at US$29 per DALY averted.

The analysis showed that in Tanzania (and probably countries with similar health systems and TB epidemiology) targeting Xpert to be used only for HIV-positive or high MDR-TB risk presumptive cases, or targeting only to smear-negative HIV-positive cases, was not cost-effective compared with scale-up of Xpert, or use of Same-day LED fluorescence microscopy for all presumptive TB cases (i.e. irrespective of HIV status). This result was different to the WHO recommendation for the targeted use of Xpert at the time[31]. This WHO recommendation has since been modified and is now consistent with the findings of this study[27]. The reason for the inferior cost-effectiveness of targeted implementation to HIV-positive presumptive TB cases is that the projected gains in DALYs averted are the same or lower than those projected from implementing Same-day LED fluorescence microscopy, and the projected costs are substantially higher. There are a number of reasons for this outcome, principally these are:-

- Most HIV-positive individuals do not know their HIV status at the point of TB diagnostic testing in Tanzania, therefore targeting only to known HIV-positive presumptive TB cases will always mean many HIV-positive individuals do not receive the new improved diagnostic tool.
- Even in a high HIV prevalent setting like Tanzania the majority of presumptive TB cases are HIV-negative. Excluding HIV-negative patients from using a more effective test has a disproportionate effect on DALYs averted, particularly as the life expectancy of HIV-negative individuals is longer than HIV-positive individuals.
- Additional ART costs of surviving HIV-positive TB cases results in higher additional costs per patient for an HIV-positive TB cure compared to an HIV-negative TB cure.

These results do not suggest that access to Xpert should be denied to the HIV-positive infected population. In fact, as indicated above, full scale-up of Xpert is the only way to ensure all HIV-positive patients receive Xpert diagnosis in the context of Tanzania.

Two diagnostic algorithms that targeted Xpert to smear-negative cases were also modelled. These were not cost effective compared to the other algorithms modelled, principally because by adding an additional test to microscopy resulted in increased diagnostic lost to follow-up, delayed diagnosis for a number of individuals, and incurred significantly higher costs than, for example, Same-day LED.

Important to the concept of cost-effectiveness is that the intervention must be affordable and sustainable. So for example, the projected 10-year incremental cost to the TB programme of Xpert scale-up (US$28·3 million) represents an increase of about 25% in funds to the present TB programme. It is interesting to note that a large proportion of these additional costs (38%) relate to the treatment of MDR-TB patients diagnosed as a result of resistance to rifampicin being detected as part of the Xpert assay. This is despite Tanzania being a low prevalence setting for MDR-TB. In addition, the HIV programme would incur incremental costs of US$8·6 million as a result of the additional cost of ART. Without a major ongoing injection of funds into the Tanzanian TB programme, the full scale-up of Xpert appears unsustainable. Therefore the programme would be well advised to consider scaling up Xpert in some districts with available funds whilst implementing other cost-effective, but less costly interventions, in other districts such as Same-day LED.

The findings of this study were compared with two other studies published on the cost-effectiveness of Xpert, namely Vassal *et al*[66] and Menzies *et al*[67]. Vassal estimated the ACER of Xpert compared to a base case of ZN microscopy to be US$52–138 per DALY averted, using decision analytical models of tuberculosis in India, South Africa, and Uganda. In another calibrated, dynamic mathematical model of five southern African countries (Botswana, Lesotho, Namibia, South Africa, and Swaziland), Menzies reported the ACER of Xpert to be US$959 (95% CrI 633–1485) per DALY averted. This compares to an ACER of US$109 (95% CrI 72–144) per DALY averted in Study 3. In addition to the expected

difference in ACER due to different epidemiology of TB and HIV in the different settings, the studies are not directly comparable as only Study 3 includes such a comprehensive assessment. For example, the projected impact on transmission and the effect of additional ART costs are not included in Vassal; the long term impact on improved life expectancy in Menzies only includes the impact up to a maximum of 10 years; and the impacts of operational bottlenecks in the health system are only included in Study 3. These differences demonstrate the potential importance of these additional factors, and suggest that Study 3 is the most comprehensive of the published studies on cost-effectiveness of Xpert at the date of publication.

The key findings from Study 3 demonstrated the value of the modelling approach in the assessment of TB diagnostics. ***Study 4*** considered whether such an approach might be useful for the assessment of impact of other new diagnostic technologies appropriate to human parasitic diseases. Impacts on patients, health systems and the scarce financial and human resources in LMIC are critical to the successful implementation of new diagnostic tools and algorithms in these disease areas. The review concluded that using data from existing diagnostic tools for parasitic diseases, alongside the results from trials of new diagnostics, to populate operational models would enable the patient and health system impacts to be projected. This would provide comparisons of the alternative options and assist in identifying the priorities that support policy decisions.

The IAF as proposed by Mann *et al*[6] was useful in defining the key questions that policy makers needed addressing to assist in decisions in relation to new TB diagnostic implementation. ***Study 5*** was able to draw lessons from the IAF's use in studies in Ethiopia and Brazil, and also from the use of linked modelling in Study 3 in Tanzania[3], to extend and reconfigure the IAF. It identified how operational modelling could assist in addressing the key questions. The IAF was also seen as a useful framework to assist researchers and policy

makers in other areas outside diagnostics for TB. For example, in the training program in Ethiopia it was successfully applied to a decision around ambulatory treatment for MDR-TB, suggesting that the approach has wider application than initially considered.

Study limitations

There are limitations in the modelling approach, for example all modelling studies inevitably require assumptions on some of the input parameters. Complete data are rarely available and some simplification of the process is necessary to make a model useable. This is true of the modelling studies discussed here as it is of all such studies, although due to the more detailed operational component, data requirements may be higher than some other modelling studies. Where important data were unavailable assumptions were explicitly made using published research. The effect of these assumptions was tested in Study 3 using uncertainty analysis. Overall, the estimated ICERs were robust to uncertainty of most input variables and the ranking of diagnostic options remained unchanged.

In order to achieve the results projected in these studies the programme will need to make a number of local infrastructural changes, such as increased availability of robust power supplies. Modelling analysis can cost these interventions, but cannot account for all the practical challenges that might arise from implementation of a new method such as Xpert. Programmes need to consider these as a separate matter.

Studies 2 and 3 focused on modelling new TB diagnostics in Tanzania where there is currently a low MDR-TB prevalence amongst TB cases (1% of TB cases). For this reason the impact of drug-resistant TB transmission was not included. It was assumed that MDR-TB would remain at the same level relative to drug susceptible TB within this context. This may mean there is an underestimate of the cost-effectiveness of Xpert because the use of Xpert could reduce the transmission of MDR-TB through increased and earlier identification

of rifampicin resistance. When modelling countries with higher MDR-TB prevalence (see Figure 10) including a component for the transmission of MDR-TB could be beneficial.

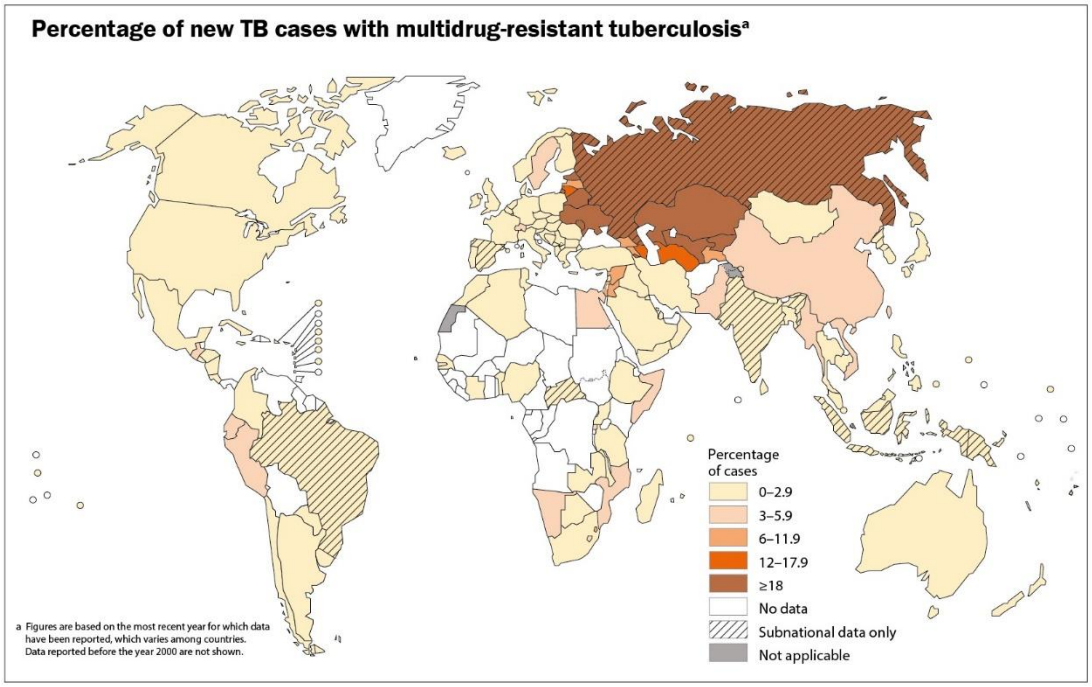


Figure 10 – Percentage of new TB cases with MDR-TB – 2014 estimate[8]

Impact on patient costs and reducing the number of TB cases experiencing catastrophic costs, is an important consideration for future new diagnostic approaches, particularly bearing in mind the END TB strategy of the WHO[9]. These costs have not been included in these studies, although the supplementary appendix to Study 3[68] does illustrate how this could be included in future studies by collecting data on the costs incurred by patients for each health facility visit. This would enable the model to project the costs accrued by patients along the alternative diagnostic and treatment pathways.

The new IAF described in study 5 will sometimes raise questions where the evidence required is unavailable or too expensive to gather. In addition, by the time results are available new questions may arise that were not considered relevant at the start of an investigation. Despite these limitations, the new IAF is a useful guide to assist policy makers

in gathering broad evidence to support policy decisions on TB diagnostic algorithms and potentially other decisions areas (e.g. ambulatory or hospital treatment of MDR-TB).

Study strengths

The linked operational and transmission modelling approach used in studies 1 and 3 is innovative and comprehensive. It allows the evaluation and projection of key outcomes that policy makers need to consider in order to make decisions not just on new diagnostic technologies for TB, but also where to place them in the diagnostic algorithm. Critical to such an analysis is not just the impact from increased bacteriologically confirmed cases, but also the impact on clinically diagnosed cases through empirical diagnosis as highlighted by Theron *et al*[69]. These empirically diagnosed cases are an important aspect of these studies that have rarely in the past received this attention. The studies project the health system, patient and community impacts as well as a detailed cost-effectiveness analysis. All these aspects have rarely if ever previously been combined in any published study.

The application of operational modelling described in papers 1, 2, 3 and 4 is new to health projects in LMIC. Using a detailed DES approach has enabled interactions and bottlenecks in the health system to be considered. The visual representation (e.g. Figure 6) of the modelled patient pathways engages policy makers, researchers, and programme staff in validating the model and understanding the outcomes. This approach has coined a new phrase, Virtual Implementation[70, 71], which many other countries are now using to assess implementation of new TB diagnostics including Ethiopia, South Africa and the Philippines[72]. So far there have been no studies applying the operational modelling approach to human parasitic disease diagnostics as proposed in Study 4, however studies using operational modelling to assist in decisions around blood transfusion services in Ghana, MDR-TB treatment trials in Ethiopia and oxygen needs for childhood pneumonia in

Gambia[73] have been progressed. This illustrates the wide application of the modelling approach to LMIC.

These studies have involved a multi-disciplinary approach (including modellers, clinicians, laboratory staff, programme managers and health economists) from multiple countries (United Kingdom, Taiwan, USA, Brazil and Tanzania) alongside national TB programme staff from countries with a high burden of TB such as Tanzania, Malawi, Ethiopia and Brazil. This has facilitated comprehensive and robust evaluation of the approaches. The studies have involved working with national policy makers with influence and a commitment to delivering improved services to people often living in poverty who experience many barriers to accessing effective health services. In Tanzania this has resulted in the development of a strategy for the scale-up of new diagnostics as well as building local capacity to model new alternative diagnostic strategies in the future.

Study 5 brings the research full circle by going back to an initial reference that inspired study 1[6]. In so doing, lessons from the intervening research were captured and revisions to the IAF proposed that could enhance its utility.

Study implications

The implications of the studies described in this document can be divided into three areas:-

1. ***Implications for TB diagnostics in Tanzania***

   For Tanzania, the integrated modelling approach predicts that full scale-up of Xpert is a cost-effective option for TB diagnosis and has the potential to substantially reduce the national burden. It also estimates the level of funding that will need to be mobilised to translate this into clinical practice. As there are likely to be insufficient funds available to scale-up Xpert as the primary TB test across the

country, policy makers should consider Same-day LED as an alternative in some centres until funds become available for the wider scale-up of Xpert. The operational modelling component and the new IAF can be used to help assess which centres should be scaled-up first and to evaluate new diagnostic tools as they become available.

2. ***Implications for the modelling of TB diagnostics***

The results from the linked operational and transmission modelling of TB diagnostics in these studies are based on the epidemiology and TB health system of Tanzania. However, in similar sub-Saharan African countries with similar epidemiology and decentralised health systems for TB, the conclusions are likely to be similar. This linked approach used for Tanzania should be adapted and replicated in other countries with a high burden of TB to inform policy. Such an approach is currently underway in Addis Ababa in Ethiopia and Cavite province in the Philippines.

3. ***Implications for projecting impacts of health system interventions in LMIC***

These studies have shown the utility of an operational modelling approach to policy decisions on TB diagnostics. Study 4 outlines how the approach could be used to assist policy decisions in the area of diagnostics for human parasitic diseases such as malaria. Study 5 has shown how the IAF used for TB diagnostics might be applied to other decisions on health interventions such as the decision on whether to use ambulatory or hospital care for MDR-TB treatment. The implication is that the IAF and the modelling approach is likely to be a useful support to policy decisions for many major health interventions in LMIC, particularly where there are multiple and uncertain impacts. The IAF is a useful tool to understand the questions

that need addressing. Operational and linked operational and transmission modelling is a useful approach to projecting the answers to these questions.

Future studies

Apart from applying the approach to new country contexts and other disease areas, future studies using the approach for assessment of TB diagnostic algorithms should consider inclusion of patient cost data and projections for MDR-TB transmission. The End TB strategy[9] outlines the importance of these two areas. Firstly in "reducing the proportion of TB-affected families facing catastrophic costs due to TB to zero by 2020". Secondly in the "early diagnosis of TB including universal drug susceptibility testing, and systematic screening of contacts and high-risk groups" alongside "treatment of all people with TB including drug resistant TB". In addition, the End TB strategy emphasises the need for "research to optimize implementation and impact; and promote innovations", the modelling approach described here is an effective way to help achieve this.

Future studies should seek to build the capacity within national TB programmes to conduct high quality research using the modelling approach as discussed here. This has been successfully piloted in Dar es Salaam and Addis Ababa by the author. Further studies in other countries should make this a priority especially as new diagnostics are continually being developed and opportunities to move diagnostics closer to where patients initially seek medical help are likely to be available in the future. The impact of such approaches will need evaluation and quantification to support policy decisions.

CONCLUSIONS

National policy makers for TB need more than simple sensitivity and specificity information to address key questions on scale-up of new technologies and algorithms. A linked operational and transmission modelling approach can help to address many of the gaps in knowledge that policy makers have on impact covering important areas affecting patients , health systems and communities. The same approach can provide cost-effectiveness measures to enable policy makers to compare health inventions. In Tanzania the approach has shown full scale-up of Xpert for TB diagnosis would provide significant benefits and is cost-effective, but is currently unaffordable as a national strategy. The alternative of targeting Xpert to HIV-positive or smear-negative presumptive TB cases is not cost-effective when compared with Same-day LED. For Tanzania the preferred strategy is to implement Xpert in all diagnostic districts (where the infrastructure is suitable) for initial TB diagnosis of pulmonary TB as a replacement for smear microscopy in as many areas as the programme can afford. Same-day LED should be considered elsewhere until funds become available for Xpert. The impact assessment framework and the operational modelling approach, which have been key elements of this research, have potential to assist policy makers in assessing many other health interventions in TB and other disease areas in LMIC. These opportunities should be further researched and explored.

REFERENCES

1. Lin HH, Langley I, Mwenda R, Doulla B, Egwaga S, Millington KA, Mann GH, Murray M, Squire SB, Cohen T. A modelling framework to support the selection and implementation of new tuberculosis diagnostic tools. Int J Tuberc Lung Dis 2011; 15: 996–1004.

2. Langley I, Doulla B, Lin HH, Millington KA, Squire SB. Modelling the impacts of new diagnostic tools for tuberculosis in developing countries to enhance policy decisions. Health Care Manag Sci 2012;15: 239–53.

3. Langley I, Lin HH, Egwaga S, Doulla B, Ku CC, Murray M, Cohen T, Squire SB. 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. 2014 Oct; 2(10):e581-91. doi: 10.1016/S2214-109X(14)70291-8. Erratum in: Lancet Glob Health. 2014 Dec;2(12):e697.

4. Langley I, Adams E, Doulla B, Squire SB. 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. 2014 Dec; 141(14):1795-802. doi: 10.1017/S0031182014000985.

5. Langley I, Squire SB, Dacombe R, Madan J, Lapa e Silva JR, Barreira D, Galliez R, Oliveira MM, Fujiwara PI, Kritski A. Developments in Impact Assessment of New Diagnostic Algorithms for Tuberculosis Control. Clin Infect Dis. 2015 Oct 15; 61 Suppl 3:S126-34. doi: 10.1093/cid/civ580.

6. Mann G, Squire SB, Bissell K, Eliseev P, Du Toit E, Hesseling A, Nicol M, Detjen A, Kritski A. Beyond accuracy: creating a comprehensive evidence base for TB diagnostic tools. Int J Tuberc Lung Dis. 2010 Dec;14(12):1518-24.

7. Squire SB, Ramsay AR, van den Hof S, Millington KA, Langley I, Bello G, Kritski A, Detjen A, Thomson R, Cobelens F, Mann GH. Making innovations accessible to the poor through implementation research. Int J Tuberc Lung Dis. 2011 Jul;15(7):862-70. doi: 10.5588/ijtld.11.0161.

8. World Health Organization – Global Tuberculosis Report 2015, accessed 24th February 2016. http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1

9. World Health Organization End TB Strategy. Accessed 24th February 2016. http://www.who.int/tb/strategy/en/

10. Pai M, Schito M. Tuberculosis diagnostics in 2015: landscape, priorities, needs, and prospects. J Infect Dis. 2015 Apr 1;211 Suppl 2:S21-8. doi: 10.1093/infdis/jiu803.

11. World Health Organization (2014), Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014), accessed January 2016, http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf

12. Ramsay A, Yassin MA, Cambanis A, Hirao S, Almotawa A, Gammo M, Lawson L, Arbide I, Al-Aghbari N, Al-Sonboli N, Sherchand JB, Gauchan P, Cuevas LE. Front-loading sputum microscopy services: an opportunity to optimise smear-based case

detection of tuberculosis in high prevalence countries. J Trop Med. 2009; 2009:398767. doi: 10.1155/2009/398767.

13. World Health Organization (1994), Framework for effective tuberculosis control, accessed 28th January 2016, http://apps.who.int/iris/bitstream/10665/58717/1/WHO_TB_94.179.pdf

14. World Health Organization, Treatment of Tuberculosis Guideline 4th Edition (2010), WHO/HTM/TB/2009.420, ISBN 978 92 4 154783 3. Accessed 1st March 2016. http://apps.who.int/iris/bitstream/10665/44165/1/9789241547833_eng.pdf?ua=1&ua=1

15. Kemp JR, Mann G, Simwaka BN, Salaniponi FM, Squire SB. Can Malawi's poor afford free tuberculosis services? Patient and household costs associated with a tuberculosis diagnosis in Lilongwe. Bull World Health Organ. 2007 Aug;85(8):580-5.

16. Ramsay A, Al-Agbhari N, Scherchand J, Al-Sonboli N, Almotawa A, Gammo M, Gauchan P, YassinMA, Cuevas LE. Direct patient costs associated with tuberculosis diagnosis in Yemen and Nepal. Int J Tuberc Lung Dis. 2010 Feb;14(2):165-70.

17. Tom A Yates, Palwasha Y Khan, Gwenan M Knight, Jonathon G Taylor, Timothy D McHugh, Marc Lipman, Richard G White, Ted Cohen, Frank G Cobelens, Robin Wood, David A J Moore, Ibrahim Abubakar. The transmission of Mycobacterium tuberculosis in high burden settings. Lancet Infect Dis 2016; 16: 227–38

18. Madan J, Lönnroth K, Laokri S, Squire SB. What can dissaving tell us about catastrophic costs? Linear and logistic regression analysis of the relationship between patient costs and financial coping strategies adopted by tuberculosis patients in Bangladesh, Tanzania and Bangalore, India. BMC Health Serv Res. 2015 Oct 22;15:476. doi: 10.1186/s12913-015-1138-z.

19. Wingfield T, Boccia D, Tovar M, Gavino A, Zevallos K, Montoya R, Lönnroth K, Evans CA. Defining catastrophic costs and comparing their importance for adverse tuberculosis outcome with multi-drug resistance: a prospective cohort study, Peru. PLoS Med. 2014 Jul 15;11(7):e1001675. doi: 10.1371/journal.pmed.1001675.

20. Squire SB, Belaye AK, Kashoti A, Salaniponi FM, Mundy CJ, Theobald S, Kemp J. 'Lost' smear-positive pulmonary tuberculosis cases: where are they and why did we lose them? Int J Tuberc Lung Dis. 2005 Jan;9(1):25-31.

21. Boehme CC, Nicol MP, Nabeta P, Michael JS, Gotuzzo E, Tahirli R, Gler MT, Blakemore R, Worodria W, Gray C, Huang L, Caceres T, Mehdiyev R, Raymond L, Whitelaw A, Sagadevan K, Alexander H, Albert H, Cobelens F, Cox H, Alland D, Perkins MD. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. Lancet. 2011 Apr 30;377(9776):1495-505. doi: 10.1016/S0140-6736(11)60438-8. Epub 2011 Apr 18.

22. Steingart KR, Henry M, Ng V, Hopewell PC, Ramsay A, Cunningham J, Urbanczik R, Perkins M, Aziz MA, Pai M. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis. 2006 Sep;6(9):570-81. Review. Erratum in: Lancet Infect Dis. 2006 Oct;6(10):628.

23. Steingart KR, Ng V, Henry M, Hopewell PC, Ramsay A, Cunningham J, Urbanczik R, Perkins MD, Aziz MA, Pai M. Sputum processing methods to improve the sensitivity

of smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis. 2006 Oct;6(10):664-74.

24. Swai HF, Mugusi FM, Mbwambo JK. Sputum smear negative pulmonary tuberculosis: sensitivity and specificity of diagnostic algorithm. BMC Res Notes 2011; 4: 475.

25. World Health Organization, Fluorescent light-emitting diode (LED) microscopy for diagnosis of tuberculosis – Policy statement. 2011. Accessed 3rd March 2016. http://apps.who.int/iris/bitstream/10665/44602/1/9789241501613_eng.pdf?ua=1&ua=1

26. World Health Organization. Same-day diagnosis of tuberculosis by microscopy: policy statement. Geneva: World Health Organization, 2011. Accessed 3rd March 2016. Accessed 3rd March 2016. http://apps.who.int/iris/bitstream/10665/44603/1/9789241501606_eng.pdf

27. World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extra pulmonary TB in adults and children. Policy update. Geneva, Switzerland: WHO, 2013. Accessed 3rd March 2016. http://apps.who.int/iris/bitstream/10665/112472/1/9789241506335_eng.pdf?ua=1

28. World Health Organization. Molecular line probe assays for rapid screening of patients at risk of multi-drug resistant tuberculosis (MDR-TB). Policy statement. Geneva, Switzerland: WHO, 2008. Accessed 3rd March 2016. http://www.who.int/tb/features_archive/policy_statement.pdf

29. World Health Organization. Use of liquid TB culture and drug susceptibility testing (DST) in low and medium income settings. Summary report of the expert group meeting on the use of liquid culture media. Geneva, Switzerland: WHO, 2007. Accessed 3rd March 2016. http://www.who.int/tb/laboratory/use_of_liquid_tb_culture_summary_report.pdf?ua=1

30. World Health Organization, The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV – Policy guidance, 2015. Accessed 3rd March 2016. http://apps.who.int/iris/bitstream/10665/193633/1/9789241509633_eng.pdf?ua=1&ua=1

31. World Health Organization, Automated Real-time Nucleic Acid Amplification Technology for Rapid and Simultaneous Detection of Tuberculosis and Rifampicin Resistance: Xpert MTB/RIF System - Policy Statement 2011. Accessed Feb 24th 2016. http://apps.who.int/iris/bitstream/10665/44586/1/9789241501545_eng.pdf

32. FIND, Xpert MTB/RIF Automated nucleic acid amplification test (NAAT). Accessed February 2016 http://www.finddiagnostics.org/programs/tb/find_activities/automated_naat.html

33. Cox S, Mbhele S, Neisha Mohess, et al. Impact of Xpert MTB/RIF for TB Diagnosis in a Primary Care Clinic with High TB and HIV Prevalence in South Africa: A Pragmatic Randomised Trial, PLOS Medicine, November 2014, Volume 11, Issue 11, e1001760.

34. Schunemann HJ, Schunemann AH, Oxman AD, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ 2008; 336:1106–10.

35. Kritski A, Fujiwara PI, Vieira MA, et al. Assessing new strategies for TB diagnosis in low- and middle-income countries. Braz J Infect Dis. 2013 Mar 2. doi:pii: S1413-8670(13)00052-4. 10.1016/j.bjid.2013.01.004.

36. Ramsay A, Steingart KR, Cunningham J, Pai M. Translating tuberculosis research into global policies: the example of an international collaboration on diagnostics. Int J Tuberc Lung Dis. 2011 Oct;15(10):1283-93. doi: 10.5588/ijtld.11.0297.

37. Cobelens F, van den Hof S, Pai M, Squire SB, Ramsay A, Kimerling ME. Which new diagnostics for tuberculosis, and when, J Infect Dis 2012; 205 (suppl 2): S191–98.

38. Lavis JN, Oxman AD, Lewin S, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP). Health Research Policy and Systems 2009, 7(Suppl 1):I1 doi:10.1186/1478-4505-7-S1-I1.

39. Theron G, Peter J, Dowdy D, Langley I, Squire SB, Dheda K. Do high rates of empirical treatment undermine the potential effect of new diagnostic tests for tuberculosis in high-burden settings? Lancet Infect Dis 2014; 14: 527–32.

40. Caro JJ, Briggs AH, Siebert U, Kuntz KM; ISPOR-SMDM Modeling Good Research Practices Task Force. Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--1. Value Health. 2012 Sep-Oct;15(6):796-803. doi: 10.1016/j.jval.2012.06.012.

41. Petrou S, Gray A. Economic evaluation using decision analytical modelling: design, conduct, analysis, and reporting. BMJ. 2011 Apr 11;342: d1766. doi: 10.1136/bmj.d1766.

42. Dye C, Garnett GP, Sleeman K, Williams BG. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. Lancet 1998;352:1886–91. doi:10.1016/S0140-6736(98)03199-7 PMID:9863786

43. Dowdy DW, Houben R, Cohen T, Pai M, Cobelens F, Vassall A, Menzies NA, Gomez GB, Langley I, Squire SB, White R; TB MAC meeting participants. Impact and cost-effectiveness of current and future tuberculosis diagnostics: the contribution of modelling. Int J Tuberc Lung Dis. 2014 Sep;18(9):1012-8. doi: 10.5588/ijtld.13.0851.

44. Murray CJ, Salomon JA. Modeling the impact of global tuberculosis control strategies. Proc Natl Acad Sci USA 1998;95:13881–6. doi:10.1073/pnas.95.23.13881 PMID:9811895

45. Pitman R, Fisman D, Zaric GS, Postma M, Kretzschmar M, Edmunds J, Brisson M; ISPOR-SMDM Modeling Good Research Practices Task Force. Dynamic transmission modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--5. Value Health. 2012 Sep-Oct;15(6):828-34. doi: 10.1016/j.jval.2012.06.011.

46. Robinson S. Simulation: the practice of model development and use. Warwick, UK: Warwick Business School, University of Warwick: John Wiley & Sons, 2003.

47. Karnon J, Stahl J, Brennan A, Caro JJ, Mar J, Möller J; ISPOR-SMDM Modeling Good Research Practices Task Force. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--4. Value Health. 2012 Sep-Oct;15(6):821-7. doi: 10.1016/j.jval.2012.04.013.

48. Günal M, Pidd M. Discrete event simulation for performance modelling in health care: a review of the literature. J Simulation 2010; 4: 42–51.

49. Mayer G, Spieckermann S. Life-cycle of simulation models: requirements and case studies in the automotive industry. J Simulation 2010; 4: 255–259.

50. Siebers P, Aickelin U, Celia H, Clegg C. Towards the development of a simulator for investigating the impact of people management practices on retail performance. J Simulation 2010; doi: 10.1057/jos.2010.20.

51. World Health Organization. Treatment of tuberculosis: guidelines. 4th edition. Accessed on 12th March 2016. http://apps.who.int/iris/bitstream/10665/44165/1/9789241547833_eng.pdf?ua=1

52. Anderson R M, May R M. Infectious diseases of humans: dynamics and control. Oxford, UK: Oxford University Press, 1991.

53. Blower S M, McLean A R, Porco T C, et al. The intrinsic transmission dynamics of tuberculosis epidemics. Nat Med 1995; 1:815–821.

54. Cepheid, accessed 11th March 2016, http://www.cepheid.com/us/cepheid-solutions/clinical-ivd-tests/critical-infectious-diseases/xpert-mtb-rif

55. Gray AM, Clarke PM, Wolstenholme J, Wordsworth S. Applied methods of cost-effectiveness analysis in healthcare. Oxford: Oxford University Press, 2010.

56. Lin HH, Dowdy D, Dye C, Murray M, Cohen T. The impact of new tuberculosis diagnostics on transmission: why context matters. Bull World Health Org 2012; 90: 739–47A.

57. Salomon JA, Vos T, Hogan DR, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2129–43.

58. Ponder EL, Freundlich JS, Sarker M and Ekins S. Computational models for neglected diseases: gaps and opportunities. Pharmaceutical Research 2014:31, 271–277. doi: 10.1007/s11095-013-1170-9.

59. Hopkins H, González I J, Polley SD, Angutoko P, Ategeka J, Asiimwe C, Agaba B, Kyabayinze DJ, Sutherland CJ, Perkins MD and Bell D. Highly sensitive detection of malaria parasitemia in a malaria-endemic setting: performance of a new loopmediated isothermal amplification kit in a remote clinic in Uganda. Journal of Infectious Diseases 2013:208, 645–652. doi: 10.1093/infdis/jit184.

60. Stothard JR. Improving control of African schistosomiasis: towards effective use of rapid diagnostic tests within an appropriate disease surveillance model. Transactions of the Royal Society of Tropical Medicine and Hygiene 2009:103, 325–332. doi:10:1016/j.trstmh.2008.12.012.l.

61. Buscher P, Gilleman Q and Lejon V. Rapid diagnostic test for sleeping sickness. New England Journal of Medicine 2013:368, 1069–1070. doi:10.1056/NEJMc1210373.

62. Naidoo P, Dunbar R, Lombard C, du Toit E, Caldwell J, Detjen A, Squire SB, Enarson DA, Beyers N. Comparing Tuberculosis Diagnostic Yield in Smear/Culture and Xpert® MTB/RIF-Based Algorithms Using a Non-Randomised Stepped-Wedge Design. PLoS One. 2016 Mar 1;11(3):e0150487. doi: 10.1371/journal.pone.0150487. eCollection 2016.

63. Kritski A, Fujiwara PI, Vieira MA, Nettod AR, Oliveira MM, Huf G, Squire SB. Assessing new strategies for TB diagnosis in low- and middle-income countries. Braz J Infect Dis 2013;17:211–7.

64. Boehme C C, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med 2010; 363: 1005–1015.

65. Barnard M, Albert H, Coetzee G, O'Brien R, Bosman M E. Rapid molecular screening for multidrug-resistant tuberculosis in a high-volume public health laboratory in South Africa. Am J Respir Crit Care Med 2008; 177: 787–792.

66. Vassall A, van Kampen S, Sohn H, et al. Rapid diagnosis of tuberculosis with the Xpert MTB/RIF assay in high burden countries: a cost-effectiveness analysis. PLoS Med 2011; 8: e1001120.

67. Menzies NA, Cohen T, Lin HH, Murray M, Salomon JA. Population health impact and cost-effectiveness of tuberculosis diagnosis with Xpert MTB/RIF: a dynamic simulation and economic evaluation. PLoS Med 2012; 9: e1001347.

68. Supplementary appendix to Langley I, Lin H-H, Egwaga S, et al. 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 2014;2: e581–591. Accessed 26th April 2016. http://www.thelancet.com/cms/attachment/2024407919/2044129472/mmc1.pdf

69. Theron G, Peter J, Dowdy D, Langley I, Squire SB, Dheda K. Do high rates of empirical treatment undermine the potential effect of new diagnostic tests for tuberculosis in high-burden settings? Lancet Infect Dis 2014; 14: 527–32.

70. The Union website accessed 26th April 2016. http://www.theunion.org/news-centre/news/treat-tb-presents-virtual-implementation-approach-in-washington-dc

71. TREAT-TB website accessed 26th April 2016. http://www.mktg.mobi/resources/TBVIBrochure.PDF

72. Liverpool School of Tropical Medicine website accessed 26th April 2016. http://www.lstmed.ac.uk/news-events/news/cahrd-receives-newton-fund-grant-for-tb-diagnostics-in-the-philippines

73. Bradley BD, Howie SR, Chan TC, Cheng YL. Estimating oxygen needs for childhood pneumonia in developing country health systems: a new model for expecting the unexpected. PLoS One. 2014 Feb 20;9(2):e89872. doi:10.1371/journal.pone.0089872. eCollection 2014.

APPENDIX A: Co-authors' statements of candidates contribution

Study 1

PhD by published work, Warwick Medical School, University of Warwick

Statement of contribution by Ivor Langley

Paper to be considered as part of the PhD by published work

Lin HH*, **Langley I***, Mwenda R, Doulla B, Egwaga S, Millington KA, Mann GH, Murray M, Squire SB, Cohen T. (2011). A modelling framework to support the selection and implementation of new tuberculosis diagnostic tools. *Int J Tuberc Lung Dis* 2011; 15: 996–1004.
* Lin HH and Langley I contributed equally in the writing of this article.

Contribution of candidate: Ivor Langley was integral to the whole study design. He led the design and development of the operational model and together with Hsien-Ho Lin the linkage between operational and transmission modelling. Ivor Langley and Hsien-Ho Lin together took the lead in writing the manuscript in liaison with co-authors and responding to reviewers.

Name	Signature	Date
Hsien-Ho Lin	[redacted]	
Ted Cohen		
S Bertel Squire		
Reuben Mwenda		
Basra Doulla		
Saidi Egwaga		
Kerry Millington		
Gillian Mann		
Megan Murray		

Study 2

PhD by published work, Warwick Medical School, University of Warwick

Statement of contribution by Ivor Langley

Paper to be considered as part of the PhD by published work

Langley I, Doulla B, Lin HH, Millington K, Squire B. (2012). Modelling the impacts of new diagnostic tools for tuberculosis in developing countries to enhance policy decisions. *Health Care Manag Sci* 2012; **15:** 239–53.

Contribution of candidate: Ivor Langley took the lead role in study design, model development, data collation, experimentation and analysis. He worked with Hsien-Ho Lin on the linkage to the transmission model. Ivor Langley took the lead in writing the manuscript in liaison with co-authors and responding to reviewers.

Name	Signature	Date
Hsien-Ho Lin	[redacted]	
S Bertel Squire		
Basra Doulla		
Kerry Millington		

Study 3

PhD by published work, Warwick Medical School, University of Warwick

Statement of contribution by Ivor Langley

Paper to be considered as part of the PhD by published work

Langley I*, Lin HH*, Egwaga S, Doulla B, Ku CC, Murray M, Cohen T, Squire SB. (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 Global Health* 2014; 2:e581–91.

* Langley I and Lin HH contributed equally.

Contribution of candidate: Ivor Langley led the design and development of the operational model and together with Hsien-Ho Lin the linkage between operational and transmission modelling. He took the lead in engaging, supporting and dissemination of results with collaborators in the National Tuberculosis Programme in Tanzania. Ivor Langley and Hsien-Ho Lin together took the lead in writing the manuscript in liaison with co-authors and responding to reviewers.

Name	Signature	Date
Hsien-Ho Lin	[redacted]	
Ted Cohen		
S Bertel Squire		
Saidi Egwaga		
Basra Doulla		
Chu-Chang Ku		
Megan Murray		

Study 4

PhD by published work, Warwick Medical School, University of Warwick

Statement of contribution by Ivor Langley

Paper to be considered as part of the PhD by published work

Langley I, Adams E, Doulla B, Squire SB. (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*, 2014 Dec; 141(14):1795-802. doi: 10.1017/S0031182014000985.

Contribution of candidate: Ivor Langley led the study design and the review. Ivor Langley led the writing of the manuscript in liaison with co-authors and responded to reviewers.

Name	Signature	Date
Emily Adams	[redacted]	
S Bertel Squire		
Basra Doulla		

Study 5

PhD by published work, Warwick Medical School, University of Warwick

Statement of contribution by Ivor Langley

Paper to be considered as part of the PhD by published work

Langley I, Squire SB, Dacombe R, Madan J, Lapa e Silva JR, Barreira D, Galliez R, Oliveira MM, Fujiwara PI, and Kritski A **(2015).** Developments in Impact Assessment of New Diagnostic Algorithms for Tuberculosis Control. *Clin Infect Dis.* 2015 Oct 15; 61Suppl 3:S126-34. doi: 10.1093/cid/civ580.

Contribution of candidate: Ivor Langley led the study design and the review. Ivor Langley led the writing of the manuscript in liaison with co-authors and responded to reviewers.

Name	Signature	Date
Squire SB	[redacted]	
Kritski A		
Dacombe R		
Madan J		
Lapa e Silva JR		
Barreira D		
Galliez R		
Oliveira MM		
Fujiwara PI		

APPENDIX B – List of all publications by candidate

- Hollingsworth TD, **Langley I**, Nokes DJ, Macpherson EE, McGivern G, Adams ER, Bockarie MJ, Mortimer K, Reimer LJ, Squire SB, Torr SJ, Medley GF. (**2015**). Infectious disease and health systems modelling for local decision making to control neglected tropical diseases. BMC proceedings, December 2015, DOI: 10.1186/1753-6561-9-S10-S6

- **Langley I**, Squire SB, Dacombe R, Madan J, Lapa e Silva JR, Barreira D, Galliez R, Oliveira MM, Fujiwara PI, Kritski A. (**2015**). Developments in Impact Assessment of New Diagnostic Algorithms for Tuberculosis Control. Clin Infect Dis. 2015 Oct 15;61 Suppl 3:S126-34. doi: 10.1093/cid/civ580

- **Langley I**, Lin HH, Squire SB.(**2015**). Cost-effectiveness of Xpert MTB/RIF and investing in health care in Africa. Lancet Glob Health. 2015 Feb;3(2):e83-4. doi: 10.1016/S2214-109X(14)70370-5.

- **Langley I**, Lin H-H, Egwaga S, et al. (**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. Heal. 2014;2(10):e581-91. doi:10.1016/S2214-109X(14)70291-8.

- Dowdy, D W, Houben, R, Cohen, T, Pai, M, Cobelens, F, Vassall, A, Menzies, N A, Gomez, G B, **Langley, Ivor**, Squire, Bertie and White, R (**2014**) 'Impact and cost-effectiveness of current and future tuberculosis diagnostics: the contribution of modelling'. International Journal of Tuberculosis and Lung Disease, Vol 18, Issue 9, pp. 1012-1018.

- **Langley, Ivor**, Adams, Emily, Doulla, Basra and Squire, Bertie (**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, Vol 141, Issue 14, pp. 1795-1802.

- Theron, Grant, Peter, Jonny, Dowdy, David, **Langley, Ivor**, Squire, Bertie and Dheda, Keertan (**2014**) 'Do high rates of empirical treatment undermine the potential effect of new diagnostic tests for tuberculosis in high-burden settings?'. The Lancet Infectious Diseases, Vol 14, Issue 6, pp. 527-532.

- **Langley I**, Doulla B, Lin HH, Millington KA, Squire SB (**2012**). Modelling the impacts of new diagnostic tools for tuberculosis in developing countries to enhance policy decisions. Health Care Manag Sci DOI 10.1007/s10729-012-9201-3

- Lin HH*, **Langley I***, Mwenda R, Doulla B, Egwaga S, Millington KA, Mann GH, Murray M, Squire SB, Cohen T (**2011**), A modelling framework to support the selection and implementation of new tuberculosis diagnostic tools. Int J Tuberc Lung Dis 15(8):996–1004, doi:10.5588/ijtld.11.0062. ** joint first authors*

- Squire SB, Ramsay ARC, Van den Hof S, Millington KA, **Langley I**, Bello G, Kritski A, Detjen A, Thomson R, Cobelens F, Mann GH. (**2011**). Making innovations accessible

to the poor through implementation research, Int J Tuberc Ling Dis 15(7):862–870, doi:10.5588/ijtld.11.0161