TB Modelling and Analysis Consortium (TB MAC)

TB MAC Global post-2015 TB Targets

Seattle, USA

2-4 June 2014

Meeting Report

www.tb-mac.org

TABLE OF CONTENTS

Executive summary

The TB modelling and analysis consortium (TB MAC) is an initiative to improve global tuberculosis (TB) control by coordinating and promoting mathematical modelling and other quantitative research activities.

Our fourth meeting was dedicated to a multi-model exercise that aims to focus efforts of modellers, economists and other experts to assess the new post-2015 GTB global TB targets (which interventions, at what scale, and what resources are required to reach them) in South Africa, India and China.

During the meeting representatives from 12 participating epidemiological models, economists, country TB programmes and other stakeholder organisations as well as the TB activist community came together to discuss progress made so far, decide on key issues and set out the path towards the next milestone, TB MAC meeting 5 and present at the Union Conference Symposium in October. While some sessions were joint, most of the meeting was streamed into economic and epidemiological sessions to allow focus and optimal progress to be made on epidemiological or economical specific issues.

Epidemiological Stream: After evaluating baseline calibration and intervention results generated by epidemiological models before the meeting, a process was decided by which to finalise the calibration and intervention implementation guidance for epidemiological models by July. In addition, a timeline was decided for submitting the next round of results for internal peer review (mid-August). Finally, decisions on implementation of Universal Health Coverage and how to deal with varying age structure between models resolved two important questions for the epidemiological side of the work.

Economics Stream: The meeting resulted in further specification on the economic evaluation question to ask, including main outcomes, comparators, perspective and timeframe. It also provided further definition of the interventions to be included recommending a process for further definition. Key decisions were taken about model outputs, including the specification of outputs to estimate disability adjusted life years. Finally all unit costs were complied and process set in place for finalising and addressing data gaps.

Overall the meeting succeeded at making informed decisions on several key issues, and highlighted the direction of the forthcoming work on this critical topic.

1.1

TB Modelling and Analysis Consortium (TB MAC)

Background

The complex natural history of TB, range of possible interventions and great variation in epidemiological settings, mean that TB policy makers and donors face great uncertainty when prioritising TB control activities.

This uncertainty can be reduced and quantified, and the cost-effectiveness of different strategies compared, using mathematical modelling and other quantitative research activities. Several groups of modellers worked separately on issues such as the impact of new diagnostics, drugs and vaccines, but although this work has contributed greatly to understanding the transmission and control of TB, the influence of the work was weakened by a lack of co-ordination, information-sharing, consensus building and prioritisation.

This led to critical research gaps and conflicting policy recommendations which served TB control poorly. Policy making and resource allocation must be based on scientific consensus derived from best analytic inputs, which draw on data and models in epidemiology, economics, demography and related disciplines. The TB Modelling and Analysis Consortium (TB MAC, www.tb-mac.org) aims to improve the interaction between quantitative researchers, policy makers, TB programmes and donors to improve global control. Meetings thus far (see website) have focussed on how modelling can support TB control in high HIV settings, the development, deployment and evaluation of novel TB diagnostics, and rational introduction of new TB regimens.

TB MAC Aim

To improve global TB control by coordinating and promoting mathematical modelling and other quantitative research activities to provide scientific support for policy decisions and implementation.

TB MAC Objectives

1) **Identify research questions** concerning TB control that require input from mathematical modelling or other quantitative research

2) Facilitate **sharing of data**, **information and expertise** to achieve consensus on current knowledge and knowledge gaps, methodological standards and current best practice for TB control decision-making

3) **Fund** small analytical /modelling research projects

4) **Disseminate results and tools** to key stakeholders including TB control programmes and donors

1.2

TB MAC meeting 4: Global post-2015 TB Targets Exercise

This report describes the fourth TB MAC meeting in Seattle, United States of America which was the first meeting on the multi-model exercise organised by TB MAC to explore the Global post-2015 TB Targets Exercise.

Objective of overall exercise:

The objective of the overall exercise is to answer two research questions, one with a specific epidemiological focus (I), and the second with a clear economic perspective (II), which builds on the results found in (I).

I. What is the health impact (TB incidence, mortality, DALYs) if a list of existing/near-existing interventions is scaled up to ambitious but feasible levels by 2025, in South Africa, India and China?

II. What are the costs and cost effectiveness of the alternative strategies, and the optimal strategies under different budget/resource constraints?

Background to meeting

The post-2015 WHO Global TB Programme Strategy was ratified by the World Health Assembly on 19th May 2014. The WHO 'End TB strategy 2016-2035' has a vision of a 'world free of TB (Zero deaths, disease or suffering due to TB)' and the goal of 'Ending the Global TB Epidemic' by 2035, defined as fewer than 10/100,000 cases. Intermediate targets (TB incidence: 50%, mortality: 75%) were proposed for 2025. These new global targets raise many questions. They were said to be ambitious to drive innovation and resource mobilisation, whilst feasible, but how achievable are they at the individual-country level? And which interventions, at what scale, and what resources would be required to achieve these targets?

In this fourth TB MAC meeting we aimed to develop the methods for a multi-model exercise by discussing progress made so far, decide on key issues and set out the path towards the next milestone, TB MAC meeting 5 in October 2014.

Meeting preparation

Following a decision on the scope and setup of the exercise in February 2014, preparations for this meeting were started at high intensity to enable fruitful discussions and decisions. Epidemiological modelling groups were invited to participate, and roles in both the epidemiology and economics streams were distributed amongst participants.

On the Epidemiological modelling side, work was mainly streamed by country. Country teams worked to define required and optional indicators for model calibration. Also, a set of broad epidemiological interventions was outlined that used existing tools only to allow exploration of objective I. For each intervention, core epidemiological parameters were defined to capture the potential epidemiological impact. Two groups (country experts and advocates) were then asked to give their definition of what 'ambitious but feasible' meant in the context of scaling up these interventions. Also, key issues were identified that required decisions during the meeting.

On the Economics side, a group of economists was formed each with the aim to work together on one cost/ cost-effectiveness model. This included economists working with key global agencies, those with expertise in costing, those with particular knowledge of economic evaluation methods and those with country experience. This group met in whole and in smaller groups prior to the meeting, to work together to compile a list of unit costs, review costing models and define a first list of model outputs.

Structure and process of meeting

The meeting was structured into three days, please see appendix 2.1 for the final agenda. While some sessions were joint, most of the meeting was streamed into economic and epidemiology sessions to allow focus on and optimal progress to be made on the specific issues for both streams. Each day was started with a joint summary of decisions made the day before and an overview of the day to come.

For the epidemiology stream, the morning of day 1 focussed on presenting initial results from model calibration and intervention implementation to highlight issues for discussion and decision on day 2. In the afternoon, all of the 12 participating models presented on their model, to generate mutual understanding and appreciation of methods used.

Day 2 was focussed around making decisions on the way forward on the baseline indicators as well as intervention model implementation and operationalization. During the morning of day 3 a joint session saw presentations on Universal Health Coverage and engaged in discussions to clarify definitions and review existing evidence around this major component of the post-2015 Global TB Strategy. The afternoon of day 3 was spent discussing how to deal with the differential age structures of models, as highlighted again during presentations on day 1.

For the economics stream day 1 focussed on defining the intervention to be costed, and familiarising the economists with the modelling plans. The afternoon examined some of the main decisions to be made in the cost modelling, and the review of the cost models. As it was not possible to sufficiently define the interventions on day 1, work continued the morning of the day 2. In the afternoon of day 2 the group divided, with most of the group working on unit costs and some of the group joining the modellers to further work on the interventions, and to better understand the way the modellers were approaching intervention effects. On day 3 the discussions continued on unit costs, but also examined the key outputs required to estimate disability adjusted life years. A summary was presented back to the modellers in the second half of day 3.

1.3

Summary of presentations and decisions Day 1

After a joint session outlining the overall aim for the exercise by Richard White, Rein Houben and Anna Vassall, the streams separated to focus on their respective priorities. The epidemiology stream is summarised below, the economics stream summary (which sums up the main decisions taken in the meeting and some additional work taken thereafter by the core economic team) is presented in terms of draft protocol attached in appendix 2.2.

1.3.1 Day 1 – Epidemiology stream

The country leads for South Africa (Tom Sumner), India (Nim Pathy/ Jeremy Goldhaber-Fiebert) and China (Grace Huynh) presented results from the baseline fits for their respective countries. Key issues that came up for discussion were the challenge of required fitting of mechanistic models to multiple indicators which may not share a mechanistic connection, as well as a trend, particularly for China. A consensus was formed that the list of required indicators would likely need to be short, balanced out by a strong internal peer review process (see day 2). Also how we would define the 2015 baseline value for mortality and incidence, given that models would fit to the available 2012 data points. The definition of TB mortality was also in need of further clarification.

The next session the country leads for South Africa (Tom Sumner), India (Nim Pathy/ Jeremy Goldhaber-Fiebert) and China (Grace Huynh) presented results from the initial intervention implementations by models for their respective countries. These highlighted relatively large differences in impact, which was in part due to differing interpretations of parts of the intervention outline and scale-up. For example, the definition of “population not accessing care” required further clarification to ensure there was a consistent understanding of these issues.

During the afternoon session, 12 short presentations covered methods and implementation of all participating models. Presenters shared key choices they made on capturing TB natural history and care in general, as well as how they implemented the interventions for the TB MAC exercise. This led to highly useful discussions between epidemiological modellers, economists and other stakeholders on whether some broad guidance on how interventions should be implemented would be useful.

1.4

Summary of presentations and decisions Day 2

After a joint session summarising the main outcomes of day 1 and outlining the overall aims for day 2, the streams separated to focus on their respective priorities. The epidemiology stream is summarised below, the economics stream summary is presented in terms of draft protocol attached in appendix 2.2.

1.4.1 Epidemiological Stream

Morning:

The morning discussions focussed on addressing three issues. Firstly clarifying the definition and calculation of the key incidence and mortality indicators, then focussing on how we would require models to match pre-2012 trends and finally how the 2015 baseline might be calculated to compare against 2025 values.

Regarding the definitions, representatives from both GTB and IHME made clear how their estimates for mortality were data driven (e.g. Verbal Autopsies) as much as possible, and as such were not mechanistically linked to values for TB incidence. On pre-2012 trends, the participants suggested that only point estimates of incidence and mortality would be required. However, where data existed on trends (e.g. prevalence surveys in China), groups would be strongly advised to match these in their calibration, as they would weigh in the internal review process. For the 2015 baseline, it was decided to use each model's individual 2015 value as reference, rather than attempt to make a shared point projection for 2015.

During the second session, country experts and advocates presented their respective scale-up scenarios and associated activities. Based on the presentations from day 1, this stimulated useful discussions on how these scenarios would be implemented in the simplified version of reality in the different models.

Afternoon:

In the third session on intervention implementation discussions focussed on how the process of implementing these interventions in the Epidemiological models should be shaped. It was decided that it would be useful to 1) provide some clear guidance to the modelling groups on how interventions should be interpreted and implemented and 2) have a process by which the method of implementation for each model would be reviewed to ensure that groups would not invest time in generating results that would not be accepted at the October meeting.

1.5

Summary of presentations and decisions Day 3

After a joint session summarising the main outcomes of day 1 and outlining the overall aims for day 2, the streams separated to focus on their respective priorities. The epidemiology stream is summarised below, the economics stream summary (which sums up the main decisions taken in a meeting and some additional work taken thereafter by the core economic team) is presented in terms of draft protocol attached in appendix 2.2.

1.5.1 Epidemiological Stream

Morning:

The morning session was spent discussing Universal Health Coverage (UHC), with the aim to decide if and how UHC would be included in the epidemiological modelling. In the morning, Knut Lönnroth and Delia Boccia (remotely) summarised current definitions of UHC, how it relates to social protection and social determinants and how it is an integral part of the post-2015 Global TB Strategy. Also, they covered the limited existing empirical evidence that exists to support implementing UHC through a mechanistic relationship of intervention and epidemiological effect, or cost UHC as a specific activity. See appendix 2.3 for a copy of these presentations.

In the discussions that followed the group explored to what extent UHC was already part of the interventions and intervention activities that were under discussion. In particular interventions aimed at increasing access to high quality care are expected to have a strong UHC component included. Given the lack of data, and explicit consideration of UHC in the intervention scenarios, the decision was taken to not include UHC as a separate intervention in the epidemiological modelling.

Afternoon:

The final session in the afternoon was spent discussing the issue of age conversions. An inventory of the models had shown that about half the models did not include <15 year old populations in their model, whereas the other half did include them to varying levels of detail. To be able to compare the results, the group had to decide to either adjust all the outcomes of one group of models, or provide initial indicators for either 'all ages' or 'adults only' models. To keep things as simple as possible, the group decided to provide 2 sets for the 2 key indicators (incidence and mortality).

1.6

Time line for next steps

Based on the meeting and post-meeting discussions, the timelines and deliverables were adjusted. For the epidemiology, modelling should start in the week of the 21st July, with full results due 22nd August. After some minor adjustments, final results should be sent in by September 15th, so they are ready for discussions at the second meeting (October 2014) and for presentation at the 2014 World Union conference in Barcelona (1st November 2014).

Economics Stream

4th of July – send outputs and combinations to modellers, receive final intervention descriptions from modellers

27th of July – finalise list of unit costs for South Africa and study protocol – send for peer/ expert review

12th Sept – finalise cost model for South Africa, finalise unit cost for all countries, receive final modelling results

6th of October – first cost results for South Africa

APPENDICES

2.1 Meeting Agenda and Participant List

2.2 Draft Protocol

2.3 UHC Presentations

APPENDIX 2.1

AGENDA and PARTICIPANT LIST

Sun 1st

17:35 - 17:50	Shuttles from Hotel 'W' to Welcome Reception
18:00 - 20:00	Welcome Reception @ Collections Cafe, Chihuly Gardens (optional)
20:00 -	Return shuttles to Hotel 'W'

TB Modelling and Analysis Consortium

TB MAC Post-2015 WHO Global TB Targets Meeting
2-4th June, 'W', 1112 Fourth Avenue, Seattle, WA 98101

Richard.White@lshtm.ac.uk; Olivia.Ross-Hurst@lshtm.ac.uk; tb-mac@lshtm.ac.uk

BILL & MELINDA GATES foundation

Presentations need to keep within time

Mon 2nd	1: Epi ('Great Room')	Speaker	Chair		Econ ('Studio 2 and 3')	Speaker	Chair
07:00 - 07:55	Breakfast in Foyer						
08:00 - 08:25	Welcome and overview	RW, AV, RH	MH		<< Joint session		
	P2: Epi - Baseline fits				**E2: Econ - Intervention def & costing scope (1)**		
08:30 - 08:35	Intro (10m present + ~15 min discuss/country)	RH	MH	08:30 - 08:35	Intro	AV	IG
08:35 -	South Africa	TS		08:35 - 09:05	Intervention definitions (so far)	RH	
	India	NP or JG		09:05 - 10:00	Work, presenatations	IG,RT,GG	
- 10:00	China	GH					
10:00 - 10:30	***Refreshments in Foyer***						
	P3: Epi - Intervention results				**E3: Econ - Intervention def & costing scope (2)**		
10:30 - 10:35	Intro (15m present + ~20 min discuss/country)	RH	MH	10:30 - 10:35	Intro	AV	IG
10:35 -	South Africa	TS		- 12:30	Work, presenatations and summary	AV,IG,RT,GG	
	India	NP/JG					
- 12:30	China	GH					
12:30 - 13:30	***Lun***						
	P4: Epi - Model descriptions				**E4: Econ - Further cost model principles**		
13:30 - 13:35	Intro (14m/ model + ~10m present, ~4m discuss)	RH		- 13:35	Intro	AV	AV
13:35 -	TIME	RH			Overview of issues & review	GG/NF	
	Hopkins TB model	DD			Small group work		
	Harvard	NM or TC		- 16:30	Summary	AV	
	STAMP	JGF					
	EMOD	GH					
	IRD	NB					
	SIPTM	AR					
	Imperial	NP					
	UGA	AH					
	Utexas	JP					
	Melbourne	JT					
- 16:25	NTU	RH					
16:25 - 16:30	Wrap up	RH					
	Refreshments in Foyer throughout afternoon						
18:00 - 18:15	Shuttle from Hotel 'W' to Group Dinner						
18:30 - 20:30	Group dinner @ Ray's Boathouse (optional)						
20:30 -	Return shuttle to Hotel 'W'						

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Presentations need to keep within time

Tue 3rd	5: Epi ('Great Room')	Speaker	Chair		Econ ('Studio 2 and 3')	Speaker	Chair
07:00 - 07:55	Breakfast in Foyer						
08:00 - 08:25	Summary of day 1 and overview for day 2	RW, AV, RH	FC		<< Joint session		
	P6: Epi - Final baseline indicators				**E6: Econ - CEA principles**		
08:30 - 08:35	Intro (5m present, ~20 min discuss/country)	RH	FC	08:30 - 08:35	Intro	AV	JS
08:35 -	South Africa	TS		08:35 -	Gates Reference Case	AV	
	India	NP or JG			ECEA	SV	
- 10:00	China	GH	*Econ thru break>>)*	11:00	CEA ranking options and previous approach	JS	
10:00 - 10:30	***Refreshments in Foyer***						
	P7: Epi - Final intervention definitions (Epi)				**E7: Econ - CEA practical**		
10:30 - 10:35	Intro	RH	JE	11:00 - 11:05	Intro	AV	GG
10:35 - 12:25	Discuss by int^{n} to finalise def (~15m/int; 5-10m p	RH		11:05 -	Review of model outputs	AV	
12:25 - 12:30	Wrap up	RH			DALY options	NM/JS	
				12:30	Discussion		
12:30 - 13:30	***Lunch ('Great Room')***						
	P8: Epi - Int^{n} operationalization (Econ) & scale-up				**E8: Econ - Unit costing - Country estimates**		
13:30 - 13:35	Intro	RH	MH	13:30 - 13:35	Intro	AV	RT
13:35 - 14:35	Int^{n} operationalization (econ) (20 pres 40 disc)	AV		13:35 -	Data availability 1	YL	
	Final scale up scenarios (Pres 10+10 & 15 discuss / country)				Data availability 2	AS	
14:35 - 15:10	South Africa	MK+CDorLD			Data availability 3	SS, SC, NF	
15:10 - 15:45	India	PD+CDorLD		16:30	'Filling the gaps'		
15:45 - 16:20	China	DC+CDorLD					
16:20 - 16:30	Wrap up	RH					
	Refreshments outside 'Great Room' throughout afternoon						

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BILL & MELINDA GATES foundation

Presentations need to keep within time

Wed 4th	**9: Epi ('Great Room')**	**Speaker**	**Chair**		**Econ ('Studio 2 and 3')**	**Speaker**	**Chair**
07:00 - 07:55	Breakfast in Foyer						
08:00 - 08:25	Summary of day 2 and overview for day 3	RW, AV, RH	PG		<< Joint session		
	P10: Epi - Universal health				**E10: Econ - Universal health coverage & CEA final**		
08:30 - 08:35	Intro	RH	RH	08:30 - 08:35	Intro	AV	RT
08:35 - 08:55	History of social prot/UHC in TB policy	KL (Skype)		08:35 - 10:00	<< Joint session (UHC). Some of group remain (CEA).		
08:55 - 09:15	Current methods and evidence base	DB (Skype)					
09:15 - 10:00	Discussion	RH					
10:00 - 10:30	***Refreshments in Foyer***						
	P11: Epi - Universal health				**E11: Econ - Universal health**		
10:30 - 10:35	Intro	RH	RH	10:30 - 10:35	Intro	AV	RT
10:35 - 11:30	Discussion & drafting epi approach	RH		10:35 - 11:30	Discussion & drafting econ approach		
11:30 - 12:00	Draft options for Epi approach	RH			<< Joint session		
12:00 - 12:30	Draft options for Econ approach	AV			<< Joint session		
12:30 - 13:30	***Lunch ('Great Room')***						
	P12: Epi - age conv/ Joint summary,next steps				**E12: Econ - Econ Summary/ Joint summary, next st**		
13:30 - 13:35	Intro (5m present, ~20 min discuss/country)	RW	CD	13:30 - 13:35	Intro	AV	AV
13:35 - 13:50	Summary of proposal	RW		13:35 - 14:30	Preparation for joint session	GG,NM,YL,IG	
13:50 - 14:30	Discussion and final decision						
14:30 - 14:55	Epi stream summary and next Epi steps	RH			<< Joint session		
14:55 - 15:20	Econ stream summary and next Econ steps	AV			<< Joint session		
15:20 - 15:30	Overall summary and next steps	RW			<< Joint session		
Refreshments outside 'Great Room' throughout afternoon							

TB MAC Targets Meeting
Participant List

	Name		Organisation
1	Nimalan	Arinaminpathy	Imperial College London
2	Nicolas	Bacaer	IRD
3	Stewart	Chang	Institute for Disease Modeling (IDM)
4	Susmita	Chattopadhyay	Public Health Foundation of India, New Delhi
5	Daniel	Chin	Bill and Melinda Gates Foundation
6	Gavin	Churchyard	Aurum Institute (remote)
7	Frank	Cobelens	AIGHD
8	Theodore	Cohen	BWH/Harvard School of Public Health
9	Colleen	Daniels	Treatment Action Group
10	Puneet	Dewan	Bill and Melinda Gates Foundation
11	David	Dowdy	Johns Hopkins Bloomberg School of Public Health
12	Jeffrey	Eaton	Imperial College London
13	Philip	Eckhoff	Institute for Disease Modeling
14	Mariam	Fofana	Johns Hopkins Bloomberg School of Public Health
15	Nicola	Foster	Health Economics Unit
16	Ines	Garcia Baena	World Health Organization
17	Geoff	Garnett	Bill and Melinda Gates Foundation
18	Philippe	Glaziou	WHO
19	Jeremy	Goldhaber-Fiebert	Stanford University
20	Gabriela	Gomez	AIGHD
21	Andreas	Handel	University of Georgia
22	Mehran	Hosseini	Global Fund
23	Rein	Houben	London School of Hygiene and Tropical Medicine
24	Grace	Huynh	Institute for Disease Modeling

25	Melissa	Kanias	Bill and Melinda Gates Foundation
26	Michael	Kimerling	Bill and Melinda Gates Foundation
27	Yoko	Laurence	London School of Hygiene and Tropical Medicine
28	Nicolas	Menzies	Harvard University
29	Katrina	Ortblad	IHME
30	Jotam	Pasipanodya	UT Southwestern Medical Center
31	Carel	Pretorius	Futures Institute
32	Allison	Rhines	Stanford University
33	Olivia	Ross-Hurst	London School of Hygiene and Tropical Medicine
34	Joshua	Salomon	Harvard School of Public Health
35	Andrew	Siroka	WHO
36	Peter	Small	Bill and Melinda Gates Foundation
37	Sze-chuan	Suen	Stanford University
38	Thomas	Sumner	London School of Hygiene & Tropical Medicine
39	Qiang	Sun	Center for Health Management and Policy, Shandong University
40	Robin	Thompson	UNITAID
41	James	Trauer	Burnet Institute
42	Anna	Vassall	London School of Hygiene and Tropical Medicine
43	Stephane	Verguet	University of Washington
44	Bradley	Wagner	Institute for Disease Modeling (IDM)
45	Ken	Warman	Bill and Melinda Gates Foundation
46	Richard	White	London School of Hygiene and Tropical Medicine

APPENDIX 2.2

DRAFT ECONOMIC EVALUATION OUTLINE

INTRODUCTION

This paper presents the draft economic evaluation protocol for the TB-MAC modelling project on the TB targets. It sums up the main decisions taken in a meeting held in June 2014, with some additional work taken thereafter by the core economic team. It will be circulated for wider review the week of the 7th of July and then to expert review at the end of July 2014. The protocol follows the CHEERS frame (introduction and methods sections). Any final version will also be reviewed to ensure it meets Gates Reference Case Economic Evaluation standards.

TYPE OF STUDY

Cost-effectiveness analysis

BACKGROUND

The post-2015 WHO Global TB Programme Strategy was ratified by the World Health Assembly on 19th May 2014. The WHO 'End TB strategy 2016-2035' has a vision of a 'world free of TB (zero deaths, disease or suffering due to TB)' and the goal of 'ending the global TB epidemic' by 2035, defined as an annual incidence of <10 cases per 100,000 of population. Intermediate targets (TB incidence and mortality reduced by 50% and 75% respectively compared to 2015 levels) were proposed for 2025.

These new global targets raise many questions from an economic perspective. In particular, what is the most cost-effective strategy for reaching controlling TB in the medium term, and what resources will be required for implementing this strategy? It is possible that financial or other constraints may limit the ability of countries to reach the new WHO targets, and in this situation; it is also important to explore the most cost-effective strategy under different resource constraints, and what is the marginal health gain that can be achieved if more funding is made available?

These questions need to be answered taking a long-term perspective; and hence require the use of TB models that include the transmission impact of different TB strategies. However, to date there is a dearth of analyses examining the cost-effectiveness of multiple interventions at the country level using dynamic models.

OBJECTIVES

MAIN OBJECTIVES

In order to provide information for countries looking to accelerate TB control, the TB Modelling and Analysis Consortium (TB-MAC) has undertaken a project to better understand policy options for TB control. This project brings together a number of modelling groups to evaluate the consequences of competing policy options, both in terms of health outcomes and resource utilization. The project focuses on three countries with high TB burden – South Africa, India and China – with intensive analysis of these settings used to derive policy insights for the named countries and more broadly. The overall objective of the exercise is to answer two research questions, one with a specific epidemiological focus (I), and the second with a clear economic perspective (II), which builds on the results found in (I).

I. What is the health impact (TB incidence, mortality, DALYs) if a list of existing/near-existing interventions is scaled up to ambitious but feasible levels by 2025, in South Africa, India and China?

II. What are the costs and cost effectiveness of alternative TB control strategies implemented by 2025, and the optimal strategies under different budget/resource constraints?

SPECIFIC OBJECTIVES (ECONOMICS ONLY)

Clarity about the decisions any analysis is intended to inform is central to any economic evaluation design. Most economic evaluations evaluate one intervention in a single setting. In this analysis the aim is to evaluate combinations of interventions, in the context of a stated policy aim. The stated policy aim of examining whether global targets can be reached is translated into a (decision analytic) economic aim to inform medium term decisions at the country level to invest in different TB control strategies to achieve maximum impact by 2025. However, it should be noted that the aim of this work is not to replace medium term country planning processes (that may be much able to achieve a greater degree of precision and accuracy), but instead to use countries as case studies to inform both national and global decision makers to set broad medium term investment priorities; and explore how they may be impacted by context.

However, there may be a conflict between the stated policy objective of reaching targets and the objective of achieving efficiency in the allocation of resources within TB control, and between TB control and other areas of investment in health (or social welfare). For example, a cost-effectiveness analysis may find that reaching TB control targets is not cost-effective, or conversely, it may find that it is cost-effective to exceed the TB targets. Furthermore, at the margin decision makers may not be able to afford all interventions that are cost-effective, and a further selection may need to be made containing feasible investments by resource constraints. Finally, decisions about TB control strategies do not happen in isolation from other TB control related policy decisions, so any decision analysis may need a broader scope that the TB targets. But within TB control, it will be important to understand the sensitivity of the results to assumptions that may be dependent on external factors. For example, it will be important to know how the above analysis is impacted by global negotiations on prices of TB commodities.

In summary therefore, the following **sub-objectives** are defined for the economic evaluation

1. What is the most cost-effective combination of (near-existing/ existing) TB control interventions that can be scaled up between 2015 and 2025?

2. What is the cost of this combination of interventions, over time and by payer?
3. Does this combination reach or exceed the TB control targets?
4. What combination of interventions is most cost-effective under different budget constraints?
5. How are the costs and cost-effectiveness of this combination of interventions impacted by different assumptions about global prices, key policy decisions, adherence and efficacy of the interventions?

This is translated into the following PICO statement:

Summary PICO statement

PICO refers to four elements that should be in the summary research question governing and economic evaluation and is as follows:
Population: General population in South Africa, China and India, with specific strategies focused on HIV positives and high risk TB groups;

Intervention: Combinations of the six main intervention groups below, scaled up before 2025 and maintained until 2035:

1. Increase access to DOTS
2. Improve DOTS and MDR-TB treatment
3. Replacing Xpert with smear
4. Active case detection
5. Active case detection with preventative therapy
6. Preventative therapy for HIV positive individuals

Comparator: maintaining current (2015) levels of coverage of all strategies up until 2035

Outcome: incremental (health system and patient) cost per outcome (specified below for a set of predefined measures of health impact)

SCOPE AND APPROACH OF THE ECONOMIC EVALUATION

POPULATION (INCLUDING SUB-GROUPS) AND SETTING:

The analysis will be at the country level for three countries: South Africa, India and China. It is recognised that taking this approach for such large countries is limited given the heterogeneity of both costs and probably impact at the regional/ provincial level. Nevertheless this is the only feasible approach given the resources available.

INTERVENTIONS, BASE CASE AND COMPARISONS:

INTERVENTION SETS

The transmission models will examine six broad intervention sets, aimed at impacting different elements of the TB development, detection, diagnosis and treatment pathway. In detail these are:

1) Increase access to high quality TB services (e.g. DOTS based passive case finding, with smear, no change in initial default, current treatment success rate)
    i) increase proportion of population with access to health care (no-care to care).
    ii) increase proportion of TB cases accessing high quality TB services
2) Improve high quality TB services-post diagnosis
    i) Increased linkage into care (reduced pre-treatment loss-to follow up)
    ii) Improving treatment success (including reducing on treatment loss to follow up) for non-MDR TB
    iii) Improving treatment success (including reducing on treatment loss to follow up) for MDR TB
3) Improve passive case finding (Xpert replaces smear as first laboratory test in high quality TB services)
    i) improves diagnosis (and potentially linkage to care) for non-MDR
    ii) improves diagnosis and therefore treatment for MDR TB.
4) Active Case Finding (ACF) in general population (e.g. using Xpert as screening tool)
5) Active Case Finding in general population (with Xpert) + (e.g. 12 wk INH/RPT) Preventive Therapy for complete population (all individuals with latent infection, regardless of HIV status)
6) **HIV SPECIFIC:** continuous IPT for all HIV positive population (assuming lifelong IPT)

BASE CASE

The base case is defined at the maintaining the current (2015) levels of achievement of the objectives for each intervention set as outlined above until 2035.

COMPARISONS

The number of comparisons run by the models may be limited, therefore the comparisons examined are divided into two stages, the first in which all models can participate, and a second more complex set of comparisons that is optional for models.

STAGE ONE - ASSESSING THE COST-EFFECTIVENESS OF EACH INTERVENTION SET AND THE AGGREGATE INTERVENTION SET

The first stage in the comparison will be to examine the cost-effectiveness of the intervention set individually and in aggregate against the base case. *In addition, for intervention set 2 as MDR treatment is likely to have a major cost; we need each row (i,ii,iii) above examined individually*

We require the following levels of intervention outcome: 25, 50, 75, 100% of the country expert, plus advocate levels for 6 interventions sets individually, for the 3 interventions in set 2, and for the aggregate intervention set so a total of 11*5 projections of impact, in addition to the base case of holding all interventions at zero improvement.

All models who wish to participate in the economic evaluation should participate in this analysis.

STAGE TWO - ASSESSING THE MOST COST-EFFECTIVE COMBINATION OF INTERVENTIONS

The second stage will be to compare different combinations of interventions, in order to explore the optimal (in terms of cost-effectiveness) combinations of interventions. ***Models can choose to participate in this element of the economic evaluation.*** Ideally one would run all the combinations of all the 8 interventions (the six sets, with set 2 split) at different objective levels (for example, 25, 50, 75, 100% of the country expert estimates). However this would involve thousands of model runs at the least. There are two options therefore: either we examine a prespecified set of intervention combinations (similar to stage one but for a wider variety of scenarios), or we sample a variety of intervention combinations and use smoothing techniques to fill in the gaps between these sample points.

Option A

For models that are able to run a high number of scenarios we could run all possible combinations of the following 4 strategies with 4 different coverage levels (256 combinations), against the same base case above, using country and advocate level levels of strategies:

i) Interventions focused on improving the access to care and diagnosis (1&3)
ii) Interventions improving treatment (and retention) (2)
iii) Active case detection (4)
iv) Preventative therapy (5,6)

Option B

To allow any combination of strategies to be compared and thus not restrict the analysis based on prior expectations about which combinations will be cost-effective an alternative approach is also suggested. Health impact and costs are likely to vary smoothly as a function of coverage. For this reason, it should be possible to estimate results for a restricted number of intervention combinations and interpolate the other points of interest using Gaussian process regression or other smoothing techniques. However, there would always be some error introduced by the fitting process – initial testing has shown that a sample of 500 intervention

combinations would probably be sufficient to fit smooth curves to the 6 intervention dimensions (even if some curves were weird), with RMSE of <1%.

DECISION RULES

Cost-effectiveness will be established in two ways. Interventions (or combination of interventions) will be ranked according to their ICERs, and prioritised in two ways (one with and without a budget constraint):

a) by selecting all below the willingness to pay thresholds of 1x/3x GNI;

b) by selecting in order of increasing ICERs all interventions below the willingness to pay threshold but where the total cost remains under a pre-defined budget constraint .

Results will be analysed for each model rather than aggregates and averaged. Given the use of thresholds or ranking, models with different impact results may still produce the same ranked order or list of interventions below the threshold. Where these differ between models this will be clearly highlighted in any summary of results rather than final recommendations coming from a mean of all model results.

DETERMINATION OF THE BUDGET CONSTRAINT

We will use a simple fiscal space analysis to determine budget constraints. This uses macro-economic indicators, public finance data (for example % of government expenditure on health and % of health expenditure on TB control) to estimate the potential fiscal space for TB. Macro-economic data however is limited in its ability to predict in the long term, so we may use different scenarios after 2020.

PERSPECTIVE (AND COSTS TO BE INCLUDED)

The study will take a health system and patient perspective. On the health system side, it will include costs to the TB programme, HIV programme (limited to testing and treatment) and include a proportion of costs of any health system expansion required to reach the relevant coverage level of each strategy. The main focus would be on human resource and infrastructure costs. On the patient side it will include both direct and indirect costs to patients. This latter analysis may be limited by country however depending on the final availability of patient cost data.

TIME HORIZON

The time horizon for the implementation of specified coverage (feasible, ambitious) is 2025, with the levels of coverage held constant at the levels of 2025 until 2035 to capture full long term impact

DISCOUNT RATE

A 3% discount rate will be used, with a sensitivity analysis around 5%, 1% and 0% given the long term nature of the effect.

EQUITY IMPLICATIONS

The TB targets included a specific aim of reducing catastrophic expenditures. While it is beyond the resources of this work to fully examine equity implications; where the data allows our estimates of patient costs will be used to assess the impact of each option in terms of changes in catastrophic expenditures. Further work on the metrics used to assess catastrophic expenditures will be discussed in the October meeting.

METHODOLOGY

OUTCOMES AND UNITS OF BENEFIT

The measure of health outcome should capture positive and negative effects on length of life and quality of life, and should be generalizable across disease states. The main measure will therefore be the Disability Adjusted Life Years (DALYs) averted.

However, both global advocates and national level decision makers may also value other health outcomes, therefore TB death averted, and life years saved will also be reported. A TB death averted will be defined as the total number of deaths among individuals with active TB or currently receiving TB treatment.

MEASUREMENT OF EFFECT (SINGLE STUDY OR SYNTHESIS BASED ESTIMATES)

QUALITY OF EVIDENCE

EVIDENCE OF THE LINK BETWEEN THE INTERVENTION SET OBJECTIVE AND HEALTH OUTCOMES

The transmission models will estimate the population impact of each intervention. For some of the intervention sets specific technologies are described (eg. Xpert, IPT) and the evidence that will be used for these has been determined. These are outline in the table directly below. For other intervention sets, country experts have made a suggestion of the technology (eg. Bedaqualine for improving treatment success for MDR-TB). Finally, country experts have also made suggestions of necessary programmatic actions (eg, tracing defaulters) for most of the interventions below. The full list of the country expert suggestions for South Africa is presented in Annex 1.

Table 1 – Evidence of Effect

Intervention	Effect	Evidence
Increase access	The direct effect of the intervention is assumed to be equal to the combination of the increase in the proportion of diagnosed cases starting treatment who then are cured.	None globally – as technology/ intervention undefined (see below for definitions for SA)
Improve quality of post-diagnostic services	The direct effect of the intervention is assumed to be equal to the combination of the increase in the proportion of diagnosed cases starting treatment who are cured.	None globally – as technology/ intervention undefined (see below for definitions for SA)
Improve passive case detection (Xpert replaces smear)	The direct effect of the intervention is assumed to be equal to the combination of the increase in TB cases diagnosed who go on to start treatment and are cured. This takes into account the following evidence related to Xpert. ◦For Xpert as initial test for pulmonary TB, sensitivity is 89% (85% to 92%) and specificity is 99% (98% to 99%) ◦For smear-positive, culture positive, sensitivity is 98% (97% to 99%) ◦For smear-negative, culture positive, sensitivity is 68% (59% to 74%) ◦For detection of rifampicin resistance, sensitivity is 95% (90% to 97%) and specificity is 98% (97% to 99%). Increase diagnosis of smear-negative pulmonary TB compared to smear microscopy	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, PaiM, Dendukuri N. Xpert® MTB/RIF assay for pulmonary tuberculosis andrifampicin resistance in adults. *Cochrane Database Syst Rev* (2013)

	Increase diagnosis of rifampicin resistance (as proxy for MDR) Some evidence that Xpert may reduce time to diagnosis (compared to culture) and therefore reduce time to treatment and initial default Population-level evidence from South Africa has shown no impact of Xpert on number of cases started on treatment or on mortality, because of high levels of empiric treatment (ref to CROI abstracts). Based on SA RCT data above and country expert opinion for China and SA, we propose that the direct effect of this intervention on additional new pulmonary smear negative cases started on treatment is zero, and the direct effect of the intervention on number of new MDR cases started on treatment is equal to the coverage of Xpert.	
Active case detection	The direct effect of the intervention is assumed to be equal to the combination of the increase in TB cases diagnosed who go on to start treatment and are cured. This takes into account the following evidence related to screening, X-ray and Xpert. The sensitivity for the various algorithms was acquired by multiplying the values from table 2 (pg 44) in the WHO guidelines: Sensitivity of test Symptom screen: 70% for China and India, 84% for South Africa Chest Xray: 90% after symptom screen, 98% as first test (any sign) Xpert: 89%	WHO, Systematic screening for active tuberculosis: principles and recommendations, WHO, Editor. 2013, World Health Organisation: Geneva. Steingart, K.R., et al., Xpert(R) MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev, 2014. 1: p. CD009593.
ACF plus IPT	The direct effect of the intervention is as above and reduction in TB incidence as defined below: IPT reduces TB incidence in HIV-s (RR = 0.4 (0.31 to 0.52))1 Effects in HIV-s observed for 2 years or longer (limited by follow up of trial)1 Reduces TB deaths in HIV-s but no impact on all cause mortality1 In high adherence (>80%) group over 2 years of follow-up (Thompson 1982 analysis of IUTD trial data), RR was 0.2 compared to placebo.1 Combination regimen of isoniazid and rifapentine administered weekly for 12 weeks as effective as 9 months INH but with higher completion rates (82% vs 69%)2 Good evidence for individual-level intervention effect over 2 years. The direct effect of the intervention is assumed to be equal to the product of prevalence of LTBI in the HIV-negative population, the proportion of latent population started on LTBI treatment, the proportion completing treatment and the empirical protection measure over 2 years in those that completed. Population level impact will be a model output.	Smieja M, Marchetti C, Cook D, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Database Syst Rev 2005 Jereb, J.A, Goldberg, S.V, Powell, K, Villarino, M.E., LoBue. P. Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection. Morbidity and Mortality Weekly Report (CDC) 2011
Continuous IPT for HIV positives	As above but, effect of IPT for PLWH not on ART During therapy: reduction in TB disease of 32% overall compared to placebo, 62% in those with positive TST. Suggest we use 32% as overall measure, since infection status (which models may know) is not the same as positive TST in this population. 1 Note: studies recorded effect beyond IPT period. Protection post-IPT (prevention of reactivation of existing infections): 0% 2 Adherence of IPT alone: In the BOTUSA study, which gave IPT mostly without ART for 36 months, 78% of participants had good adherence (>80% of refill visits completed).	Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev 2010; (1): CD000171. Houben RM, Sumner T, Grant AD, White RG. Ability of preventive therapy to cure latent Mycobacterium tuberculosis infection in HIV-infected individuals in high-burden

	Effect of IPT for PLWH on ART During therapy (in trial of 12m IPT): 37% additional reduction in risk of TB disease during study (Rangaka et al, Lancet 2014). No evidence for difference by TST status Post therapy (prevention of reactivation of existing infections): not yet clear, potentially higher – results being worked on. Adherence IPT in combination with ART: In the IPT+ART study, lost to follow-up was 11%. This included those who defaulted on the study drug for >3 months. Good evidence for individual-level intervention effect over 3 years. Assume protection continues beyond 3 years in adherers. The direct effect of the intervention is assumed to be equal to permanently reducing the rate of TB disease progression in a proportion of Mtb infected pre-ART and on-ART individuals. The size of this group is calculated below. Population level impact will be a model output.	settings. Proceedings of the National Academy of Sciences of the United States of America 2014; 111(14): 5325-30. Samandari, T., et al., 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet, 2011. 377(9777): p. 1588-98.

Based on the above and the country lists of technologies and programmatic actions, the following levels of achievement of each intervention set objectives will be used in the country expert and advocates scenarios by the modeling teams (table below). These estimates have been made on expert opinion and in a relatively short timeframe. Given the centrality of the link between investment in a technology/programmatic action and effect to any economic evaluation, further work will be undertaken by the economic group to refine the list of technologies and programmatic actions (before embarking on costing the extensive list of technologies and programmatic activities proposed) in July and August.

This work will:

a) Where possible first consolidate interventions into a shorter list (for example combine technologies and corresponding programmatic actions into on intervention where possible)
b) Conduct a rapid review of all evidence of effectiveness around each of the intervention listed in either the Table above or by the country specialists.
c) Review all interventions against WHO guidelines
d) For all interventions with efficiency provide point estimates and uncertainty bounds
e) For interventions that currently have no evidence of effect further discuss with NTPs and either exclude or provide uncertainty bounds
f) For each intervention provide sufficient detail for costing
g) Where no current cost evidence is available, identify sources of prices

The starting point will be South Africa and if a similar approach may be applied in India and China.

The review of effectiveness may result in the intervention set having a different performance in terms of the levels of reaching each of the indicators for effect/ coverage used by the modelling teams – however as the combination work above requires more levels of intervention effectiveness/ coverage than those pre-specified by the country experts there should be some flexibility to incorporate this additional analysis into the economic evaluation.

Table 2 – Levels of coverage/ effect used in the models

			Country experts		Advocates	
Target Population Population in Epi model *(Real life population reflected)*	Intervention parameter	Baseline	Target value	Target year+ shape	Target value	Target year+ shape
Intervention set 1 – Increasing access						
Population not accessing TB services	% not accessing any care	**Ch**: 5% **In**: 9.5% **SA**: 0%	**Ch**: 2% **In**: 4.75% **SA**: 0%	**Ch**: 2025 **In**: 2024 **SA**: NA	**Ch**: 0% **In**: 0% **SA**: 0%	**Ch**: 2020 **In**: 2020 **SA**: 2020
Proportion of TB cases accessing high quality TB services (of those accessing care)	% accessing high quality care	**Ch**: 80% **In**: 50% **SA**: 11%*	**Ch**: 95% **In**: 75% **SA**: 100%	**Ch**: 2025 **In**: 2024 **SA**: 2021	**Ch**: 100% **In**: 95% **SA**: 100%	**Ch**: 2020 **In**: 2020 **SA**: 2020
Intervention set 2 – Increasing post-diagnostic						
TB case population diagnosed in high quality TB services	% Initial default in HQ TB service	**Ch**:3% **In**:10% **SA**:17%	**Ch**:1.5% **In**:5% **SA**:5%	**Ch**: 2025 **In**: 2015 **SA**:2025	**Ch**: 0% **In**:0% **SA**:0%	**Ch**: 2020 **In**:2020 **SA**:2020
TB cases starting TB treatment for correctly diagnosed drug sensitive TB in high quality TB services	% DS TB Rx success in HQ TB services	**Ch**: 82% **In**:75% **SA**:76.1%	**Ch**: 90% **In**:85% **SA**:90%	**Ch**: 2025 **In**:2019 **SA**:2025	**Ch**: 95% **In**:90% **SA**:85%	**Ch**: 2020 **In**:2020 **SA**:2020
TB cases starting treatment for correctly diagnosed MDR TB in high quality TB services	% MDR TB Rx success in HQ TB services	**Ch**: 55% **In**:48% **SA**:28%	**Ch**: 65% **In**:67% **SA**:75%	**Ch**: 2025 **In**:2022 **SA**:2025	**Ch**: 80% **In**:80% **SA**:75%	**Ch**: 2020 **In**:2020 **SA**:2020
Intervention set 3 – Passive case detection						
TB cases with MDR TB (*TB suspects accessing high quality care*)	Coverage of Xpert	**Ch**: 0% **In**:0% **SA**:87%	**Ch**:100% **In**:30% **SA**:100%	**Ch**: 2022* **In**:2019 **SA**:2019	**Ch**:100% **In**:100% **SA**:100%	**Ch**:2020 **In**:2020 **SA**:2015
Intervention set 4 – Active case detection						
General population (implemented to reflect targeting high risk groups, following scale up scenarios)	% of total population reached	Assume no ACF at baseline	**Ch**: 13%^ **In**:1.2%* **SA**: 27%**	**Ch**: 2015 **In**: 2018 **SA**: 2016	**Ch**: 30% **In**: 30% **SA**:50%	**Ch**: 2020 **In**: 2020 **SA**: 2020
General population (implemented to reflect targeting high risk groups, following scale up scenarios)	Frequency	Assume no ACF at baseline	**Ch**:1x/year **In**:1x/year **SA**:1x/year	-	**Ch**: 2x/year **In**: 2x/year **SA**:2x/year	-
General population (implemented to reflect targeting high risk groups, following scale up scenarios)	Algorithm sensitivity	Assume no ACF at baseline	**Ch**: symptom+Xray: 63% **In**: Algorithm not specified **SA**: sympto+Xpert: 75%	-	**Ch**: Xray+Xpert: 87% **In**: Xray+Xpert: 87% **SA**: Xpert only: 89%	-

Intervention set 5 – Active case detection with IPT						
General population (implemented to reflect targeting childhood and adult contacts of TB cases, following scale up scenarios)	% population in latent infection compartment started on LTBI Rx	**Ch:**0% **In:**0% **SA:**0%	**Ch:**NA **In:**NA **SA:**1%*	**Ch:**NA **In:**NA **SA:**	**Ch:**NA **In:** 30% **SA:** 1%**	**Ch**:NA **In**:2020 **SA**:2020
Intervention set 6 – IPT for HIV+						
HIV positive population (by ART)	Coverage of continuous IPT	**Ch:** 0% **In:** 0% **SA:**15% (of those on ART) or 6% (of all HIV+)	**Ch:** N/A **In:** N/A **SA:** 100% of ART receiving population. 0% of HIV positive not on ART	**Ch:** N/A **In:** N/A **SA**:2019	**Ch:** 100% of all HIV positives with known status **In:** 100% of all HIV positives with known status **SA:** 100% of all HIV positives with known status	**Ch:** 2020 **In:** 2020 **SA:**2020

UTILITIES

DALYs will be estimated both with and without discounting and no age weighting. DALYs and other outcomes will be derived using the following key model outputs. To estimate years living with disability (YLDs) and (YLLs) respectively:

YLDs: For each year, the total number of individuals in each health state and each age group at the midpoint of the year (N_tia)

YLLs: For each year, the number of deaths for each age group and health state (D_tia)

Total YLLs will be estimated using the mean age of death and national age specific life expectancy. Where models are unable to produce deaths for different age groups, mean age at death will be sourced from the models that are able to produce age specific death rates.

For YLDs, the following disease weights will be used for the individuals living in each health state:

HIV / TB	No Active TB	Active TB
HIV negative	0.000	0.331
Asymptomatic HIV (CD4>350)	0.054 [1]	0.331 [2]
Symptomatic HUV (CD4 350-200)	0.221	0.399
AIDS (CD4<200)	0.547	0.547 [3]
ART	0.053	0.331 [2]

[1] Assumed equal to generic uncomplicated disease [2] Assumed equal to 'Active TB, HIV negative' [3] Assumed equal to 'AIDS, No active TB' Also: currently ignoring background population distribution of disability

MEASUREMENT AND VALUATION OF COSTS

The total and incremental costs will be estimate for each intervention set and combinations of interventions. Levels of costs to be considered include TB-related health provider, programmatic costs, as well as health systems (running and development) costs.

The costs of each intervention will be measured using model outputs that either directly or indirectly provide a level of resource use for each intervention (ie numbers of Xpert tests, numbers of people screened). The extent to which models are able to provide the outputs required is anticipated to vary by model.

A cost model common to all models will be built around these outputs and country-specific unit costs. Prior to June's meeting a full review of cost models publicly available was carried out. These included the WHO TB Financing, Planning and Budgeting tool, the Management Sciences for Health TB costing tool, OneHealth, and Marginal Budgeting for Bottlenecks. Following discussions at the meeting, it was decided to build on the Excel based World Health Organization Costing and Budgeting Tool for cost estimates. This tool was assessed to be comprehensive and transparent enough to be adapted to the scope of this evaluation as outlined above.

ESTIMATES OF RESOURCE USE (NUMBERS OF TECHNOLOGY/PROGRAMMATIC ACTIONS)

The following model outputs on resource use are required:

Table 3 – Model outputs required for the cost model

Intervention	Model output	Unit cost
Intervention set 1		
Population not accessing TB services		Intervention cost
Proportion of TB cases accessing high quality TB services (of those accessing care)	Annual suspects Annual persons diagnosed with TB through passive case detection Total number of months for those with TB to remain unscreened (also applies active case detection) by year	Screening cost (symptoms, other) Cost stratified by diagnostic approach (see 2 below) Intervention cost Patient cost per month of being undiagnosed
Intervention set 2		
TB case population diagnosed in high quality TB services	Total number of months for those with TB to remain untreated following screening by year	Patient cost per month of being untreated
TB cases starting TB treatment for correctly diagnosed drug sensitive TB in high quality TB services	Annual first line patient months stratified by new and retreatment (DOTS) Annual first line patients started on treatment stratified by new and retreatment (DOTS) **OR** Mid-point numbers of first line patients on treatment stratified by new and retreatment by year	Treatment cost by month (IP and CP) HCT Intervention cost Patient cost of treatment

TB cases starting treatment for correctly diagnosed MDR TB in high quality TB services	Annual secondline patient months stratified by new and retreatment Annual patients started on treatment stratified by new and retreatment **OR** Mid-point numbers of first line patients on treatment stratified by new and retreatment by year	Treatment cost by month (IP and CP) (may include additional drugs) Intervention cost Patient cost of treatment
Intervention set 3		
TB cases with MDR TB (*TB suspects accessing high quality care*)	Fraction of suspects receiving the Xpert algorithm Fraction of suspects receiving DST	Xpert Culture DST X-ray Antiobiotic trial
Intervention set 4		
General population (implemented to reflect targeting high risk groups, following scale up scenarios)	Annual suspects screened by suspect group Annual numbers diagnosed with TB through active case detection Mean number of months for those with TB to remain undiagnosed (also applies passive case detection) by year	Cost stratified by screening approach (see 1 and 3 above) Intervention cost (case finding) Intervention cost (linkage to care) Patient cost per month of being undiagnosed
Intervention set 5		
General population (implemented to reflect targeting childhood and adult contacts of TB cases, following scale up scenarios)	Annual persons started on IPT **OR m**id-point numbers of persons on IPT Annual person months on IPT	IPT Intervention cost Patient cost per month of treatment
Intervention set 6		
HIV positive population (by ART)	Annual persons started on IPT **OR m**id-point numbers of persons on IPT Annual person months on IPT	IPT Intervention cost to maintain adherence Patient cost per month of treatment

In addition we will include the costs of ART and end of life care

ART		
ART	Annual persons started on ART Annual person months on ART	ART (first year and subsequent years) Patient cost per month of treatment
End of life care		
Deaths	Annual deaths	End of life care cost

PRICES (UNIT COSTS)

During the meeting, we reviewed the cost data published (systematic review of TB treatment (1st line), MDR treatment and diagnostic costs from provider's and patient's perspective), publicly available (WHO unit costs), and unpublished data from studies in India, China and South Africa. Overall, it was estimated there is sufficient unit cost data to cost the suggested interventions.

Where data are missing, we will first extrapolate resource use from other (similar) settings, but only where the intervention is identical. If not we will need to build unit costs using this with local prices. If we don't have data on the inputs required, then we will use WHO guidelines. Consideration was given to using an econometric model or a GDP adjustment, but the experience of the group suggested that although TB costs are substantially determined by GDP, given the heterogeneity of the cost studies used (in methods and the precise nature of the intervention costed) to estimate costs, it was hard to develop good predictive models for any particular setting with a data gap (please note though this does not include the use of WHO unit costs, these use extrapolation and will be used, this point on applies for areas where no cost data is available from the WHO).

With regards to systems costs, we will aim to estimated overall requirements of each intervention, and review secondary data to conduct a limited capacity assessment of HR and facilities in the health system. Results will be presented showing costs where the full health system cost is considered incremental, where all 'running' human resource and infrastructure costs in service provision are included; and also where it is assumed that 100% of all additional TB human resource and infrastructure requirements can be absorbed within existing capacity – to show the sensitivity of our results to decisions made about the incremental nature of human resource and infrastructure requirements. Where feasible a best estimate will be made, supported by local data on human resource and infrastructure availability however this may not be possible given the data requirements involved.

All costs will be reported in 2014 US$.

METHODS FOR HANDLING UNCERTAINTY

While ideally a full sensitivity analysis should be conducted, in practice running probabilistic sensitivity analyses may not be practical (although may be considered for specific models). Uncertainty around the effectiveness of each intervention in achieving its objective will be addressed through the combinations above. In addition on the cost side of the model we consider uncertainty around price. This will include uncertainty around unit costs estimates from the literature, from choices made about the model of service delivery (for example ambulatory or hospitalized MDR-TB treatment), prices (drugs and technology prices) and around the intervention design. We will use one-way and multi-way analyses to explore the impact of these factors on ICERS and also the combination of interventions that is found to be optimal.

OUTPUTS

Finally we anticipate two core papers from this analysis:

a) One involving all models estimating the costs and cost-effectiveness of reaching the resource requirements using country and advocate based approaches
b) A second, involving a selection of models looking at the most cost-effectiveness TB control strategies by 2025
c) Possibly additional articles based examining patient costs and catastrophic expenditures; and one on health systems costs of achieving TB control objectives
d) TBD policy documents and country dissemination

APPENDIX 2.3

PRESENTATIONS

The impact of social protection on TB: evidence available and the role of mathematical modelling

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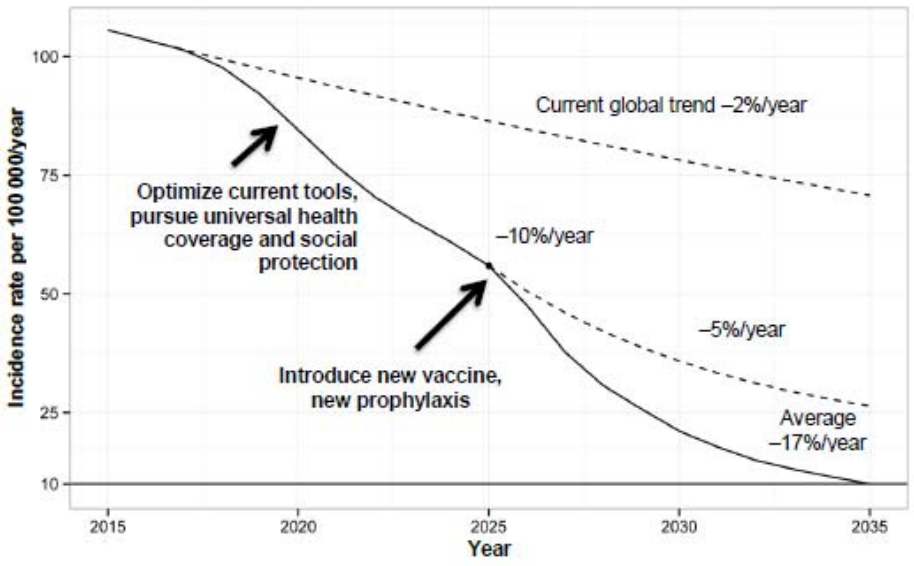
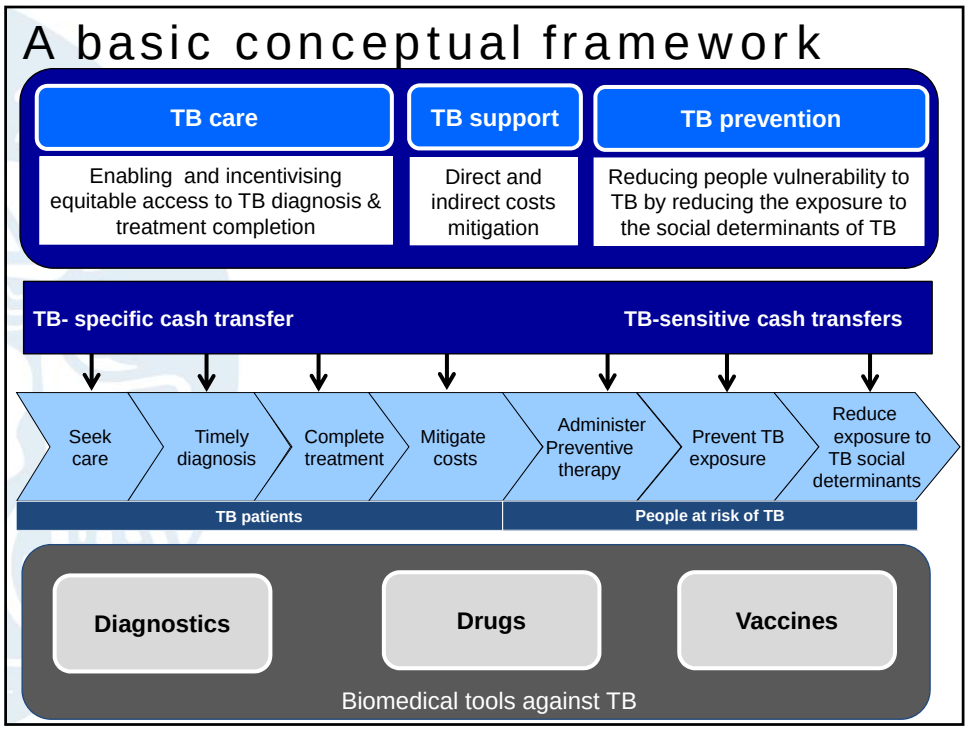
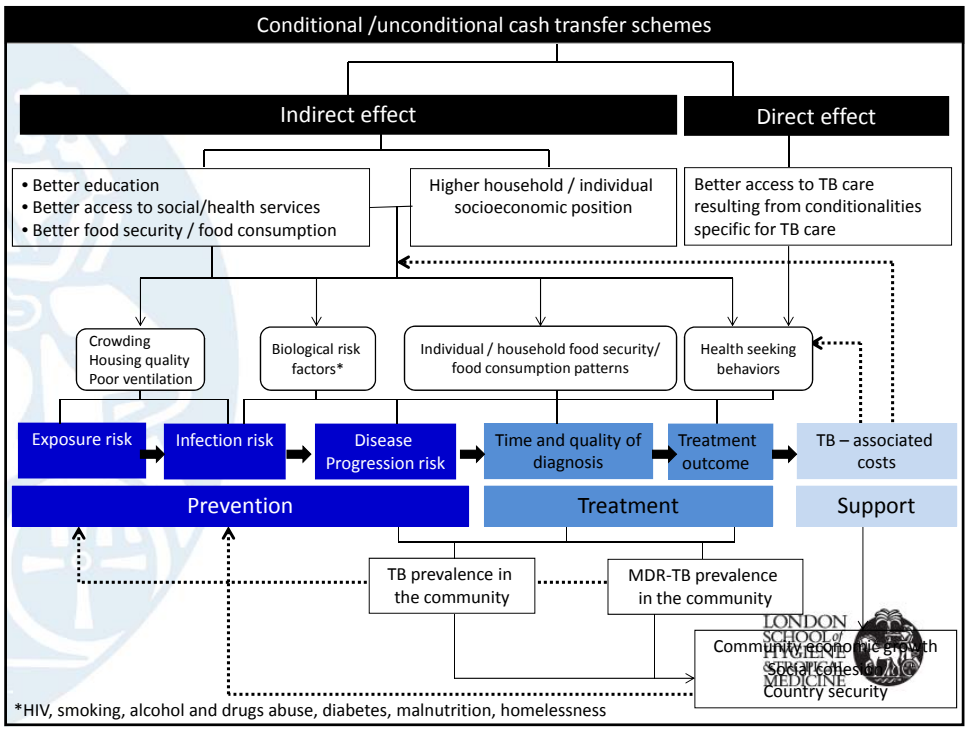
LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

The role of social protection for TB




A basic conceptual framework
TB care
TB support
TB prevention
Enabling and incentivising equitable access to TB diagnosis & treatment completion
Direct and indirect costs mitigation
Reducing people vulnerability to TB by reducing the exposure to the social determinants of TB
TB- specific cash transfer
TB-sensitive cash transfers
Seek care
Timely diagnosis
Complete treatment
Mitigate costs
Administer Preventive therapy
Prevent TB exposure
Reduce exposure to TB social determinants
TB patients
People at risk of TB
Diagnostics
Drugs
Vaccines
Biomedical tools against TB


Conditional /unconditional cash transfer schemes
Indirect effect
Direct effect
• Better education
• Better access to social/health services
• Better food security / food consumption
Higher household / individual socioeconomic position
Better access to TB care resulting from conditionalities specific for TB care
Crowding
Housing quality
Poor ventilation
Biological risk factors*
Individual / household food security/ food consumption patterns
Health seeking behaviors
Exposure risk
Infection risk
Disease Progression risk
Time and quality of diagnosis
Treatment outcome
TB – associated costs
Prevention
Treatment
Support
TB prevalence in the community
MDR-TB prevalence in the community
Community economic growth
Social cohesion
Country security
*HIV, smoking, alcohol and drugs abuse, diabetes, malnutrition, homelessness

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Cash transfer and microfinance interventions for tuberculosis control: review of the impact evidence and policy implications

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SUMMARY

OBJECTIVE: To quantify the impact of cash transfer and microfinance interventions on a selected list of tuberculosis (TB) risk factors and assess their potential role in supporting TB control.

DATA SOURCE: Published and unpublished references identified from clinical and social electronic databases, addressed TB or any other respiratory infection. Of 11 cash transfer and four microfinance interventions, respectively seven and four reported a positive impact on indicators of economic well-being. A positive impact on household food security was documented in respectively eight of nine and three of five cash transfer and micro-

Impact on poverty and living standards

Country / Intervention	Impact
Mexico / PROGRESA	Poverty rate reduction by 17%
Nicaragua / RPS	Extreme poverty rate reduction by 22 percentage points Annual total household expenditure increased by 219%
Colombia / PFS	Extreme poverty rate reduction by 5.8 percentage points
Bangladesh / RMP	Reduction of people living below the poverty line by 16%
Malawi / Mchinji	Improved economic situation: 87% (intervention) vs 4.3% control Improved housing quality: 47.3% (intervention) vs 11.5% (control)

Source: Boccia D, Hargreaves JR, Lonnroth K, Jaramillo E, Uplekar M, Porter JDH, et al. Cash transfer and microfinance intervention for tuberculosis control: review of the impact evidence and policy implications. International Journal of Tuberculosis and Lung Disease 2011;15(Supplement 2):S37-S49.

Impact on food security and food consumption

Country / Intervention	Food intake: quality and quantity
Mexico / PROGRESA	Mean caloric availability per person/day + 7.8%
Nicaragua / RPS	Increased consumption of meat (+2.2%) and fats (+2.4%)
Zambia / SCT	Households living with 1 meal / day: 9% (baseline) vs 13% (follow up) Households still hungry after each meal : 56% (baseline) vs 34% (follow up) Households having fats at least 1/week: 18% (baseline) vs 48.2% (follow up)
	Food expenditure
Mexico / PROGRESA	Median value for food consumed/person +11%
Nicaragua / RPS	Annual per capita food expenditure + US $78
Malawi / Mchinji	Household monthly food expenditure + 3,125 Malawian Kwacha in the intervention group

Source: Boccia D, Hargreaves JR, Lonnroth K, Jaramillo E, Uplekar M, Porter JDH, et al. Cash transfer and microfinance interventions for tuberculosis control: review of the impact evidence and policy implications. International Journal of Tuberculosis and Lung Disease 2011;15(Supplement 2):S37-S49.

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Impact on access and health seeking behaviou

Country / Intervention	Impact
Mexico / PROGRESA	Overall mean monthly consultation +6% Mean monthly consultation per public provider + 9% Mean daily hospital consultation -5%
Honduras / PRAF	Antenatal care visits +19% in the intervention group Visits (under 3 years of age) +20% in the intervention group
Nicaragua / RPS	Children taken to the growth monitoring check +24% in the intervention group
Malawi / Mchinji	Adults seeking health care when sick: 84% (intervention) vs 10% (control) Households spending nothing on health care: 25.3% (intervention) vs 63% (control)
Nepal / SDIP	In government facility birth +24% in the intervention group
Jamaica / PATH	Preventive health care visits among children (0-6 years) +38% in the intervention group

Source: Boccia D, Hargreaves JR, Lonnroth K, Jaramillo E, Uplekar M, Porter JDH, et al. Cash transfer and microfinance interventions for tuberculosis control: review of the impact evidence and policy implications. International Journal of Tuberculosis and Lung Disease 2011;15(Supplement 2):S37-S49.

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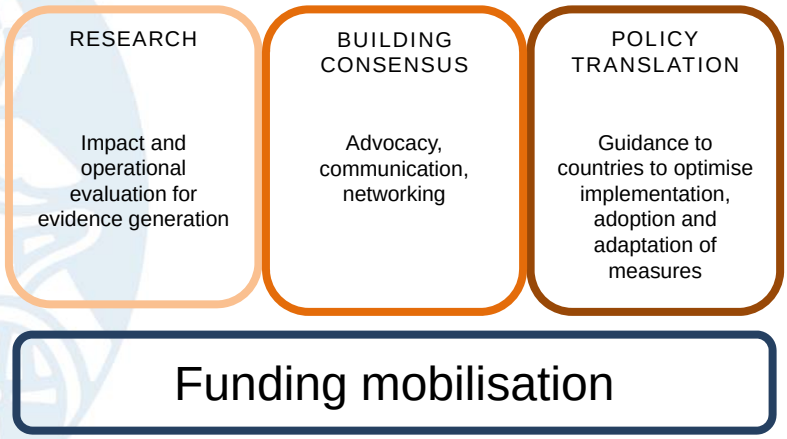
Three areas of work



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Cash transfer interventions for TB control: current research gaps

Direct impact on TB indicators not yet available
Targeting: Low coverage and stigma associated with TB-affected families
Conditionality: heavily dependent on quality and availability of TB care services
Duration of coverage and exit strategy
Possible perverse incentives (i.e. Remaining sick)
Cash and / or food transfers
Administration problems: inefficiencies due to complex system, high transaction costs, and high risk of corruption
Potential negative impact on social cohesion (i.e. Jealousy)
Affordability, capacity

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Three areas of work

RESEARCH BUILDING POLICY

PERSPECTIVE

Weigh all TB risks

A narrow definition of risk is hampering the search for new methods of tuberculosis control, say **Christopher Dye** and **Mario Raviglione**.

measures

try and housing. This demands a big but potentially rewarding programme of data collection, quantitative analysis and modelling — one that enlarges the idea of risk to unify TB treatment and prevention, and places both in the wider context of health and development. ■

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Research questions for modelling from a non-modeller

- Knowing their impact on TB social determinants, what is likely to be the impact of cash transfers on TB control?
- What is the added value of incorporating cash transfer interventions into TB control program practices?
- How large would the effects of cash transfer need to be to accelerate our progress towards TB elimination?
- Are cash transfer interventions cost-effective compared with biomedical interventions for TB control?
- How would this compare with alternatively investing these resources in diagnostic and treatment tools?
- What parameters, in terms of population targeted (e.g. poor household versus TB-affected families), benefits transferred (i.e. food or cash) and conditionality applied, are most critical to maximise the impact of cash transfer interventions on TB control?
- What partnership models are likely to be more effective and cost-effective?

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The case of Brazil

- High TB burden country
- Incidence and mortality rates declining since early '90s, but operational indicators (such as case finding and cure rates) are stable and below the elimination 70/85% targets
- Strong political commitment to address TB through multidisciplinary actions involving TB control programme and the Ministry of Welfare and Development
- Linkage between TB register (Sinan) and CadUnico, a census of poor people in Brazil eligible for social protection programs, including Bolsa Familia

CadUnico

- Tool to characterise poor households in Brazil: "socioeconomic diagnosis"
- Aim: to identify households in needs of social protection and have a census of households benefitting from social protection interventions (biannual review of eligibility criteria)
- Data collected: family composition, civil status, educational level, employment status, income and expenditure data
- Individuals are identified through a Social identification number that can be linked to other databases, including the national TB registry
- 25% of TB patients are included in CadUnico (approx 18,500)
- 14% of TB patients are enrolled in Bolsa Familia (approx 10,300 patients)

*Source: www.who.int/tb/barreira_**brazil**experience.pdf*

Bolsa Familia

- Governmental conditional cash transfers: 13,3 millions of beneficiary households (approx 50 million of people)
- Financial impact: 0.46% of GDP, US$ 10 billion
- Aim: to relief households from extreme poverty
- Target households: households living below the poverty line (per capita monthly income ranging US$35-70.
- Cash size: US$18-175 per month depending on household composition
- Conditions: 1) prenatal and postnatal checks; 2) nutrition and vaccination monitoring for children aged 0-7; 3) school attendance.

*Source: www.who.int/tb/barreira_**brazil**experience.pdf*

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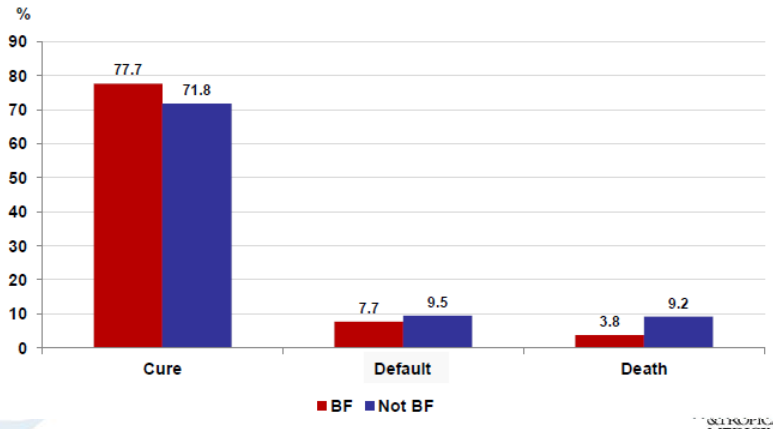
Preliminary evidence on the impact of Bolsa Familia on TB (2011)

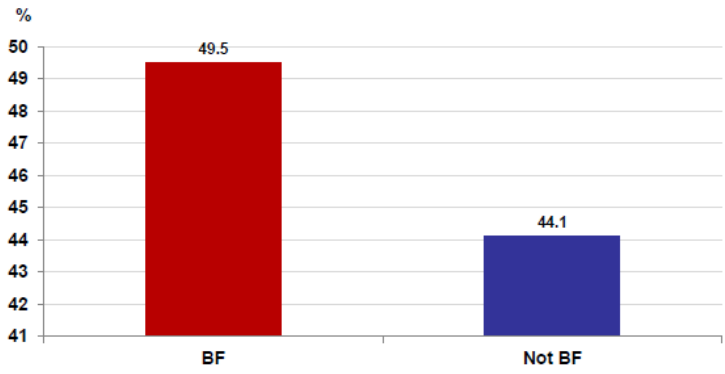
Treatment outcome



*Source: www.who.int/tb/barreira_**brazil**experience.pdf*

Preliminary evidence on the impact of Bolsa Familia on TB (2011)

Case finding under DOTS



*Source: www.who.int/tb/barreira_**brazil**experience.pdf*

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Our research agenda with Brazil

Investigation	TB outcome	Methods	Data
Linkage CadUnico/SINAN	Treatment adherence	Quasi-experimental design	Secondary
Trial	TB treatment adherence and support	RCT with three arms: 1. TB patients receiving standard of care 2. TB patients recruited "passively" on Bolsa Familia 3. TB patients recruited "actively" on B	Primary and secondary
Modelling	TB prevention	Prediction of impact of Bolsa Familia on TB trends in Brazil under different scenarios of Bolsa Familia and NTP performance	Secondary
Case-control	TB prevention and treatment	Case-control study using prevalent cases possibly	Primary

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Our Wellcome Trust proposal

- Objective 1: To explore the impact of Bolsa Familia on key social determinants of TB and ultimately the expected impact on TB incidence
- Methods: a Population Attributable Fraction approach to calculate the change in the proportion of TB incidence (i.e. number of TB cases that could be averted) as a consequence of the: a) *direct* effect of Bolsa Familia effect on household socioeconomic position and other social determinants of TB and; b) *indirect* effect of Bolsa Familia on TB risk factors.
- Data: Literature data
- Outcome: Estimate of the proportion of TB cases potentially averted by Bolsa Familia

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Our Wellcome Trust proposal

- Objective 2: To quantify the full long-term population effect of Bolsa Familia on TB incidence using a novel dynamic TB transmission model
- Methods: adaptation of a standard compartmental TB transmission model to account for the effect of any socioeconomic improvement on TB secular trends that may have happened in Brazil independently from Bolsa Familia. Then the model will be stratified by enrollment in Bolsa Familia.
- Data: data from CadUnico analysis on the impact of Bolsa Familia on health seeking behaviours and TB indicators, socioeconomic and TB trends
- Outcome: impact of a Bolsa Familia on TB incidence rates on top of background economic changes in Brazil

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1

New stuff in pillar 2:
UHC, regulation, social protection, social determinants

Knut Lönnroth
GTB/WHO

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Draft Post-2015 Global TB Strategy

Integrated, patient-centered TB Care and Prevention

- Early diagnosis of TB including universal drug-susceptibility testing ; systematic screening of contacts and high-risk groups
- Treatment of all forms of TB including drug -resistant TB with patient support
- Collaborative TB/HIV activities and management of co-morbidities
- Preventive treatment for high-risk groups and vaccination of children

Bold policies and supportive systems

- Government stewardship , commitment, and adequate resources for TB care and control with monitoring and evaluation
- Engagement of communities , civil society organizations, and all public and private care providers
- **Universal health coverage** policy; **regulatory framework** for case notification, vital registration, drug quality and rational use, and infection control
- **Social protection, poverty alleviation, and actions on other determinants of TB**

Intensified Research and Innovation

- Discovery, development and rapid uptake of new tools, interventions and strategies
- Operational research to optimize implementation and impact, and promote innovations

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Milestones in WHO's draft post-2015 global TB strategy

2020	2025	2030	2035
TARGETS	**TARGETS**	**TARGETS**	**GOAL**
• 35% reduction in TB deaths	• 75% reduction in TB deaths	• 90% reduction in TB deaths	• **95% reduction in TB deaths**
• 20% reduction TB incidence rate (≤85/100 000)	• 50% reduction TB incidence rate (≤55/100 000)	• 80% reduction TB incidence rate (≤20/100 000)	• **90% reduction TB incidence rate (≤10/100 000)**
• No affected families with catastrophic costs due to TB	• No affected families with catastrophic costs due to TB	• No affected families with catastrophic costs due to TB	• **No affected families with catastrophic costs due to TB**

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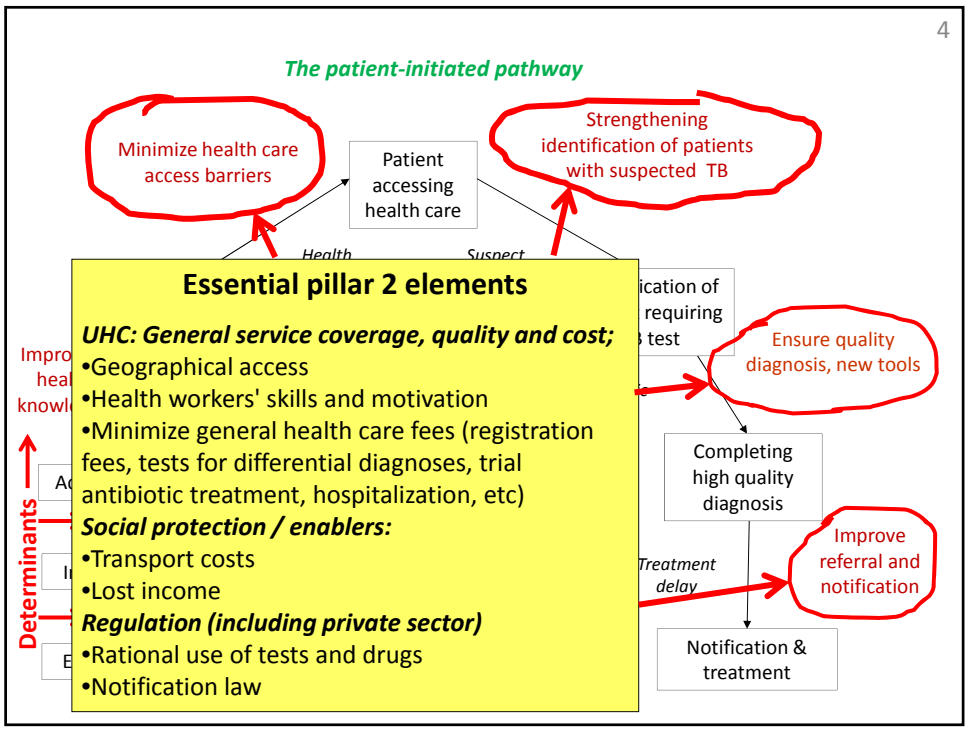

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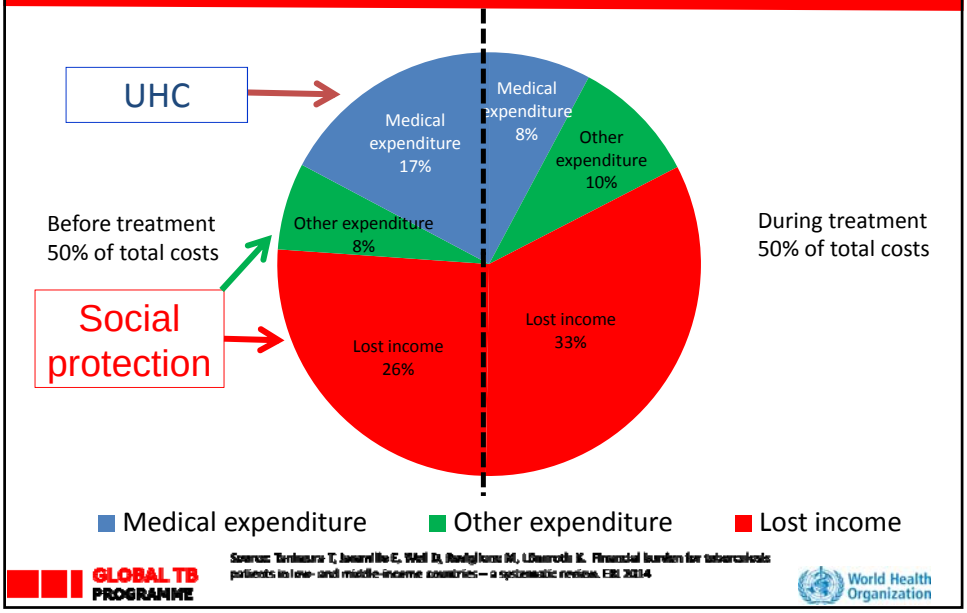
Average composition of TB-patients' costs



Source: Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low- and middle-income countries—a systematic review. EJE 2014

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Tentative definition of "catastrophic cost for TB-affected families"

- Numerator: All direct medical and non-medical costs plus income loss during TB illness
- Denominator: Annual household income
- Threshold for "catastrophic"?
  - To be determined
  - One option is >20% (WHO task force on patient cost measurements; Wingfield et al 2014)

Definition / scope	Who does / pays?
Universal health coverage (WHO definition): a)universal access to needed health services (beyond TB tests and drugs!); b)without financial hardship in paying for them (out-of-pocket medical costs only)	• TB programme budget (only a minor part) • General health system investment
Social protection (ILO definition): a)Essential Services (water and sanitation, education, HEALTH, etc); b)Essential Social Transfers (cash or kind) ➢ Enhance food security and nutrition, ➢ Minimum income security ➢ Income replacement and social support in the event of illness	• Social welfare ministry/authority, labour sector, national sickness insurance fund
Regulations: drugs, notification, vital registration	• MoH, etc
Social determinants and TB risk factors: a)Poverty, undernutrition, poor housing b)HIV, smoking, diabetes, alcohol, IAP, etc	• Poverty reduction policies • Health in all policies • Public health interventions

7

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What to cost and model?

8

- Cost:
  - ➢ Link to general UHC, social protection, and social determinants costing exercises as part of the broader post-2015 agenda (as a principle, no need to do the actual costing)
  - ➢ TB specific costs: Process costs of linking with UHC, SP, regulators, all sectors, to make policies and systems TB sensitive (10% additional costs of TB budget?)
- Links to epi impact targets:
  - ➢ "Upstream" from all pillar 1 elements: i.e. fundamental condition for all TB specific interventions to be accessible and effectively delivered (additional input without additional output).
  - ➢ Some determinants/risk factors can be modelled
- Link to financial risk protection target:
  - ➢ In principle, will be reached if UHC and SP are scaled up
  - ➢ Will contribute "cost saving" from a societal viewpoint – should go into the costing of the plan

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