Tuberculosis Research Investment Case Study
Technical Advisory Group Meeting
Hosted by Global TB Programme/Research for TB Elimination
World Health Organization
Geneva, Switzerland 9-10 March, 2016
Meeting Report prepared by Priya B. Shete and Christian Lienhardt (GTB/RTE)
Executive Summary

To achieve targets of the WHO End TB strategy, there is a need for intensified research to deliver new tools and strategies to combat the disease, linked with relevant epidemiological, health system, and operational research to ensure their adoption and implementation to scale. It is expected that, over the next decade, low and middle-income countries with substantial TB burden progressively enhance their investment in TB research through the creation of a strong domestic research capacity with the necessary international collaboration. To achieve this, WHO has developed with a large group of stakeholders a “Global Action Framework for TB Research” that sets the principles for action on TB research to promote, stimulate and intensify research and innovation worldwide.

A key element of supporting high TB burden countries in the implementation of national research strategies is to assist them in identifying targeted and effective research. The first meeting of the Technical Advisory Group (TAG) for TB Research Investment met in Geneva on the 9-10th March to discuss the development of targeted models for TB decision-making, with a focus on heterogeneity of risk in key subpopulations and with a goal of informing research prioritization for high burden countries. The meeting convened country and global level policymakers, researchers, modellers, and epidemiologists. Discussions and presentations focused on background of modelling as a tool for decision-making, the use of heterogeneity in assessing intervention impact, and country level epidemiology and priorities (Annex 1).

Based on discussions regarding feasibility and impact, a ‘Proof-of-concept framework’ is proposed for moving the project forward. The TAG agreed that the process to developing a model evaluating the potential impact of interventions addressing a specific high risk subpopulation(s) in each of the model countries (Vietnam, Brazil and South Africa) will start with a detailed situational analysis of these respective risk groups in each country, along with a data inventory to provide a basis for the model evaluating risk heterogeneity. Based on these results, and utilizing existing or planned (multi-) intervention mathematical models already being conducted in each country, the impact of hypothetical interventions targeted at these high-risk groups in achieving End TB 2025 goals will be evaluated.

The objectives of this Proof-of-Concept Framework are:
1) To provide countries with an assessment of the impact of targeted intervention(s) in a subpopulation(s) with high TB risk to inform the countries’ National TB Strategic Plans;
2) To provide proof-of-concept evidence of the importance of taking into account the heterogeneity of risk at population level and assessing intervention impacts at the national and sub-population levels;
3) To provide a use case for the use of heterogeneity in developing models aimed at answering policy questions in terms of intervention deployment and potentially further (operational) research investment.
Introduction

The global End TB Strategy approved by the World Health Assembly in May 2014 aims to end the global tuberculosis (TB) epidemic by 2035, with the targets of a 95% reduction of TB mortality and a 90% decline in TB incidence, and zero catastrophic costs. The strategy relies on three fundamental pillars: (1) Integrated, patient-centered care and prevention; (2) Bold policies and supportive systems; and (3) Intensified research and innovation (1). To achieve these targets of the WHO End TB strategy, there is a need for intensified research to deliver new tools and strategies to combat the disease, linked with relevant epidemiological, health system, and operational research to ensure their adoption and implementation to scale. It is expected that, over the next decade, low and middle-income countries with substantial TB burden progressively enhance their investment in TB research through the creation of a strong domestic research capacity with the necessary international collaboration. To achieve this, WHO has developed with a large group of stakeholders a “Global Action Framework for TB Research” that sets the principles for action on TB research to promote, stimulate and intensify research and innovation worldwide (2).

As an extension of this framework and to assist high-burden countries with prioritizing investment in research in order to achieve the highest impact, the development of epidemiologic-economic models focused on research investments should be undertaken. The goal of this effort is to assist countries with incorporating targeted research agendas within their National TB Strategic Plans in keeping with the Global Action Framework for Research that will take into account prioritization of interventions that are of the highest yield for achieving End TB targets and curbing local epidemics. While mathematical modelling has widespread use in understanding aspects of TB transmission dynamics and intervention at the population level, epidemiologic-economic models to date have not been devised to characterize the impact of heterogeneity of risk of subpopulations who may be epidemic drivers nor have they been designed to show the impact of targeted interventions that may equalize risk across subpopulations. While many researchers, program directors and key stakeholders agree that interventions developed keeping in mind heterogeneity of risk have the potential for high impact at the theoretical level, no models currently exist which demonstrate this effect using empirical data.

An inaugural meeting of the TB Research Investment Case Technical Advisory Group (TAG) was convened to establish a core methodology for an empirical epidemiologic-economic model for each country that will characterize high-risk subpopulations and assist countries in identifying high impact research priorities for incorporation into National Strategic Plans.

Project Aims and Objectives

The overall aim of the project is to develop “TB Research Investment Cases” that will inform the operationalization of the End-TB strategy based on estimates of epidemiologic impact and cost-effectiveness of existing and hypothetical interventions in specific settings.

The specific objectives of the project were presented to the TAG and are as follows:

1) Utilize data collected as part of an initial situational analysis for the selected countries to estimate the burden of TB in different subpopulations, evaluate the distribution of risks, gaps in the cascade of care, their impact on the burden of TB and on the performance of health interventions at the population level.

2) Develop mathematical models that account for risk heterogeneity, to estimate changes in TB burden resulting from utilization – nationally, and in these restricted populations – of new diagnostic, treatment and prevention tools or strategies.
3) Evaluate the cost and cost effectiveness of implementation of various novel interventions at both the population level as well as in targeted sub-populations.

4) Using results of above, and linking to models of risk heterogeneity, develop a targeted TB research investment case aimed at assisting local stakeholders as well as global stakeholders in prioritizing investment in research. This prioritization will then assist countries in integrating research into their TB National Strategic Plans.

**Technical Advisory Group Participants and Objectives**

In order to achieve these objectives, a Technical Advisory Group (TAG) was established to develop consensus agreement on approach, ensure in-country and global stakeholder engagement, and provide consultation on all elements of protocol development, model development, and interpretation of results. This TAG includes representatives from National TB Programmes, in-country researchers, policy makers, epidemiologists, health economists, and global experts in TB models with a particular expertise in the TB epidemic in Brazil, South Africa, and Vietnam (see **Annex 2**). These countries were chosen because of their high burden of TB, interest in TB research, and interest in developing additional tools for prioritizing national research agendas will be established.

**Provisional Members of the TB Research Investment Case Technical Advisory Group**

- Richard White
- Gavin Churchyard
- Viet Nguyen Nhung
- Salome Charalambous
- Guy Marks
- David Dowdy
- Ted Cohen
- Nguyen Binh Hoa
- Gabriela Gomes
- Ethel Maciel
- Denise Arakaki

**WHO/GTB Members**

- Christian Lienhardt
- Priya Shete
- Knut Lönnroth
- Ines Garcia Baena
- Philippe Glaziou
The role of the TAG is to consult on key elements of the project. This includes (but is not limited) to:

1) Review the approach taken in preparing for the TB Research investment case in each country;

2) Review the inventory of suitable data sources available on the epidemiology of TB at national level and in specific sub-populations in the three countries, identify key risk groups for use in model and review relevant data sources;

3) Review the current modelling activities in the three pathfinding countries and the gaps in current approaches for addressing key risk groups and heterogeneity in decision-making;

4) Advise on the development of an initial protocol at country level for the undertaking of the work including a description of the methods to be used and a suitable timeline with due deliverables and outputs

5) Identify core modelling team as well as in-country capacity for the work.

**Meeting Process and Roles of Participants**

The TAG meeting centered around 3 key themes:

1) Identification of key TB risk groups in each country and analysis of data sources related to each.

2) Implications of risk heterogeneity on impact of TB interventions and methods for evaluating this impact.

3) Development of tools to inform TB research prioritization for country stakeholders including a research investment case.

Participants agreed to not only provide advice and recommendations based on their technical areas or expertise (modelling, epidemiology, health economics, policymaking) but also to contribute with a presentation to the group regarding their technical or country-specific expertise. The meeting agenda (Annex 3) was structured to provide background information on concepts related to TB high risk groups, data availability and sources, the role of mathematical modelling, the utility of exploring risk heterogeneity, and necessary outputs to provide direction for policymakers and other stakeholders. The three core themes of the meeting were understood to form the basis for further discussion about the development of a central methodology.

**Data Collection and Situational Analysis**

The TAG reviewed presentations from three pathfinder countries regarding current and potential subpopulation with high heterogeneity of TB risk as well as data sources that inform current epidemiology. As background for the development of a project methodology, through stakeholder discussion and expert consultation, GTB/RTE identified these three countries for initial participation from the larger pool of early adopters of Pillar 3 of the End TB Strategy.
The TAG agreed that the first phase of the project should include a **baseline situation analysis** in each country that will serve for the subsequent development of the modelling analysis. This situational analysis will assess each country’s data systems, the variables of interest that are currently known, and identify data sources for ascertaining the epidemiology of TB in key populations that are not currently captured by standard reporting systems.

This baseline situational analysis, conducted in each country, will include:

1) An assessment of current use of mathematical modelling or other decision-making tools by the National TB Programme (NTP);

2) An assessment of current TB research projects and in-country research priorities (if formalised);

3) The development of a data inventory to describe available data sources related to the current TB epidemic within each country.

Examples of key data sources discussed include (but are not limited to): National TB Programme surveillance data, Programmatic sources of data including prevalence surveys, research databases, databases related to comorbid conditions, census data, socioeconomic surveillance data from non-health related governmental organizations, data from available social protection systems and data from partnering non-governmental organizations (NGOs). In addition, data on special populations including marginalized populations (such as migrants) may be accessible from advocacy groups. An initial inventory of data sources known by in-country partners will be conducted with an aim towards collecting variables of interest and accessibility through informal interviews with key stakeholders. Refinement and improvement to this list will depend on needs for parameterization of the model and country stakeholder identified high priority groups. Sensitivity analyses may be conducted to further estimate the impact of identified risk groups as drivers of the epidemic to further inform prioritization within the model later in the project.

To operationalize future aspects of the model, it was recommended that a standard protocol for data cleaning and structure be created. Identified team members from each country will be tasked with conforming country-based data to this structure for inclusion in the larger scale database. Collaborating researchers who wish to participate in this exercise with unpublished data may also access this database interface. In order to evaluate heterogeneity within key subpopulations, summary data may be discouraged.

Presentations by country stakeholders to the TAG led to discussion of preliminary results of a situational analysis. Several conclusions were made by the TAG:

1) As expected, each country identified different but occasionally overlapping high risk groups which likely drive local TB epidemics

2) Data sources and availability within each country are extremely different, which may contribute to pathfinder countries being at different stages of assessments of heterogeneity and modelling. Varying data cleaning protocols may be required.

3) Local modelling and data management experience is non-uniform between countries, which may contribute to different resource requirements for conducting the work.

4) Based on preliminary situational analysis, initial efforts should be made to isolate 1-2 key high risk groups for further detailed elaboration in modelling efforts. The results of this are shown in Annex 5.
5) Mathematical modelling for TB decision-making is in many ways limited not simply by computational considerations, but also by the quality and uncertainty of empirical data which informs both inputs to the model as well as structure of the model.

Presentations described the current field of modelling as related to TB policy and decision-making at the global and country level, with special attention to current derived mathematical models and use cases that have informed TB strategic plans. At the global level, models such as TIME and OPTIMA were described which provide evidence of decision making by using simple transmission models that incorporate population level summary data. While these models have had success in reaching policymakers as a key audience and have informed some country level decisions, they are limited in that they do not include assessment of many specific risk groups. In addition, these models are limited by lack of data availability and modules to address not only cost effectiveness but also resource allocation.

Subsequently, the TAG noticed that:
1) Modelling activities should consider ways for building local capacity to conduct this work independently of global level technical support in the future.

2) Because of resource and capacity constraints, in country stakeholders in particular favor developing a modelling approach that utilizes current models that are in use within that context as the framework for testing heterogeneity of risk and risk equalization impacts of interventions. In Brazil, where capacity is slightly more robust, this will include social protection models (S-Protect) or other models, while for both South Africa and Vietnam this will utilize TIME model.

3) Further discussion will be required to determine how to structure the modelling teams to include global level as well as local level technical support in keeping with existing project resources.

4) From a technical perspective, attempting to incorporate a multitude of potential risk factors with each being assessed in terms of risk heterogeneity represents a significant undertaking and will require resources beyond those currently available at the global and local level. Simplification, including developing a proof-of-concept pilot project may be more feasible initially.

**Importance of Risk Heterogeneity**

A key presentation demonstrated the theoretical basis for assessment of risk heterogeneity in multiple disease models including TB. This framework has thus far relied on using a top-down approach to re-estimate relative risk of transmission of disease in various high-risk subpopulations but has not yet utilized empirical data sources. Key highlights from this discussion included:

1) Heterogeneity in disease risk can lead to underestimated transmission potential and over-predicted intervention impact;

2) Relative risks cannot be measured directly due to selection biases;

3) Data collected uniformly across multiple populations open new perspectives for inference based on epidemiological models.
Based on this discussion the TAG approach to consideration of risk heterogeneity includes:

1) Developing a modelling approach that takes into account heterogeneity of TB disease risk using high quality data where available but which is based on individual level data.

2) Testing the impact of heterogeneity of risk based on empirical individual data rather than larger level population data in theoretical frameworks.

**Key Decision-Making Outputs**

Model outputs will be determined in coordination between modellers as well as the Technical Advisory Group. Traditional outputs will include epidemiologic indicators important in considering each risk factor, such as TB incidence, prevalence, case detection rates, proportion of patients incurring catastrophic costs, and mortality. The inclusion of additional risk factor specific outputs in the realm of HIV or MDR-TB, as well as social determinants, geographic coverage, etc, may be included in consultation with expert stakeholders and where necessary to inform particular policy questions. Then modelling will estimate impact of various combinations of implementation of new tools, plus in sensitivity analyses will estimate the additional impact of potential (social or medical) interventions aiming at equalizing risks, predict the potential impact of new tools and interventions and describe conditions for optimizing their impact at the population level.

Discussions of TAG underlined the followings:

1) The structure of an epidemiologic-economic model to assess impact of interventions may need to be structured very differently than a more economic-only focused model that looks at far upstream interventions such as research funding inputs and allocation. Outcomes of interest may also be different, with larger scale research investments informing 2035 End TB targets and more immediate research activities in operational research informing 2025 targets. TAG recommends focusing initially on 2025 targets for the model.

2) All models should focus on key and simplified TB indicators as outcomes in order to be most readily used by policymakers.

**Costing, Cost Effectiveness and Budget Prioritization**

As part of the protocol discussion, an additional cost effectiveness and/or cost mitigation component to the model was considered, to provide estimate of economic impact of specific interventions. Where available, costs from local and health systems surveys within the country are typically used as a baseline to estimate threshold costs for scaling up new tools and interventions nationally. Appropriate and context specific discounting will be assessed for each scenario. CEA outputs will include cost per DALYs averted. These costs will then be assessed for budgetary acceptability based on standard Willingness to Accept thresholds as well as by context-specific stakeholder consultation. In addition, based on assumptions of epidemiological impact of the heterogeneity of sub-populations, impact and costs overall and in subgroups will be calculated. These estimates can then be used to advise countries on scale-up of interventions to maximize impact in these sub-populations as well as nationally using budget-guiding tools which take into account NTP financial constraints.

The additional component of considering more upstream interventions such as research investment was initially presented as a Phase 2 of the project. The specific objective of this phase of the project is to create tools that will assist countries with determining areas of
research to consider prioritizing for maximum impact. The aim is to provide countries with a powerful tool for guiding investment decisions in research and intervention development in order to meet End TB targets toward TB elimination. Outputs for this phase of the project will focus on 2035 End TB targets.

TAG discussion on these costing and cost effectiveness components led to the following key points for clarification and development:

1) Additional health economist expertise will be needed to provide technical support of cost, cost-effectiveness, and cost mitigation work.

2) Because the structure of the modelling work may differ between Phase 1 and Phase 2, separate costing components will need to be developed.

3) A clear description of an investment case as donors understand it and other stakeholders must be presented and understood and work to develop a research investment case modelled according to those parameters.

4) Phase 1 should be the initial focus, and can be completed by the modelling team as such components are included in most modelling activities.

TAG propositions

TAG propositions for the project as outlined in each section below culminated in the agreement to begin with a proof-of-concept pilot study that uses mathematical modelling to evaluate the impact of potential interventions addressing specific high risk subpopulation(s) in each of the model countries. This will require that a detailed situational analysis of these respective risk groups be conducted in each country, along with a data inventory to provide a basis for the model evaluating risk heterogeneity in these countries. Based on these results, and utilizing existing or planned (multi-) intervention mathematical models already being conducted in each country, the impact of hypothetic interventions targeted at these high-risk groups in achieving End TB 2025 goals will be evaluated.

The objectives of this newly-proposed initial proof of concept are:

1) To provide countries with an assessment of the impact of a targeted intervention in a subpopulation with high TB risk to inform the countries’ National TB Strategic Plans;

2) To provide proof-of-concept evidence of the importance of taking into account the heterogeneity of risk at population level and assessing intervention impacts at the national and sub-population levels;

3) To provide a use case for the use of heterogeneity in developing models aimed at answering policy questions in terms of intervention deployment and potentially further (operational) research investment.

The timeline (Annex 6), describes the plan of work going forward and culminating with a second TAG meeting in December 2016 in Geneva on “Test of heterogeneity analysis on multi-intervention models on achieving 2025 End TB targets”. The goal will be to present situational analysis of key risk factors undertaken in Objective 2 (above), and agree on modelling approach based on country situational analysis and existing mathematical model(s). In addition, presentations of any use case scenarios or model outputs that operationalize evaluation of heterogeneity of risk will be presented.
<table>
<thead>
<tr>
<th>Action Points of the TAG</th>
<th>Key Participant/Country</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each pathfinder country partner group to identify and confirm point person and team for</td>
<td>Salome Charalambous, Nguyen Binh Hoa, Ethel Maciel/Denise Arakaki</td>
<td>April 2016</td>
</tr>
<tr>
<td>participation which includes at least one local modeller</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Each pathfinder country partner group to conduct a situational analysis of potential</td>
<td>Brazil- Ethel Maciel, Denise Arakaki</td>
<td>April-August 2016</td>
</tr>
<tr>
<td>risk group/subpopulation of interest - initially using summary data – on which to focus</td>
<td>Vietnam- Viet Nguyen Nhung, Nguyen Binh Hoa</td>
<td></td>
</tr>
<tr>
<td>for initial analysis, in consultation with NTP and stakeholder groups - and develop</td>
<td>South Africa- Salome Charalambous</td>
<td></td>
</tr>
<tr>
<td>key policy related questions related to this risk factor (country teams)</td>
<td>WHO- Priya Shete</td>
<td></td>
</tr>
<tr>
<td>Each group to comment on the outputs related to the identified risk factor in each</td>
<td>All</td>
<td>April 2016</td>
</tr>
<tr>
<td>country based on the initial table presented at the TAG meeting (all)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Each pathfinder country partner group to create a data inventory- based on interest in</td>
<td>WHO- Priya Shete Country teams</td>
<td>August-October 2016</td>
</tr>
<tr>
<td>risk group to be studied initially. This may include development of a specific</td>
<td></td>
<td></td>
</tr>
<tr>
<td>computer program that can be used for each project or separate for each country</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circulation of the project Protocol and revision based on feedbacks</td>
<td>WHO- Priya Shete</td>
<td>April 2016</td>
</tr>
<tr>
<td>Prepare meeting report</td>
<td>WHO- Priya Shete</td>
<td>May 2016</td>
</tr>
<tr>
<td>Preparation of Proof of Concept Framework</td>
<td>WHO- Priya Shete</td>
<td>April 2016</td>
</tr>
<tr>
<td>Each pathfinder country partner group to create a protocol of the proof of concept pilot</td>
<td>Brazil- Ethel Maciel, Denise Arakaki</td>
<td>April-June 2016</td>
</tr>
<tr>
<td>focusing on evaluation of heterogeneity</td>
<td>Vietnam- Viet Nguyen Nhung, Nguyen Binh Hoa</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>South Africa- Salome Charalambous</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WHO- Priya Shete</td>
<td></td>
</tr>
</tbody>
</table>
Annexes and Supplementary Material
Annex 1. Background and Objectives of the TB Research Investment Case Project
Annex 2. Meeting Participants
Annex 3. Agenda
Annex 4. Draft Protocol and References
Annex 5. Table of Key Risk Groups by Country
Annex 6. Timeline
Annex 1. Background and Objectives of the TB Research Investment Case Project

Background and Rationale
To achieve the goals of the WHO End TB strategy, there is a need for intensified research to deliver new tools and strategies to combat the disease, linked with relevant epidemiological, health system, and operational research to ensure their adoption and implementation to scale. It is expected that, over the next decade, low and middle income countries with substantial TB burden progressively enhance their investment in TB research. To assist high-burden countries with prioritizing investment in research in order to achieve the highest impact, development of epidemiologic-economic models focused on research investments are being developed for three model countries: Brazil, South Africa, and Vietnam. The goal of this effort is to assist countries with devising National TB Strategic Plans in keeping with the Global Action Framework for Research.

The purpose of this meeting is to establish a core methodology for an empirical epidemiologic-economic model for each country that will characterize high risk subpopulations and assist countries in identifying high impact research priorities for incorporation into National Strategic Plans. This group is comprised of technical experts in TB modelling, programme managers, clinicians, and researchers from each model country.

Objectives of the meeting
1. Review current modelling activities in key countries, and gaps in current approaches for addressing key risk groups and heterogeneity in decision-making.

2. Review a systematic inventory of suitable data sources available on the epidemiology of TB at national level and in specific sub-populations in the three countries;
   2.a Identify key risk groups for use in model
   2.b Review relevant data sources

3. Develop an initial protocol for the undertaking of the work including a description of the methods to be used and a suitable timeline with due deliverables and outputs;

4. Identify core modelling team as well as in-country capacity for the work.

Expected outcomes
This meeting will culminate in the development of a common methodology for the modelling work to be carried out at country level along with draft protocol. A core modelling team will be identified with timeline of for project deliverables and outputs.
## Annex 2. Meeting Agenda

### Day 2 – 10 March 2016 (Thursday)

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Presenter/Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00 – 09:15</td>
<td>Welcome and Introduction</td>
<td>Christian Lienhardt, Richard White</td>
</tr>
<tr>
<td>09:15 – 09:45</td>
<td>Objectives and Background of the Meeting</td>
<td>Christian Lienhardt</td>
</tr>
<tr>
<td>09:45 – 10:15</td>
<td>Recap 1st day</td>
<td>Richard White</td>
</tr>
<tr>
<td>10:45 – 11:00</td>
<td>Country specific data availability: Brazil</td>
<td>Denise Arakaki</td>
</tr>
<tr>
<td>10:45 – 11:00</td>
<td>Exploration of Heterogeneity and importance of risk group stratification</td>
<td>Gabriela Gomes</td>
</tr>
<tr>
<td>11:00 – 11:45</td>
<td>Filling the gaps: structure and collection of data needs</td>
<td>David Dowdy</td>
</tr>
<tr>
<td>11:45-12:45</td>
<td>Overview of Draft Protocol</td>
<td>Priya Shete</td>
</tr>
<tr>
<td>12:45 – 13:45</td>
<td>Lunch</td>
<td></td>
</tr>
<tr>
<td>13:45-14:30</td>
<td>Current Country-based Modelling Activities and Role in Decision Making</td>
<td>Ethel Maciel, Gavin Churchyard, Viet Nguyen Nhung</td>
</tr>
<tr>
<td>14:30 – 15:15</td>
<td>Discussion: Social determinants and Socioeconomic Risk Factors</td>
<td>Knut Lonnroth</td>
</tr>
<tr>
<td>15:15 – 15:45</td>
<td>Tea break</td>
<td></td>
</tr>
<tr>
<td>15:45-16:30</td>
<td>Discussion: ACT2 and the role of secondary data sources</td>
<td>Guy Marks</td>
</tr>
<tr>
<td>09:00 – 09:30</td>
<td>Recap 1st day</td>
<td>Richard White</td>
</tr>
<tr>
<td>09:30 – 10:00</td>
<td>Country specific data availability: Brazil</td>
<td>Denise Arakaki</td>
</tr>
<tr>
<td>10:00 – 10:30</td>
<td>Country specific data gaps and availability: South Africa</td>
<td>Salome Charalambous</td>
</tr>
<tr>
<td>10:30 – 11:00</td>
<td>Country specific data availability: Vietnam</td>
<td>Nguyen Binh Hoa</td>
</tr>
<tr>
<td>11:00-11:15</td>
<td>Coffee and Tea Break</td>
<td></td>
</tr>
<tr>
<td>11:15-13:00</td>
<td>Discussion: Revision of Protocol Key Elements of Discussion: Risk Stratification, Model Structure</td>
<td>Gabriela Gomes</td>
</tr>
<tr>
<td>13:00 – 14:00</td>
<td>Lunch</td>
<td></td>
</tr>
<tr>
<td>14:00 - 15:30</td>
<td>Discussion: Revision of Protocol Key Elements of Discussion: Common Outcomes</td>
<td>Philippe Glaziou</td>
</tr>
<tr>
<td>15:15 – 15:45</td>
<td>Coffee and Tea Break</td>
<td></td>
</tr>
<tr>
<td>15:45 - 16:45</td>
<td>Project Phases, Team development, Next Steps</td>
<td>Christian Lienhardt</td>
</tr>
<tr>
<td>16:45 - 17:00</td>
<td>Closure</td>
<td>Mario Raviglione</td>
</tr>
</tbody>
</table>
Annex 3. List TAG Meeting Participants

1. Dr Richard White (Chair)
   Reader, Infectious Disease Modelling
   London School of Hygiene and Tropical Medicine London

2. Dr Denise Arakaki
   National Tuberculosis Control Programme
   Brazilian Ministry of Health
   Brasilia Brazil

3. Dr Salome Charalambous
   Director of Research
   Aurum Institute for Health Research
   Johannesburg South Africa

4. Dr Gavin Churchyard
   Director
   Chief Executive Officer
   Aurum Institute for Health Research
   Johannesburg South Africa

5. Dr Ted Cohen (remote)
   Associate Professor of Epidemiology
   Yale University School of Public Health
   New Haven United States

9. Dr Ethel Maciel
   Researcher University of Espirito Santo
   REDE-TB
   Espirito Santo Brazil

6. Dr David Dowdy (remote)
   Associate Professor
   Johns Hopkins Bloomberg School of Public Health
   Baltimore United States

7. Dr Gabriela Gomes
   Reader in Biomathematics
   Liverpool School of Tropical Medicine
   Liverpool United Kingdom

8. Dr Nguyen Binh Hoa
   Officer
   National Tuberculosis Programme
   Ha Noi Vietnam

10. Dr Guy Marks
    Professor
    University of Sydney
    Sydney Australia

11. Dr Viet Nguyen Nhung
    Director, National Lung Hospital
    Manager, National Tuberculosis Programme
    Ha Noi Vietnam

OBSERVERS
12. Dr Melvin Sanicas
    Program Officer
    Bill & Melinda Gates Foundation
    Seattle
    United States

13. Dr Draurio Barreira
    TB Technical Manager
    UNITAID
    Geneva
    Switzerland

WHO/HQ
14. Dr Christian Lienhardt, GTB/RTE
15. Dr Priya Shete, GTB/RTE
16. Ms Ines Garcia Baena, GTB/TME
17. Dr Anna Dean, GTB/TME
18. Dr Nebiat Gebreselassie, GTB/RTE
19. Dr Philippe Glaziou, GTB/TME
20. Dr Knut Lonnroth, GTB/PSI
21. Dr Linh Nhat Nguyen, GTB/LDR
DRAFT Protocol: TB Research Investment Cases
Presented to Technical Advisory Group for TB Research Investment Cases
9-10 March, Geneva

Background

The global End TB Strategy approved by the World Health Assembly in May 2014 aims to end the global tuberculosis (TB) epidemic by 2035, with the targets of a 95% reduction of TB mortality and a 90% decline in TB incidence, and zero catastrophic costs. The strategy relies on three fundamental pillars: (1) Integrated, patient-centered care and prevention; (2) Bold policies and supportive systems; and (3) Intensified research and innovation (1). To achieve these targets of the WHO End TB strategy, there is a need for intensified research to deliver new tools and strategies to combat the disease, linked with relevant epidemiological, health system, and operational research to ensure their adoption and implementation to scale. It is expected that, over the next decade, low and middle-income countries with substantial TB burden progressively enhance their investment in TB research through the creation of a strong domestic research capacity with the necessary international collaboration. To achieve this, WHO has developed with a large group of stakeholders a “Global Action Framework for TB Research” that sets the principles for action on TB research to promote, stimulate and intensify research and innovation worldwide (2).

A key element of supporting high TB burden countries for the implementation of national research strategies is to assist them in identifying targeted and effective research priorities that take into account the context specific nature of their TB epidemic, as well as matching financial and resource constraints. Mathematical modelling of tuberculosis in context specific ways can be a useful tool in public health decision-making and may provide a structured framework to assist countries in prioritising research investments (3). TB specific models to date have focused on describing population level changes to transmission dynamics that may occur as a result of interventions that occur at the population level in a quantitative way. These models are especially helpful by allowing researchers, policymakers and other stakeholders to make strategic assessments and comparisons of public health interventions when empirical data (such as a randomized controlled trial, or large scale prevalence survey) are infeasible because of time and cost (4). Many current models exist to aid NTPs in TB public health decision-making taking into account summary epidemiologic data as well as budgetary constraints (5, 6) and have had success in focusing programmatic priorities and securing additional TB program funding in these countries.

Despite these successes, current TB models have several limitations that may substantially affect the usefulness of model outputs in specific contexts. First, most epidemiologic parameters come from population level aggregated data from sources that do not reflect the diversity of subpopulations at risk for TB. Although these limitations may be computational necessities to retain a simple structure, they limit the impact of many of these models to provide targeted guidance for policymakers. Previous work has demonstrated that various risks among subpopulations can be important determinants of the TB epidemic, by driving transmission in geographic ‘hotspots’ (7) accounting for disproportionately high individual susceptibility to disease (8) and creating network associations between those in high risk groups that amplify risk (9). The danger in not accounting for this risk heterogeneity within our existing epidemiologic-economic models of TB would be to potentially incorrectly estimate effect of TB control programs and waste valuable resources only to fall short of 2035 End TB goals. Second, while
current models may be able to answer specific and concrete research questions, current models are not equipped to analyse large scale trends in TB epidemiology in order to devise a menu of potentially high impact research questions for policymakers to further address. Finally, current epi/econ models of “impact” and cost effectiveness do include in their scope the impact of research investment, which will become more important to key stakeholders at the global and local levels with the implementation and scale-up of the End TB Strategy.

With more novel diagnostics, therapeutics, and social interventions gaining momentum in the End TB era, there is an obvious need for more targeted approaches to prioritize country based research and programmatic investments. By building on current epidemiologic-economic models with an eye toward incorporating heterogeneity, additional high impact advances to End TB can occur.

**Aim and objectives**

The overall aim of the project is to develop “TB Research Investment Cases” that will inform the operationalization of the End-TB strategy based on estimates of epidemiologic impact and cost-effectiveness of existing and hypothetical interventions in specific settings.

The specific objectives of the project are as follows:

1. Utilize data collected as part of an initial situational analysis for the selected countries to estimate the burden of TB in different subpopulations, evaluate the distribution of risks, gaps in the cascade of care, their impact on the burden of TB and on the performance of health interventions at the population level.
2. Develop mathematical models that account for risk heterogeneity, to estimate changes in TB burden resulting from utilization – nationally, and in these restricted populations – of new diagnostic, treatment and prevention tools or strategies.
3. Evaluate the cost and cost effectiveness of implementation of various novel interventions at both the population level as well as in targeted sub populations.
4. Using results of above, and linking to models of risk heterogeneity, develop a targeted TB research investment case aimed at assisting local stakeholders as well as global stakeholders in prioritizing investment in research. This prioritization will then assist countries in integrating research into their TB National Strategic Plans.

To devise the ‘TB research investment case’, the project will be undertaken in 2 consecutive phases:

- **Phase 1** will focus on expanding on existing transmission models to incorporate more nuanced epidemiologic data in model parameterization to improve specificity of model outputs with regards to key subpopulations. For this, methods in TB disease modelling will be developed, which will include not only population level parameters of TB epidemiologic burden, but which will also incorporate the heterogeneity of risk within specific subpopulations in order to derive context-specific, targeted estimates of the impact of various existing and hypothetical interventions on reducing the burden of disease. In particular, work will be conducted to quantify and characterize TB burden and associated risks in given subpopulations, estimate the epidemiological and economic impact of a set of interventions in specific settings, and evaluate the impact of changes in risk distribution. These outputs will be correlated with costing data and economic and budgetary analysis where available. Outputs will for this phase of the project will focus on 2025 WHO targets for TB control.

- **Phase 2** will focus on establishing models of more abstract and upstream investments for research as an intervention. The specific objective of this phase of the project is to create
tools that will assist countries with determining areas of research to consider prioritizing for maximum impact. The aim is to provide countries with a powerful tool for guiding investment decisions in research and intervention development in order to meet End TB targets toward TB elimination. Outputs for this phase of the project will focus on 2035 End TB targets.

**Approach**

Within the context of the development of the National TB Research Plans, WHO and partners will work more specifically with 3 path-finding countries (Brazil, South Africa, and Vietnam) on the definition of research priorities using an epidemiologic-economic mathematical model through collaboration with global experts in epidemiology, economics, TB modelling and policy making. For this, in addition to basic situation analysis, we will attempt to further quantify and characterize TB burden and associated risks in specific subpopulations that are important drivers of the TB epidemic as well as identify those risk groups that are specifically important to consider in each particular country context. The objective of the model(s) will be to estimate the epidemiological and economic impact of a set of targeted interventions in specific settings, and evaluate the impact of changes in risk distribution with the introduction of novel interventions. It is expected that this information will help refine the operationalization of the Pillar 3 of the End-TB strategy in these countries. Work will be carried out by National TB Programmes in collaboration with relevant academic/research groups involved in modelling of TB interventions. It is expected that the results of such work (grounded on actual experience) will in turn inform adaptations of the Global Action Framework.

A Technical Advisory Group (TAG) will be established to develop consensus agreement on approach, ensure in-country and global stakeholder engagement, and provide consultation on all elements of protocol development, model development, and interpretation of results. This TAG will include representatives from National TB Programmes, in-country researchers, policymakers, epidemiologists, health economists, and global experts in TB models with a particular expertise in the TB epidemic within the model countries identified (see Annex 1). The first task of the TAG is to develop consensus on the methodological approach using the present draft protocol as reference.

A Technical Advisory Group (TAG) comprised of National TB Programme (NTP) representatives and country level stakeholders, policymakers, TB modellers, health economists and epidemiologists will be established. This TAG will consult on key elements of the project including but not limited to:

**Provisional Members of the TB Research Investment Case Technical Advisory Group**

<table>
<thead>
<tr>
<th>Name</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richard White</td>
<td>David Dowdy</td>
</tr>
<tr>
<td>Gavin Churchyard</td>
<td>Ted Cohen</td>
</tr>
<tr>
<td>Viet Nguyen Nhung</td>
<td>Nguyen Binh Hoa</td>
</tr>
<tr>
<td>Afranio Kritski</td>
<td>Gabriela Gomes</td>
</tr>
<tr>
<td>Salome Charalambous</td>
<td>Ethel Maciel</td>
</tr>
<tr>
<td>Guy Marks</td>
<td>Denise Arakaki</td>
</tr>
<tr>
<td>Mauricio Barreto</td>
<td>Reza Yaesoubi</td>
</tr>
</tbody>
</table>
**WHO/GTB Members**

Christian Lienhardt  
Priya Shete  
Ines Garcia Baena  
Knut Lønnroth  
Philippe Glaziou

**Project implementation:**

**Phase 1:**

The core of the ‘TB Research Investment Case’ project is the development of mathematical model(s) of TB to use as a tool that estimates changes in TB burden and impact of investment in TB research that may result from novel tools or interventions, either existing or hypothetical, while accounting for heterogeneity of risk. The first phase of the project includes a baseline situation analysis in each country, that will serve for the subsequent development of the modelling analysis. This situational analysis will assess each country’s data systems, the variables of interest that are currently known, and identify data sources for ascertaining the epidemiology of TB in key populations that are not currently captured by standard reporting systems.

1. **Baseline situational analysis.**

This baseline situational analysis, conducted in each country, will include:

a) an assessment of current use of mathematical modelling or other decision making tools by the NTP;

b) an assessment of current TB research projects and in-country research priorities (if formalised);

c) the development of a data inventory to describe available data sources related to the current TB epidemic within each country.

Examples of key data sources will include (but are not limited to): National TB Programme surveillance data, Programmatic sources of data including community based TB control programs, prevalence surveys, research databases, databases related to comorbid conditions, census data, socioeconomic surveillance data from non-health related governmental organizations, data from available social protection systems. In addition, data on special populations including marginalized populations (such as migrants) may be accessible from advocacy groups (10). An initial inventory of what data sources are known by in-country partners will be conducted with an aim towards collecting variables of interest and accessibility through informal interviews with key stakeholders. Refinement and improvement to this list will depend on needs for parameterization of the model and country stakeholder identified high priority groups. Sensitivity analyses may be conducted to further estimate the impact of identified risk groups as drivers of the epidemic to further inform prioritization within the model later in the project.

In collaboration with the modelling team, a **standard protocol for data cleaning and structure** will be created. Identified team members from each country will be tasked with conforming country-based data to this structure for inclusion in the larger scale database. Collaborating researchers who wish to participate in this exercise with unpublished data may also access this database interface. In order to evaluate heterogeneity within key subpopulations, summary data may be discouraged.

2. **Development of mathematical models as TB Research Investment Case tool.**
The core of the TB Research Investment Case project will be mathematical model(s) of TB to use as a tool that estimates changes in TB burden and impact of investment in TB research that may result from novel tools or interventions, either existing or hypothetical, while accounting for heterogeneity of risk. These models will assess each new tool or intervention individually to estimate their impact using common metrics in order to allow for relative comparisons of a panel of potential interventions (and their derivative research questions).

In the first phase of the project, we will focus on developing an innovative mathematical model that incorporates heterogeneity of risk among key subpopulations in analysis of TB interventions.

The initial TAG meeting in March 2016 will focus on protocol development for this model. The modelling team(s) will be identified in consultation with local and global level stakeholders. Of primary importance in this exercise is defining risk groups and research questions based on country determined needs. In addition, building research capacity in disease modelling for participating countries should be a priority when forming the modelling team. For these reasons, representation from each country to the core modelling team will be sought. As this project represents a complex and substantive body of work, a senior TB disease modeller (or a group thereof) to oversee the activities of the team may be required.

Building on existing compartmental models of TB epidemiology and transmission, as well as existing models specific to country context where they exist, and based on discussions of the key areas of epidemiologic priority by country stakeholders, the modelling team will work with the technical advisory group to construct a model structure to reflect heterogeneity of subpopulations considered to be at-risk groups for TB. Based on the needs of the country in terms of policy questions, the model structure will be constructed as either compartmental or individual-based model, with dynamic or static time relationship, and will be either deterministic or probabilistic with respect to transition states. While the simplest model structure possible for any given analysis will be preferred, it is understood that in order to account for heterogeneity within subpopulations, additional complexity will be required. Model calibration will occur to fit the model to existing data sources, but may also use secondary data sources.

Risk groups for parameterization of the model will be determined in coordination between the modelling team and country based experts (including TAG members). Some risk factors are known to be common in the global epidemic and include HIV, age, sex, and poverty. However, additional risk factors may be important and drivers within subpopulations within each country context and will be identified by primary NTP surveillance data, secondary data (including programmatic data and local epidemiologic data sources) and expert consultation. These may be determined by separate sensitivity analyses to prioritize which subpopulations to include and will likely undergo some additional priority setting exercise with stakeholder consultation.

Model outputs will be determined in coordination between modellers as well as the Technical Advisory Group. These outputs should include epidemiologic indicators important in considering each risk factor compartmentalized, such as TB incidence, prevalence, case detection rates, and mortality. Additional risk factor specific outputs in the realm of HIV, MDR, social determinants, geographic coverage, etc, will be included as part of consultation with expert stakeholders. Then modelling will estimate impact of various combinations of implementation of new tools, plus in sensitivity analyses will estimate the additional impact of social or medical interventions aiming at equalizing risks, predict the potential impact of new tools and interventions and describe conditions for optimizing their impact at the population level.
3. Costing, Cost Effectiveness and Budget Prioritization

For the Phase 1 model, an additional cost effectiveness and/or cost mitigation component to the model will be considered to provide estimate of economic impact of specific interventions. Where available, costs from local and health systems surveys within the country will be used as a baseline to estimate threshold costs for scaling up new tools and interventions nationally. Appropriate and context specific discounting will be assessed for each scenario. CEA outputs will include cost per DALYs averted. These costs will then be assessed for budgetary acceptability based on standard Willingness to Accept thresholds as well as by context-specific stakeholder consultation. In addition, based on assumptions of epidemiological impact of the heterogeneity of sub-populations, impact and costs overall and in subgroups will be calculated. These estimates can then be used to advise countries on scale-up of interventions to maximize impact in these sub-populations as well as nationally using budget guiding tools which take into account NTP financial constraints.

Phase 2:

The overall goal of the ‘TB Research investment case’ is to provide countries with a powerful tool for guiding investment decisions in research and intervention development in order to meet 2035 End TB targets toward TB elimination. Therefore, the second phase of the project will focus on more upstream considerations of impact of research investment on TB control at the country level using some of the targeted data from Phase 1. Economic and epidemiologic impact of investment (infrastructure, human resource, etc) of developing research capacity in a variety of realms including hypothetical research areas based on results of the Phase 1 modelling analysis will be modelled. This model will be constructed keeping in mind local stakeholders as primary consumers of the “investment case” but also designed to be usable by global level stakeholders as appropriate. More detailed methodology for this phase of the project will be developed in consultation with health economists and other experts after Phase 1 is piloted.

Project deliverables

1) Pilot country situational analysis
2) Phase I - Construction of TB Research Prioritization epidemiologic-economic model(s)
3) Phase II - Cost effectiveness analysis module and Research Investment Case

Impact

It is expected that country stakeholders especially those participating in the Technical Advisory Group will use data collected and generated by these models to inform the development of the National TB Research plans (to be included in the country’s specific NSP, as appropriate). Additional priority setting exercises and stakeholder consultations within the country research networks will be required to operationalize the research questions raised by model outputs. In Phase 1, the development of an innovative model that accounts for risk heterogeneity has the potential to be a highly impactful epidemiologic tool for the TB research community. Such a model will also provide an evidence based method for countries to prioritize national research. Phase 2 will provide countries with a tool for estimating the impact of research investment on local epidemiology and economy which may be helpful in advocating for the 3rd pillar of the
End TB strategy. The results of this modelling project are expected to generate several publications as well as preliminary data for larger scale proposal to expand this work in other model countries.

References

### Annex 5. Table of suggested Key Risk Groups by Country

<table>
<thead>
<tr>
<th>Risk Factors of Interest (ideally if anticipated impact on the national epidemic is significant)</th>
<th>Brazil</th>
<th>South Africa</th>
<th>South Africa</th>
<th>Vietnam</th>
<th>Vietnam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poverty</td>
<td>Informal settlements</td>
<td>Prisons</td>
<td>Diabetes</td>
<td>Household contacts</td>
<td></td>
</tr>
</tbody>
</table>

#### Outcome measurement

<table>
<thead>
<tr>
<th></th>
<th>SINAN Vital registration</th>
<th>Case notifications VR</th>
<th>Prevalence (excluding new entrants) sensitive to frequency of ACF Incidence</th>
<th>Case notifications</th>
</tr>
</thead>
</table>

#### Size of group exposed to risk

<table>
<thead>
<tr>
<th></th>
<th>Cadastro Unico Geo information (IBGE)</th>
<th>Census data by district</th>
<th>160000 at any time in a prison</th>
<th>5+million, 2/3 not controlled</th>
<th>0.6m</th>
</tr>
</thead>
</table>

#### Burden of TB in exposed

<table>
<thead>
<tr>
<th>Education level as a proxy (SINAN)</th>
<th>Notifications by district, compare districts according to % informal settlements</th>
<th>Prevalence data</th>
</tr>
</thead>
</table>

#### Mixing with rest of the population

<table>
<thead>
<tr>
<th></th>
<th>Through employees, public places Assume random mixing? If not, what data source / approach to quantification (social sc. Research?)</th>
<th>Not random – assortative mixing</th>
<th>After release from prison</th>
<th>yes</th>
</tr>
</thead>
</table>

#### Relative Risk Why >1

<table>
<thead>
<tr>
<th>Clearly &gt;1 Crowding is greater, poor sanitation, lesser access to health services, greater exposure to other risk factors</th>
<th>&gt;1 Higher HIV prevalence, poverty, lower access to care, crowding</th>
<th>&gt;&gt;1</th>
</tr>
</thead>
</table>

#### Intervention(s)

<table>
<thead>
<tr>
<th>Cash transfers, incentives/enablers (e.g. food) – S-Protect, outcomes of tx ACF? Research question: how do we improve coverage/effectiveness of contact investigations</th>
<th>ACF, contact tracing, social programme (refined after prevalence survey)</th>
<th>HIV testing, ART, IPT ACF Ventilation + reduced overcrowding + separation of coughers and TB cases</th>
</tr>
</thead>
</table>

#### Cost of intervention

<table>
<thead>
<tr>
<th>Cash transfers (social protection)ACF – need details of intervention</th>
<th>ACF cost info available</th>
<th>Cost data available on most items</th>
</tr>
</thead>
</table>
1. April – August 2016:
   a. Situational analysis and identification of key risk group/subpopulation by country level partners/team leaders;
   b. Identification of existing mathematical model within each local context for expansion to include test of heterogeneity.

2. Sept – Nov 2016:
Pilot proof of concept test of input parameters addressing heterogeneity into existing model(s) for one risk group. This will be done in pathfinder countries which have achieved milestones 1a and 1b above.

3. Dec 2016:
Technical Advisory Group Meeting – Geneva: Theme: “Test of heterogeneity analysis on multi-intervention models on achieving 2025 End TB targets”. The goal will be to present situational analysis of key risk factors undertaken in milestone 2 (above), and agree on modelling approach based on country situational analysis and existing mathematical model(s).