TB Modelling and Analysis Consortium

TB Modelling and Analysis Consortium (TB MAC)

Rational Introduction of New TB Drugs and Regimens

Beijing, Republic of China

11-12 September 2013

Meeting Report

www.tb-mac.org

BILL & MELINDA GATES foundation

TB Modelling and Analysis Consortium

TABLE OF CONTENTS

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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.

At our third meeting, held September 2013 in Beijing, our aims were to bring together a wide range of experts in the field of Tuberculosis drug development, within-host and population modellers and epidemiologists to share ongoing analyses and shape the direction of future modelling research in 5 specific areas: 1) Epidemiological impact of improved application of existing drugs and drug regimens, 2) Host and within-host approaches for understanding drug effects, 3) Epidemiological impact and cost-effectiveness of introducing novel TB drugs and novel TB drug regimens, 4) Approaches for the introduction and delivery of new drugs and new drug regimens and 5) Market dynamics.

After series of presentations, the participants separated into groups to formulate the most pressing research modelling questions under each theme, and identify and develop one of these questions into a funding call. These were combined into a Request For Applications which has been released by TB MAC. Two of the modelling research questions will be funded within seven weeks.

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. A first meeting (September 2013, Johannesburg) focussed on TB control in high HIV settings. TB MAC's focus then shifted to applying modelling in support of the development, deployment and evaluation of novel TB diagnostics.

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 3: Rational introduction of new drugs and regimens

This report describes the third TB MAC meeting in Beijing, The Republic of China which covered the research area "Rational introduction of new drugs and regimens".

Meeting objectives

I. Share ongoing analyses in 5 key areas:
   1. Epidemiological impact of improved application of existing drugs and drug regimens
   2. Host and within-host approaches for understanding drug effects
   3. Epidemiological impact and cost-effectiveness of introducing novel TB drugs and novel TB drug regimens
   4. Approaches for the introduction and delivery of new drugs and new drug regimens and
   5. Market dynamics

II. To shape the direction of future modelling research in these areas by:
   1. Determining gaps in existing studies and ongoing analyses
   2. Prioritizing future modelling work that can help address these gaps

Background to meeting

Tuberculosis drug development is experiencing rapid developments, with new compounds and drug regimens in all phases of testing. While these new drugs and regimens promise to improve care for patients affected by TB, policy makers are faced with great challenges when identifying the most effective and cost-effective regimens, as well as the means by which these new agents should be introduced into populations.

In this third TB MAC meeting we aimed to understand how mathematical modelling and economic analysis can be utilized to assist rational decision-making about the introduction of new drugs and drug regimens.

Meeting preparation

Participants were organised into groups according to preference. A list of selected papers was selected by each session chair. These were summarised in a separate document (Appendix 2.1) which was made available to the participants.

Structure and process of meeting

The meeting was structured into one full day of presentations and a second day of small group discussions and reporting, as can be seen in the meeting agenda (Appendix 2.2). After a day of plenary presentations and discussions around each theme, groups would discuss their respective remits during breakout sessions on day two. Interim results from these discussions were reported during a plenary session after lunch, during which each group received wider input. Taking these comments into account, the groups then prepared their final list of key questions, and a draft Request For Applications, which were presented during the final plenary meeting.

1.3

Summary of plenary presentations (Day 1)

After introductory remarks by the meeting organiser (Ted Cohen, BWH, HMS) and Richard White (chair TB Modelling and Analysis Consortium), Mel Spiegelman (TB Alliance) delivered a stimulating presentation on the pitfalls and potential opportunities for models to contribute to more rational development of target product profiles and the different stages of drug development. The presentation also covered the issue of the need for better data before more advanced modelling is done, and the importance of early links between modellers and policy makers to ensure more effective use of modelling.

This was followed by presentations for each of the 5 themes.

1. Epidemiological impact of improved application of existing drugs and drug regimens (chair: Chris Dye, WHO)

   Hsien-Ho Lin (NTU) presented his model that looked at the impact of current and alternative interventions on the epidemiology of MDR TB China, after which Grace Huynh (Intellectual Ventures) presented an individual based model of the TB epidemic in China that explored sensitivity of assumptions, such as age-dependence of parameters or patterns of infectiousness during TB disease. Helen Jenkins (BWH, HMS) analysed global surveillance data of MDR trends, illustrating the limitations of available data and that improving trends were associated with strong surveillance, greater health investment and lower disease burden. Pierre Ankomah (Emory) presented a novel way to integrate in-vitro testing with mathematical modelling.

2. Host and within-host approaches for understanding drug effects (chair: Sarah Fortune, HSPH)

   Sarah Fortune presented work on in-vivo models to estimate state and lineage dependent rate of mutation, and applying mathematical models to understand the risk of resistance emerging within the host. Pia Abel zur Weisch (BWH, HMS) presented a simple modelling approach focussing on antibiotic target-binding and dissociation, which can help to better understand within host drug kinetics and identify key parameters for drug and regimen development. David Hermann (GL Drug Development) illustrated the increasingly central position within the Gates Foundation of PK/PD modelling in drug development, and acceptance within the pharmaceutical industry as cost and time saving. Two further presentations by Rada Savic (UCSF) and Kelly Dooley (JHMI) presented further examples of how statistical models could improve understanding of Phase II studies, and the use of within-host modelling to identify optimal dosing of new regimens, as well as identify heterogeneity in patient or pathogen response to treatment. A presentation by Patrick Phillips (MRC Clinical Trials) discussed the role innovative trial designs had to play in facilitating the development of new drugs and regimens. The primary focus was on the gap between phase II and phase III trials, with Bayesian approaches and seamless phase II/III design described. The need for improved biomarkers of the sterilizing capacity of regimens was also highlighted.

3. Epidemiological impact and cost-effectiveness of introducing novel TB drugs and novel TB drug regimens (chairs: David Dowdy (JHSPH) and Anna Vassall (LSHTM))

   Here William Wells (USAID) gave a program implementer's perspective on new drugs and regimens and highlighted the need for moving beyond solely technological solutions towards health system solutions. Other presentations focussed on the impact and cost-effectiveness of shortened treatment for drug sensitive TB. Gaby Gomez (AIGHD) presented initial results from a cohort model of REMOX which showed high probability of cost-savings. A dynamical transmission model by Mariam Fofana (JHMI) suggested that the effects of shortened regimens on transmission may be more limited than previously assumed, and Josh Salomon showed that the impact of a new regimen will depend on what it replaces and the health system context it is placed in.

4. Approaches for introduction and delivery of new drugs and regimens (chair: Christian Lienhardt, WHO)

   Christian Lienhardt (WHO) outlined the WHO approach to support the introduction of new TB drug regimens which recognises the challenges to provide guidance in a highly heterogeneous epidemiological and health system environment. Matteo Zignol (WHO) illustrated the importance of drug sensitivity testing to support the introduction of new regimens, but that capacity is highly variable. Lixia Wang (Chinese CDC and NCTCP) provided a country implementers perspective and highlighted challenges regarding organisation, strategy and coordination between existing national policy and international guidance. Finally Lara Wolfson (Janssen) showed an industry perspective, including the challenges associated with the initial launch of a product, such as the need to ensure responsible access, appropriate use and surveillance. A staged introduction is therefore preferred, so that these issues can be managed.

5. Market Dynamics (chair: Prashant Yadev, U Mich)

   The presentation by Prashant Yadev (U Mich) focused on how to influence markets to get better outcomes for patients, populations and companies. Based on experiences with antimalarial drugs, an approach was suggested that integrates transmission dynamic, procurement and provider choice models. Nim Pathy (Imperial) then described his work on the influence of the Global Drug Facility on the TB drug market dynamics, followed by a presentation on the current global MDR market by Sana Mostaghim (CHAI), which illustrated the limited size, fragmentation and unpredictability, and the significant room for improving coordination.

1.4

Group discussions and prioritisation of research questions (Day 2)

Area 1: Epidemiological impact of improved application of existing drugs and drug regimens (chair: Chris Dye, WHO)

The discussion began by recognizing (a) that much more can be achieved in TB control with the drugs we already have, and (b) that the "Rational Introduction of New TB Drugs and Regimens" has much to learn from the successes and failures of current TB control programmes. Before settling on the priority questions listed below, the discussion ranged widely on topics including: active case finding and the measurement of infectious periods, choice of drug regimens, maintaining the lifespan of drugs under threat of antibiotic resistance, strengthening surveillance, the value of systems analysis (e.g. the epidemiological consequences of within-host phenomena), treatment of latent infection (preventive therapy), and TB control within health systems.

Priority Questions

1. What is the optimal allocation of 1 million USD to the control of MDR TB using currently available drugs and diagnostic tools?
2. Explore the relative importance of mutation rate, drug pressure, fitness compensation on the acquisition of MDR?
3. What is the intensity of transmission of TB cases before (first) diagnosis, between diagnosis and start of treatment or after failed treatment?
4. Can modelling contribute to the design and/or impact quantification of Universal Health Coverage?

Area 2: Host and within-host approaches for understanding drug effects (chair: Sarah Fortune, HSPH)

The discussion began by a discussion of major challenges facing the development of new drug regimens. There are a number of preclinical models for TB drugs and drug regimens—*in vitro* under a variety of conditions, in different strains of mice and in nonhuman primates. These build towards phase 1 and 2 clinical trials where surrogate markers of drug effect are used—most often early bactericidal activity. It is only very late in the process –in phase 3 trials –that TB cure is the endpoint for a given drug or drug regimen. Unfortunately, no one preclinical or early clinical model has strong predictive power for later clinical trials. To improve the field's ability to develop and prioritize drug regimens, we seek to understand whether mathematical modelling can be used to integrate the results of a subset of preclinical and early clinical data to predict the likelihood of success in the phase III trial.

Priority Questions

1. Develop and use models to maximize the probability of technical success in phase III trials of new drug regimens
2. Develop and use models to predict risk/benefit profile of a TB drug regimen
3. Develop and use models to help us identify and quantify contributors to variability in patient response to treatment
4. Develop and use models to predict which new drug regimens will be robust to the emergence of drug resistance

5. Develop and use models to design better phase II and phase III trials – specifically to better understand the operating characteristics of these trials
6. Develop and use models to support the assumptions and optimize the design of phase II and phase III trials— specifically choice of drug dosing schedule and duration, best combinations of mechanisms of action
7. Use these models to identify important data gaps and critical next experiments

Area 3: Epidemiological impact and cost-effectiveness of introducing novel TB drugs and novel TB drug regimens (chairs: David Dowdy (JHSPH) and Anna Vassall (LSHTM))

Members of this area started with a broad "brainstorming" session in which all members were encouraged to list research topics in this realm that they felt might be important and addressable by models. A list of 26 different topics was generated, which was subsequently structured by consensus into four categories:

(1) What are the best attributes of a new regimen?
(2) What are the best strategies for roll-out or implementation of a regimen?
(3) How should we consider new regimens in the context of broader systems?
(4) What methodological or data needs must be filled for models of new regimens to be successful?

Area members also highlighted four important principles:

(1) Models of drugs should consider diagnosis as part of the treatment pathway.
(2) Modeling efforts should inform (and consider including) empiric data collection.
(3) Models of drug delivery should consider health systems ("strategies not technologies").
(4) Models should begin to consider effects outside the strict confines of the TB control system.

After obtaining feedback from the larger group, area members participated in an anonymous interactive online poll in which each member was shown the full list of possible questions (listed according to the four categories above) and asked to rank them as "top three," "top half," "bottom half," and "bottom three." Five questions clearly garnered the most votes through this process and comprise the priority question list below.

Priority Questions

1. Impact of "magic bullet" regimen vs. better incremental combinations of drugs
2. Impact of different public/private mix options
3. Impact of expansive vs. limited scale-up of novel regimens
4. Impact of prioritizing novel drugs vs. other components in a TB control program
5. What is the impact of patient movement and pathways to care?

Area 4: Approaches for introduction and delivery of new drugs and regimens (chair: Christian Lienhardt, WHO)

The group first addressed the issue of the variety of situations and needs, and hence the need to know which data should be collected at country level and how, so as to assess heterogeneity. From there, the importance was to try and model countries' capacity to introduce the new TB drugs/regimens, evaluate the feasibility and assess related risks (introduction in private markets, misuse, off-label use, additional needs, etc.). These should integrate the various aspects of the local TB epidemic, the health environment (health system structure, NTP) and cost-effectiveness analyses, leading to an evidence-based decision making at country level. All elements/steps along the pathway of introduction and relevant variables to consider should be made explicit, so as to decide, for each of these respectively, whether there should be a "go/no-go", a "trade-off" or the need to weight

importance/impact, so as to take rational decisions on introduction of new TB drugs and various options for scale-up.

Priority Questions

1. Overarching Feasibility and Timing of the introduction
2. Takes into account impact assessment and CEA (area 3) as well as epidemiological background and health system environment (heterogeneity +++)
3. Introduce a "common language" for policy makers around the world and donors
4. Evidence-based decision making process
    - tool for country level
    - tool for supranational prioritization
5. Explicit all elements and impediments, including budget implications
6. Risks assessment around different modes of introduction
7. Ability to evaluate trade-offs between various investments and strategies
8. Heterogeneity of various locations/situations
9. Protocol of data collection to better understand system barriers to scaling-up existing or introducing new interventions/programmes

Area 5: Market Dynamics (chair: Prashant Yadev, U Mich)

The group agreed that lack of harmonization of treatment regimens for MDR-TB both within and among countries is resulting in fragmentation of overall demand for MDR-TB medicines and hurts the market. The ensuing discussion centred on how to understand the key tradeoffs involved. On one side there may be some population level health benefits that result from more specific regimens and therefore higher treatment regimen heterogeneity. On the other hand lack of harmonization of treatment regimens results in more fragmented markets leads which in turn lead to higher prices, longer lead times and a less sustainable market for MDR-TB medicines. The group felt that understanding these tradeoffs more clearly will be critical to successful introduction of new regimens for MDR-TB. The group also discussed the modelling approaches have been used to project the impact of using treatment regimens on MDR-TB disease dynamics and to understand the market impact of using more harmonized regimens. It was clear that separate models are used to understand market impact and disease transmission dynamics. Other points of discussion were around supply side market structure for TB medicines and the role of pooling and demand smoothing. The group felt that rigorous analysis of the supply side issues requires a stronger understanding of production economics for TB medicines.

Priority Questions

1. Model the market impact of reducing unnecessary variation in MDR-TB regimens e.g. reduced price, more resources for treating/diagnosing larger number of patients
2. Model the health outcomes impact of reducing variation: individual vs. population level effects
3. Diffusion models to select private laboratories that are initial adopters of Xpert in order to optimize market outcomes and disease dynamics
4. Diffusion models (converse of diffusion) to select distribution channel strategies that can create selective and targeted access to new products
5. Impact of pooled purchasing of TB medicines: order smoothing effects versus bargain power advantages- once again requires understanding of production economics
6. Understanding optimal market structure for API and Finished Product Formulation- interactions between API and Finished Product Manufacturing-requires understanding of production economics

1.5

Request For Applications

Each group developed one of their questions to be included in a Request For Applications (RFA). After all five were reviewed, the decision was taken that question for group 4 could be incorporated in the other questions, reducing the number of questions in the final RFA to four.

TB MAC has released this RFA, which invites applications on any of the four research questions (see www.tb-mac.org/RFAs). US$145,000 is available in total, and two awards of up to US$72,500 will be made before the end of December 2013. Details of the four modelling research questions are shown below.

1.5.1 Question Area 1**:** What is the optimal allocation of a limited resource to the control of MDR TB? (The limited resource could be a finite sum of money e.g. USD 1 million)

Background
The effective management of MDR-TB is a high priority for tuberculosis control, but how should limited funds be allocated so as to achieve the best possible outcome? The standard approach to resource allocation, namely cost-effectiveness analysis, does not solve the problem of how to distribute a finite resource among competing priorities -- for instance, the balance of investment in treating drug sensitive and drug resistant TB to minimize MDR-TB. Results from this study would inform the rational use of both present and future drug regimens in preventing and reversing the spread of drug resistance.

Work Required
Interventions on MDR TB control broadly separate into 1) preventing acquired TB through improving the existing diagnosis and treatment of drug sensitive TB cases, and 2) preventing transmission of MDR by more/earlier diagnosis and successful treatment of existing MDR TB cases, but could also include treatment of latent TB infection or alternative creative approaches. Successful applications will consider different combinations of interventions.

Specific consideration should be given to:
A. Model requirements
- Using currently available drugs and diagnostic tools
- In two or more contrasting epidemiological settings (Incidence, HIV, MDR) selected (relevant) epidemiological settings
- We expect that the model considers both economical and epidemiological models

B. Applicants should clearly specify, and consider how the sensitivity of their results depends on:
- Epidemiological setting (TB incidence and mortality, initial prevalence of MDR and HIV)
- Choice of MDR-TB indicators to be optimized
- Current levels of TB control
- Scale of interventions

Aim
The aims are (1) to develop a mathematical framework for optimal allocation of resources to MDR-TB control, and (2) to present results for two or more epidemiological settings.

Objectives
1. To develop a mathematical framework for optimal allocation of resources to MDR-TB control
2. To present results for two or more epidemiological settings

1.5.2 Question Area 2: Application of models to maximize the probability of success in phase 3 clinical trials of new drug regimens

Background
Currently, the development of new drug regimens for TB is held back because we cannot predict success until the end of a phase 3 trial. Our aim is to avoid late stage attrition and mitigate the risk of developing regimens that are of limited value in the TB health care system. Availability of quantitative models linking the connection between preclinical models, early clinical outcomes, and late stage durable cure is essential. In the near term, developing the connection between in vivo animal experiments and early clinical trials would provide a useful 1st step to the long term aim of building a comprehensive TB drug & disease model capable of identifying new regimens that are likely to be successful in phase 3 clinical trials.

Work Required
The goal of this research project is to develop models to maximize the probability of success in phase 3 clinical trials of new drug regimens. More specifically, as a first step we seek proposals to develop a model that links two or more categories of early experimental or preclinical data to results observed in later development. This could include establishing the link between results in animal models to predict the results of early clinical trials (i.e., 2-week or 8-week trials) or outcomes of late stage clinical develop (i.e., durable cure).

Aim
The aim is to develop a model to maximize the probability of success in phase 3 clinical trials of new drug regimens.

Objectives
1. To identify, obtain access, and organize relevant preclinical and clinical data to support the model development effort (the Gates Foundation may be able to assist with this)
2. Identify data gaps
3. To identify relevant model components & model building methodology
4. Develop model structure, fit data, explore goodness-of-fit and posterior predictive checks

1.5.3 Question Area 3: Assessing the health outcomes and economic consequences of different strategies for scale-up of novel regimens

Background

It is anticipated that, in the coming five years, several new TB drugs and regimens will need to be adopted and rolled out at the country level. While there is broad modelling work at the global level examining the impact and economic consequences of new regimens, there has been little examination of the optimal strategy for actually rolling out these regimens. This work aims to fill this gap, by investigating and comparing the health outcomes and economic consequences of expansive vs limited roll-out strategies in a number of settings. As this would be the first work in this area, and data are scarce, this work will be exploratory in nature, and should guide both future data needs and an approach for using modelling to best support early adopters of novel TB regimens.

Work Required

The modelling should focus on the use of one or more regimens/drugs likely to be available in next 5 years (Bedaquiline, FQ-based regimens, PaMZ) and should investigate roll-out strategies of larger/more rapid versus smaller/slower scope. The model should be calibrated to one or more specific settings and not focus purely on outcomes over the very long-term (i.e., should report outcomes within 20 years as a primary result). Depending on the setting(s) selected, examples of useful comparisons might include (but are not limited to):

- Staging or speed of implementation (High ["pilot first"] vs. low ["disseminate immediately"] initial coverage)
- Channel of delivery (for example, rapid vs. measured engagement with private sector)
- Placement in the health system (for example, centralized vs. decentralized)
- Target patient groups (broad vs. narrow indication)

The modelling should also assess the consequences of their analysis for future data needs and modelling support in the selected setting(s), including the data that would be most important to obtain in order to improve the decision-making process.

Applicants may also wish to assess wider economic or epidemiological issues that might be important to decision makers, such as:

- Economic consequences in the form of budget impact as well as cost-effectiveness
- The optimal balance between short term gains vs longer term risks in areas (in terms of flexibility for future regimens)
- Equity implications of different roll-out strategies

Aim

To assess the health outcomes and economic consequences of different strategies for the roll-out of novel TB regimens

Objectives

1. To identify a range of strategies for the roll-out of novel TB regimens in one or more key settings.
2. To develop a framework for assessing the short and long term health outcomes and economic consequences of the selected strategies.
3. To inform practical decision-making about the roll-out of novel TB regimens in one or

more key settings.
4. To identify the most important data gaps that currently limit decision-making ability related to roll-out of novel TB regimens.
5. To disseminate findings to key stakeholders involved in rolling out new TB drug regimens in the selected setting(s).

1.5.4 Question area 5: Modelling to Understand the Epidemiological Impact and Market Impact of Harmonized Regimens for MDR-TB

Background
The lack of harmonization of treatment regimens for MDR-TB both within and among countries results in fragmentation of overall demand for MDR-TB medicines and hurts the market. There have been some efforts to harmonize and rationalize regimens but some argue that different regimen options are required in order to adapt treatment for each individual patient's needs and the resistance patterns in a country or region. There is no clear or objective way to capture the population level health benefits that result from more specific regimens. On the other hand it is clear that more fragmented markets leads to higher prices, longer lead times and a less sustainable market for MDR-TB medicines. New regimens for MDR-TB or TB more generally will be introduced in this context.

Traditionally, separate modelling approaches have been used to project the impact of using treatment regimens on MDR-TB disease dynamics and to understand the market impact of using more harmonized regimens. Assessing the total effect of harmonizing regimens requires explicitly capturing the impact of this at the population level and for the market as a whole.

Work Required
An urgent need has been identified for a new type of model which includes the dynamic epidemiological effects of treatment harmonization and the market impacts of treatment harmonization with feedback loops to capture the inter-relationships. A combined model is needed that captures the most important features of both the market side and the epidemiological characteristics. Such a model should be calibrated to existing epidemiological data and market parameters such as price.

The model should include 1) A disease progression model that includes resistance spread (2) A market impact model that considers differences in prices between products and potentially decrease in prices as a result of volume shift. The time horizon of the model should be: 5-10 years. The geography and scale is: 1 large MDR-TB high burden country e.g. Russia or China where there sufficient data on resistance patterns for SLDs. The model structure should be usable for other countries and scaleable to be a global model. The first phase paramterization and validation could be done for the selected country.

Aim

To develop model(s) that project the epidemiological impact and market impact of harmonizing treatment regimens for MDR-TB, including new regimens, within particular country and across countries

Objectives

1. To develop a model that included a disease progression model that includes resistance spread and a market impact model that considers differences in prices between products and potentially decrease in prices as a result of volume shift.
2. To parameterize and validate the model for a selected country.
3. To make projections over 5-10 years in at least 1 large MDR-TB high burden country
4. Show that the model structure is usable for other countries and scaleable to a global model.

1.6

Outcomes and next steps

The meeting consolidated the ongoing process of activating and expanding the field of modelling in the field of drug and regimen development. The wide participation and presence of young scientists shows that this process is already underway, and will be further supported by the connections made during the meeting and the research funded by TB MAC. TB MAC will continue to bring together new and experienced TB modellers with data experts around specific topics in the field of TB to improve global tuberculosis (TB) control by coordinating and promoting mathematical modelling and other quantitative research activities.

APPENDICES

2.1 Summary of selected papers for area discussions

2.2 Meeting agenda + participant list

TB Modelling and Analysis Consortium

Appendix 2.1 Summary of selected papers for area discussions

Summary of selected papers for area Discussions.

Theme chairs were asked to provide a small number of key publications with high relevance to the discussions. All papers can be downloaded using the following link: https://docs.google.com/file/d/0B4uik1Ch5qzqR1pMWjFKTzdnSms/edit?usp=sharing. [Click on 'File' in top left of screen, choose 'Download'. This will start the download of the zip-file.

This document gives a very short summary of the papers. Participants are encouraged to read through the papers that apply to their session, and are invited to explore the other papers as time permits.

Theme 1: Epidemiological impact of improved application of existing drugs and drug regimens (Dye)

Ref	Main question(s)	Methods	Conclusion(s)
1	1. How is MDR Mtb selected within individuals? 2. What is the threat of ongoing spread of (M)DR? 3. What interventions are needed to stop spread of (M)DR?	Narrative review of evidence from modelling, observational and experimental studies. Areas for further study are highlighted	1. Random DR mutations are selected through inadequate treatment or suboptimal drug exposure within host 2. The effective Reproductive number depends on biological factors (e.g. reduced fitness of DR strain) and contextual factors (e.g. longer duration of infectiousness due to delayed appropriate treatment 3. Effective detection and treatment of DS TB, and DR specific measures (depending on local epidemiology) can slow spread of DR
2	Will a constant Case Detection Rate (CDR) lead to sustained annual declines in TB incidence?	Dynamic transmission model that explored impact of varying CDR scenarios on long term changes in annual TB incidence.	After a decade of a sustained CDR of 70%, the annual decline will reduce to a low constant level. For a higher and constant annual decline in TB incidence, gradual and continuous increases in CDR would be required.
3	Can good treatment practices reverse the spread of MDR TB?	Review and statistical analysis of empirical data and dynamical model of MDR generation and transmission	Current diagnostic and treatment strategies can bring the effective Reproduction number below 1, i.e. force are decline in MDR incidence. However, this decline will be slow, leading to elimination in centuries rather than decades.

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2. Dowdy, D.W. and R.E. Chaisson, The persistence of tuberculosis in the age of DOTS: reassessing the effect of case detection. Bull World Health Organ, 2009. 87(4): p. 296-304.
3. Dye, C. and B.G. Williams, Slow Elimination of Multidrug-Resistant Tuberculosis. Science Translational Medicine, 2009. 1(3).

Theme 2: Host and within-host approaches for understanding drug effects (Fortune)

Ref	Main question(s)	Methods	Conclusion(s)
1	Does population wide Isoniazid Preventive Therapy (IPT) for HIV positive individuals contribute to the emergence of drug resistance?	Dynamic transmission model that included HIV strata and allowed for acquisition of drug resistance, as well as infections with drug sensitive and/or, drug resistant strains	Community-wide IPT can increase the selective pressure for Isoniazid resistance, even if it doesn't directly cause acquired resistance among those treated. Potential perverse effects on selection of resistant strains imposed by community-wide IPT can best be mitigated by early detection and appropriate treatment of resistant disease.
2	1. Is there a difference in the rate of resistance conferring mutations between Mtb lineages? 2. How does this affect the chance of a patient harboring MDR bacteria at time of diagnosis?	A combination of in vitro and in vivo analyses of rates of resistance mutations in 9 Mtb strains of lineage 2 (n=4) and lineage 4 (n=5), as well as within-host mathematical modeling	Across all techniques, the analysed strains from lineage 2 had statistically significantly higher rates of developing resistance conferring mutations compared to lineage 4. In a mathematical model, even relatively small differences in mutation rates can create substantial differences in the risk of the presence of MDR bacteria by the time of treatment initiation.
3	What is the benefit of Directly Observed compared to Self-Administered Therapy) DOT vs SAT) with regard to microbiological failure, relapse and acquired drug resistance?	Systematic literature review	There was no difference between DOT and SAT for any of the outcomes. Control and care programmes should focus efforts on other causes of poor microbiologic outcomes.
4	What is the impact of non-adherence and between patient pharmacokinetic variability on developing MDR?	In-vitro experiments and Monte Carlo modelling of Cape Town patients	The in-vitro experiments showed high levels of non-adherence (≥60%) were required to generate therapy failure. Monte-carlo simulations showed that even with 100% adherence, between host differences in pharmacokinetics alone could result in MDR in 1% of patients

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4. Srivastava, S., et al., Multidrug-resistant tuberculosis not due to noncompliance but to between-patient pharmacokinetic variability. J Infect Dis, 2011. 204(12): p. 1951-9.

Theme 3: Epidemiological impact and cost-effectiveness of introducing novel TB drugs and novel TB drug regimens (Dowdy & Vassall)

Ref	Main question(s)	Methods	Conclusion(s)
1	What is the projected population level impact of more effective drug regimens, vaccines and diagnostics?	Dynamical transmission model of global TB population.	Model estimations suggested that novel drug regimens, which are both shorter and increasingly effective against MDR strains, could reduce TB incidence in South-East Asia region by 13-42% between 2015 and 2050
2	What is the potential population level impact of novel, shorter regimens?	Dynamic transmission model of TB in South-East Asia region	Given current (2005) levels of coverage, a 2 month regimen introduced in 2012 could prevent 20% of new TB cases by 2030. Increased coverage of current regimens (DOTS) and 10-year delay of the introduction of novel therapies would reduce the impact to 13% and 5% respectively.

References

1. Abu-Raddad, L.J., et al., Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. Proc Natl Acad Sci U S A, 2009. 106(33): p. 13980-5.
2. Salomon, J.A., et al., Prospects for advancing tuberculosis control efforts through novel therapies. PLoS Med, 2006. 3(8): p. e273.

Theme 4: Approaches for the introduction and delivery of new drugs and new drug regimens (Lienhardt)

Ref	Main question(s)	Methods	Conclusion(s)
1	What is progress towards 2015 target of universal access to MDR treatment?	Analysis of data from 30 countries representing 90% of 2011 global MDR TB burden	Six out of 30 countries (Belarus, Brazil, Kazakhstan, Peru, South Africa, and Ukraine) currently treated ≥50% of estimated MDR cases, and could achieve the 2015 target. Based on data from 23 countries, a median of 53% of MDR patients completed their treatment in 2011 (started in 2008/09)
2	Considerations around introductions of new drugs for active TB.	Narrative review	Central guidance is needed on country policies for the use of new drugs to optimise access to, and limit inappropriate use of new drugs
3	Given currently available evidence, what is WHO recommendation on use of bedaquiline in treatment of MDR TB	Expert group review	- Evidence suggests adding bedaquiline to an MDR regimen improves microbiological outcomes, but the expert group expressed concerns about the representativeness of the study population, and strong evidence for an increase in deaths in the bedaquiline group, which remains unexplained. - WHO interim guideline: bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB (conditional recommendation, very low confidence in estimates of effects)
4	What are current rates and trends and of TB drug resistance?	Survey and surveillance data from 88 countries or territories, collected between 2007-2010	- Based on current data, the proportion MDR of new TB cases ranged between 0-29%, in retreatment cases the range was 0-65%. - Largest nationwide survey (China) reported 5.7%/25.6% MDR in new and retreatment cases respectively - 5 countries/territories reported >10% of MDR cases to XDR - Both increasing (e.g. Botswana, Peru) and declining trends (e.g. Estonia, Latvia) were observed

References

1. Falzon, D., et al., Universal access to care for multidrug-resistant tuberculosis: an analysis of surveillance data. Lancet Infect Dis, 2013. 13(8): p. 690-7.
2. Lienhardt, C., et al., New drugs for the treatment of tuberculosis: needs, challenges, promise, and prospects for the future. J Infect Dis, 2012. 205 Suppl 2: p. S241-9.
3. WHO, The use of bedaquiline in the treatment of multidrug-resistant tuberculosis - Interim policy guidance 2013, World Health Organisation: Geneva.
4. Zignol, M., et al., Surveillance of anti-tuberculosis drug resistance in the world: an updated analysis, 2007-2010. Bull World Health Organ, 2012. 90(2): p. 111-119D.

Theme 5: Market dynamics (Yadav)

Ref	Main question(s)	Methods	Conclusion(s)
1	What is the role of the Global Drug Facility (GDF) in the TB market for first-line and second-line drugs?	Analysis of GDF internal data and global TB estimates	- GDF plays an intermediary role between National TB Programmes, donors and drug manufacturers - GDF current supplies about between 2.0-2.5 million first line treatments annually, which has been relatively stable since 2005. - The market share in first-line drugs varies strongly between regions. GDF holds >25% of market share in the African, South-East Asia and Eastern-Mediterranean regions. - For second line drugs, GDF market share has been increasing, and is currently just below a third of all notified cases.
2	How can we improve demand forecasting (the ongoing process of projecting which products will be purchased, where, when, by whom and in what quantities)? Paper focuses on new products and new markets	Expert opinion	The paper suggests 3 key components to improving demand forecasting - Improvement of technical forecasting ability - e.g. create models for country level forecasts - Creation of Global Health Infomediary - collect data to better inform demand forecast models - Share risk and align incentives through a broader menu of contracting options - e.g. to find innovative ways to ensure pooled purchasing mechanisms achieve their objectives
3	What is the optimal number of drugs/regimens for a country to include in the supply chain with respect to emergence of resistance and procurement and safety stock holding costs?	Dynamical malaria transmission model that includes a variable number of available treatments (n=1-10), emergence of resistance and disease burden (DALY). The model is linked to a cost function including procurement and stock holding costs, with 1 DALY costed at	- Initial increase of number of available regimens has major beneficial impact on DALYs saved, through reduction in risk of resistance and decrease in disease prevalence. But the marginal benefit of an extra drug drops steeply at threshold. - Procurement costs decrease when more drugs are procured, but slower than the decrease in DALYs lost, because of added costs of variety (e.g. initial costs per supplier). - Safety stock costs are low compared to DALY and procurement costs. - These findings are strongly dependent on total disease burden/volume of procured treatments, drug price and size of volume discounts.

		$1000	- In the scenario includes a high disease burden and high drug costs (>$100), and substantial volume discounts are available, a low number of drugs appeared optimal. While this could apply to TB (authors caution that the transmission model was not reflective of TB natural history)

References

1. Arinaminpathy, N., et al., The Global Drug Facility and its role in the market for tuberculosis drugs. Lancet, 2013.
2. Levine, R., et al., Demand Forecasting for Essential Medical Technologies. American Journal of Law and Medicine, 2008. 34: p. 269-297.
3. Spiliotopoulou, E., F.B. Maciej, and Y. Prashant, Impact of treatment heterogeneity on drug resistance and supply chain costs. Socio-Economic Planning Sciences, 2013: p. 1-14.

TB Modelling and Analysis Consortium

Rational introduction of new drugs and regimens

TB Modelling and Analysis Consortium Meeting #3
Beijing, China
September 11 and 12, 2013

We are in the midst of an exciting era in TB drug development, with new compounds and drug regimens in all phases of testing. While these new drugs and regimens promise to improve care for patients affected by TB, the identification of most effective and cost-effective regimens and the means by which these new agents should be introduced into populations will bring challenges for policy makers.

In this meeting, we aim to understand how mathematical modeling and economic analysis can be utilized to assist rational decision-making about the introduction of new drugs and drug regimens.

Goals of meeting:

1) To share ongoing analyses related to 5 themes:
    a. Epidemiological impact of improved application of existing drugs and drug regimens. (session chair: Chris Dye)
    b. Host and within-host approaches for understanding drug effects (session chair: Sarah Fortune)
    c. Epidemiological impact and cost-effectiveness of introducing novel TB drugs and novel TB drug regimens (session chairs: David Dowdy and Anna Vassall).
    d. Approaches for the introduction and delivery of new drugs and new drug regimens (session chair: Christian Lienhardt)
    e. Market dynamics (session chair: Prashant Yadav)
2) To shape the direction of future modelling research in these areas by:
    a. Determining gaps in existing studies and ongoing analyses and
    b. Prioritizing future modeling work that can help address these gaps

Meeting format:

The meeting will take place over 2 days. Short lists of key papers will be circulated before the meeting. Day 1 will consist of a plenary session and 5 sessions of brief research presentations, many of which will consist of work in progress. In Day 2, we will spend most of the day in smaller working groups, returning to meet as a larger group for mid-stream and final feedback. These working groups will parallel the themes covered in the 5 sessions from Day 1. A detailed agenda is attached on the following pages.

Meeting deliverables:

By the end of the meeting, each working group will develop and share a prioritized list of research questions modelling and/or economic analyses that will help direct new research activities toward most the most pressing questions. These prioritized lists of questions will be used to develop a Request For Applications to fund new modeling work in this area directly through TB MAC funds. A detailed meeting report will be written and circulated to all participants and made available through the TB MAC website.

BILL & MELINDA GATES foundation

TB Modelling and Analysis Consortium

Agenda

September 10, 2013:

6-8p	Pre-meeting reception *[Signature Ballroom B]*	

September 11, 2013:

8-8:30a	Brief introductions Review of goals and format of meeting *[Signature Ballroom B]*	Ted Cohen (BWH, HSPH) Richard White (LSHTM)
8:30-9a	Plenary presentation: *Models for New TB Therapy: Road from Form to Substance*	Mel Spigelman (TB Alliance)
9-10:20a	**#1 Epidemiological impact of improved application of existing drugs and drug regimens**	Chair: Chris Dye (WHO)
	9-9:15 *Modeling the control of multidrug-resistant tuberculosis in China's health system*	Hsien-Ho Lin (NTU)
	9:15-9:30 *Pathways to care and treatment quality: modeling the impact on TB burden in China*	Grace Huynh (IV)
	9:30-9:45 *Can we control MDR-TB with existing drugs?*	Helen Jenkins (BWH, HMS)
	9:45-10 *The intersection between the pharmacodynamics of antimycobacterial drugs, non-adherence to therapy and the evolution of multi-drug resistance*	Pierre Ankomah (Emory)
	10-10:20 DISCUSSION	
10:20-10:45a	Break	
10:45-12:30p	**#2 Host and within-host approaches for understanding drug effects**	Chair: Sarah Fortune (HSPH)
	10:50-11:05 *(Avoiding) resistance is futile*	Sarah Fortune
	11:05-11:20 *Linking chemistry with bacterial population biology: Simple models explain complex patterns of antibiotic action*	Pia Abel zur Weisch (BWH, HMS)
	11:20-11:35 *Modeling & Simulation in TB: An Integrated Development Perspective*	David Hermann (GL Drug Development)
	11:35-11:50 *Modeling and Clinical Trial Simulation to Guide Phase 3 Trial Design of New Treatment Regimens*	Rada Savic (UCSF)
	11:50-12:05 *New treatment regimens for TB – how modeling can help us get it right: the clinical trialist's point of view*	Kelly Dooley (JHMI)
	12:05-12:20 DISCUSSION	
12:20-1:30p	Lunch *[Elements]*	

1:30-2:50p	**#3 Epidemiological impact and cost-effectiveness of introducing novel TB drugs and novel TB drug regimens**	Chairs: David Dowdy (JHSPH) and Anna Vassall (LSHTM)
	1:30-1:45 *Modeling the impact and cost-effectiveness of new TB drug regimens: development and policy perspective*	William Wells (USAID)
	1:45-2 *Cost-effectiveness of two new shortened regimens (REMox) for first-line treatment of active tuberculosis*	Gaby Gomez (AIGHD)
	2-2:15 *Population-level impact of shorter-course TB drug regimens: Are we being too optimistic?*	Mariam Fofana (JHMI)
	2:15-2:30 *Population-level impact of novel TB drug regimens: insights from modeling analyses*	Josh Salomon (HSPH)
	2:30-2:50 DISCUSSION	
2:50-3:20p	Break	
3:20-4:40p	**#4 Approaches for the introduction and delivery of new drugs and new drug regimens**	Chair: Christian Lienhardt (WHO)
	3:20-3:35 *Models of introduction for new TB drugs/ regimens*	Christian Lienhardt
	3:35-3:50 *The importance of knowledge of DST patterns and MDR treatment coverage for design and introduction of new MDR regimens*	Matteo Zignol (WHO)
	3:50-4:05 *Initial consideration on introduction of new TB drugs*	Lixia Wang (Chinese CDC and NCTCP)
	4:05-4:20 Industry perspective in introduction/roll-out/scale-up of new TB drugs	Lara Wolfson (Janssen)
	4:20-4:40 DISCUSSION	
4:40-5:10p	Break	
5:10-6:30p	**#5 Market Dynamics**	Chair: Prashant Yadev (U Michigan)
	5:10-5:25 *Treatment Regimens, Market Choice, and Disease Modelling: Experiences from Malaria Medicines*	Prashant Yadev
	5:25-5:40 *Which kinds of interventions influence TB market dynamics?*	Nim Pathy (Imperial)
	5:40-5:55 *The current structure of the market for MDR-TB medicines and challenges/opportunities for new products/regimens*	Sana Mostaghim (CHAI)
	5:55-6:10 *New approaches to trial designs for TB drug regimens*	Patrick Phillips (MRC Clinical

		Trials Unit)
	6:10-6:30 DISCUSSION	
6:30-7p	Break	
7p	Dinner *[The Work Room]*	

September 12, 2013:

9-9:30a	Recap of Day 1, outline goals and structure for Day 2 *[Signature Ballroom B]*	Ted and Richard
9:30-12p	Breakout sessions with 5 workstreams: *Workstream1: Vision 7* *Workstream 2: Vision 8* *Workstream 3: Signature Ballroom B* *Workstream 4: Vision 4* *Workstream 5: Vision 6*	Discussions facilitated by workstream chairs
12-1p	Lunch *[Elements]*	
1-2:30p	Large group reconvenes for discussion of informal preliminary presentations from each workstream on progress giving opportunity for feedback from whole group (5*15 mins) *[Signature Ballroom B]*	
2:30-3:45p	Workstream sessions reconvene *[Rooms as above]*	Discussion facilitated by workstream chairs
3:45-4p	Break	
4-5p	Large group reconvenes for final presentations of priority lists of research questions from workstreams (5*10 mins) *[Signature Ballroom B]*	
5-5:30p	Meeting wrap-up and next steps	Ted and Richard

Participant List and Workstreams

Name	Organisation	Workstream
Mel Spigelman	TB Alliance	1
Chris Dye	WHO	1
Hsien-Ho Lin	National Taiwan University	1
Grace Huynh	Intellectual Ventures	1
Pierre Ankomah	Emory	2
Helen Jenkins	Harvard	1
David Dowdy	JHU	3
Anna Vassall	LSHTM	3
William Wells	USAID	3
Gaby Gomez	AIGHD	3
Gwen Knight	LSHTM	2
Mariam Fofana	JHMI	3
Josh Salomon	Harvard	3
Sarah Fortune	Harvard	2
David Hermann	GL Drug Development	2
Kelly Dooley	JHMI	2
Pia Schulz zur Wiesch	Harvard	2
Rada Savic	UCSF	2
Christian Lienhardt	WHO	4
Matteo Zignol	WHO	4
Wang Lixia	China TB	n/a
Lara Wolfson	Janssen	4
Prashant Yadav	Michigan	5
Nim Pathy	Princeton	5

Sana Mostaghim	Clinton Health Access	5
Patrick Phillips	MRC	2
Richard White	LSHTM	2
Michael Kimerling	BMGF	3
Ted Cohen	Harvard	1
Philip Eckhoff	Intellectual Ventures	4
Rein Houben	LSHTM	1
Jan Gheuens	BMGF	2
Sun Yanni	WHO	n/a
Andrew Jones	BMGF	5
Daniel Chin	BMGF	3
Fabio Scano	WHO	1
Claver Bhunu	University of Zimbabwe	3
Gesham Magombedze	NIMioS	2
Pieter Uys	SACEMA	1
Peter Small	BMGF	4
Allison Rhines	BMGF	4
Joanne Yoong	University of Singapore	3
Zhongwei Jia	Peking University	5
Carole Mitnick	Harvard	3
Helen Cox	Burnet	3
Colleen Daniels	Treatment Action Group	4