TB Modelling and Analysis Consortium

TB Modelling and Analysis Consortium / World Health Organisation / Global Health Costing Consortium (TB MAC / WHO / GHCC)

Annual meeting

Country-level modelling & TB Prevention, Diagnosis & Vaccines

Washington DC, USA
10-14 September 2018

Meeting Report

www.tb-mac.org

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Executive summary

The TB Modelling and Analysis Consortium (TB MAC) is a public good initiative to improve global tuberculosis (TB) control by coordinating and promoting mathematical modelling and other quantitative research activities.

At our ninth meeting, held in September 2018 in Washington DC, USA, our aims were twofold. The first of these, as part of TB MAC's work supporting the WHO Global Task Force on TB Impact Measurement, was to discuss a number of ongoing activities looking to strengthen TB country-level modelling, including the establishment of benchmarks which country-level TB models, reporting and review frameworks for country level modelling applications, the filling of key evidence gaps, and a variety of initiatives to improve the use of economics in TB modelling. Our second aim, as part of TB MAC's Modelling Research Group, was to facilitate discussion around TB prevention, vaccines and diagnostics, updating stakeholders on developments in the field, improving networking within the community and highlighting a recent funding opportunity.

To meet these aims, we brought together a large number of experts and stakeholders - from modellers, economists and epidemiologists to funders and policy representatives. The meeting included a number of discussion sessions, enabling engagement from all present and ensuring that a broad number of views were heard to guide the direction of future work.

Each topic lead to clear outcomes and specific actions to improve support for evidence informed decision making in TB. Examples follow. In the country-level modelling session a strong demand for piloting of the country level modelling Benchmarking, Reporting and Review was identified, and will be taken forward by TB MAC, modelers and the TB Modelling Roadmap Steering Committee. In terms of filling evidence gaps, it has been proposed that TB MAC facilitate the construction and maintenance of a structured database to link activities data to coverage changes, populating this with evidence collated by modellers during modelling applications. In the country-level economics session, the desire for additional case studies to further work on equity was highlighted. From the TB prevention session, a discussion group to focus on the impact of subclinical TB disease on transmission was proposed, and will convene at the Union meeting. In the vaccines session a key research question that emerged was the use of modelling to help guide new Phase 3 trial designs and vaccine implementation planning, as well as estimating the impact of BCG revaccination. Finally, the diagnostics session identified the need for transdisciplinary work linking models with unique sources of laboratory, epidemiological, and policy-level data, and it was envisaged that this would be carried forward by funding applications to TB MAC.

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 coordination, 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 focussed on TB control in high HIV settings. TB MAC's focus then shifted to diagnostics and drugs, followed by a multi-model comparison exercise (over three meetings: 1, 2 and 3) to evaluate the feasibility of the End TB Strategy targets in China, India and South Africa, and subsequently a consideration of the socio-economic determinants of TB as well as country-level modelling and case detection.

TB MAC Aim

To reduce the global burden of TB by increasing the effectiveness and efficiency of TB control policy and practice at global and country level.

TB MAC Objectives

1) Create improved coordination, knowledge sharing and management within the TB community
2) Create new high quality modelling guidelines and resources
3) Develop better informed TA/decision making communities and modellers

1.2 Meeting overview:

Background to meeting

In this meeting, TB MAC sought to address each of TB MAC's 3 main objectives, as well as to continue to develop materials in support of the 2020 Country-level Modelling Roadmap agenda, developed by key TB funding bodies and stakeholders.

In order to contribute towards TB MAC's objectives of sharing of knowledge (objective 1) and better informed communities (objective 3), the meeting brought together participants from a number of different viewpoints, including funding agencies, technical assistance organisations, clinicians, epidemiologists and modellers. These participants initially discussed key resources that TB MAC had been developing (objectives 2 and 3), including benchmarks, a reporting template and review process to aid in assessing modelling to inform country-level TB decision making, as well as a proposed framework to collate data for key evidence gaps linking programmatic activities to epidemiological impact. In addition, various economic tools and considerations were discussed.

In the second part of the meeting, as part of objective 1 the TB MAC Modelling Research Group identified key areas of interest to discuss during the annual meeting. Following a community-wide consultation process, modelling of TB prevention was chosen, followed by two shorter sessions on TB vaccines & diagnostics. Similar groups of participants from a range of backgrounds (with some overlap in participants from different parts of the meeting) were brought together to discuss the challenges and future direction of modelling prevention, vaccines and diagnostics, from a range of perspectives.

Structure and process of meeting

The meeting focused on five topics:

1) **Country-level modelling benchmarking, reporting & review**
    - *Monday 10th 09:00 to Tuesday 11th September 13:00*

   A discussion around two separate activities: (i) benchmarking, reporting & review (ii) data gaps linking activities to impact and a framework for data collation to fill these evidence gaps.

2) **Country-level modelling and economics**
    - *Tuesday 11th September 14:00 - 17:30*

   A discussion of TB MAC activities and external links around the theme of economics, including an introduction to new economic tools and considerations.

3) **TB prevention**
    - *Wednesday 12th 08:30 to Thursday 13th September 16:00*

   A discussion of the key considerations when modelling TB prevention.

4) **TB vaccines**
    - *Friday 14th September 08:30-17:30*

A discussion on the utility and optimisation of modelling to support TB vaccine candidate development and implementation

5) **TB diagnostics**
    - *Friday 14th September 08:30-17:00*

A discussion about the future of modelling TB diagnostic testing across the disease spectrum.

1.3 Country-level modelling benchmarking, reporting, review and data gaps (DAYS 1-2)

1.3.1 Background

At the request of the TB Modelling Roadmap Steering Committee, TB MAC is leading an initiative to promoting the quality and transparency of country-level TB modelling. This initiative includes (i) developing a set of benchmarks against which modelling assumptions and results can be compared, (ii) developing standard reporting templates and checklists, and (iii) developing an external review system.

Over recent months, a small working group developed a draft approach for each of these activities, which have subsequently been reviewed by a wider group of stakeholders, including modellers, funders and technical experts. The aim of this meeting was to discuss these draft approaches, and the questions/comments that have been provided through review, in order to suggest improvements and next steps.

1. Benchmarks
These benchmarks describe features of TB natural history, epidemiology, health services, and costs. Modelling assumptions and results can be compared to these benchmarks to assess the appropriateness of a modelling application for a given policy question and country context. Some benchmarks are universal, while others are specific to a country and policy question. These benchmarks are not expected to be met dogmatically -- in a given modelling application the requirement would be to compare modelling results with the benchmarks relevant to the application, and discuss/justify any major deviations. The form also requests several additional outputs (without any benchmark) to aid in interpreting model results.

2. Reporting template
This is a standard format for reporting modelling results. The template describes both quantitative comparisons (linked to the benchmarks outlined above) and process indicators, as well as including a checklist that can be used by reviewers to assess the completeness of reporting. The intention of this template is for adoption where desired by individual funders or modelling TA organisations in order to ensure completeness of information reported and straightforward synthesis and review of a modelling application.

3. Review process
This is a process for facilitating external review of modelling results. The system outlines how expert reviewers will be engaged and linked to requests to review country modelling applications. These expert reviewers will represent themselves, and not TB MAC. It is not expected that every modelling application will involve external review, and the decision at to whether external review is needed would be made by the funders and stakeholders for a given modelling application. Funding for reviews would need to be included as part of the funding for the modelling exercise, or arranged separately by the funding agency.

In these activities TB MAC's role is to provide 'public good' activities that support the TB modelling community as a whole, include collating, and sharing, information on activities towards the TB Modelling Roadmap, and developing guidance. Any funding or prioritisation decisions remain those of the individual funder/stakeholders.

A high-level summary of comments and suggestions from the first round of review by stakeholders was presented and discussed at the meeting.

4. Activities to impact
TB Programme funders and governments are looking to optimise the returns on their investments and therefore are placing greater emphasis on tools and programmes that demonstrate allocative efficiency. The previous TB MAC Targets exercise highlighted the severe lack of empirical evidence on suggested activities and their costs that might lead to the targeted coverage increases. In the last year, efforts undertaken by the GHCC have been made to collect cost data on specific activities.The other side of this, the link between activities and impacts, remains poorly unevidenced. Without better evidence NTPs, TA agencies, and modelling groups, are forced to rely upon educated guess-work to inform policy decisions on resource allocation.

An example framework and proposed project aim was presented and discussed at the meeting. This looked to identify, collate and summarise evidence on activities leading to coverage increases, along the prevention and care cascade, to better inform TB resource allocation.

1.3.2 Aims and objectives

Aim: outline and improve on benchmarks, reporting template, review process, and activities-to-impact framework

Objective 1: summarise rationale and efforts so far
Objective 2: discuss how to improve approach
Objective 3: identify next steps for implementation

1.3.3 Summary

Day 1 & (morning of) Day 2 Summary
Michael Kimerling chaired the first session, which included an introduction and overview of the entire week's agenda from Richard White, and an outline of the the motivation, efforts to date and session objectives of the Benchmarks, Reporting and Review (BRR) planned activities from Nick Menzies. The session also included the funders perspective, given by Daniel Chin of the Bill and Melinda Gates Foundation and Shufang Zhang of The Global Fund to Fight AIDS, Tuberculosis and Malaria, as well as a series of presentations and open floor discussions on each of the four benchmark areas, given by members of the BRR working group.

In his introductory remarks, Richard White drew attention to a number of recent outputs from the TB MAC group. These included a catalogue of country-level TB models, a collation of

country-level modelling applications, a collection of case studies of working with decision makers, and a list of external modelling tools, all available through the TB MAC webportal. He also introduced a two-sided brochure for modellers and policy makers, and summarised a document providing Guidance for Country-level TB Modelling currently being produced by TB MAC and the World Health Organization.

Nick Menzies' BRR overview reiterated Richard White's introductory sentiment that TB MAC's position is as an entity that generates and facilitates "public good" activities, but abstains from involvement in funding decisions or prioritization of models. As such, efforts undertaken by TB MAC to provide benchmarking, reporting and review frameworks look to improve model accuracy and reproducibility, as well as support evaluation that model applications are "fit-for-purpose".

The first half of the session ended with the address from two funding representatives. Shufang Zhang reminded the group of the power of models to inform national TB targets and voiced the Global Funds support and priority for initiatives that improve model rigor. Meanwhile, Daniel Chin emphasised the need for models to be incorporated into national TB programme planning to ensure efficient resource allocation.

In the second half of the session, each of the four Benchmark areas (general epidemiology, country-specific epidemiology, country-specific economics and additional standard outputs) where presented by a member of the BRR working group (here Nick Menzies, Andrew Siroka, Anna Vassall and Ted Cohen). The presenters provided a rational and outline to the benchmarks/outputs in each area, as well as evidence from modelling technical assistance organisations as to the useability of each benchmark or benchmark-associated output. Prior feedback was used to frame discussion questions, which were then opened to the floor.

Frank Cobelens chaired the second (and afternoon) session of day 1. The second session included a presentation and discussion on the proposed process for generating model reports, by Finn McQuaid, and the review of modelling applications, by David Dowdy. A similar process of rationale and outline, and subsequent general discussion informed by previous feedback, followed.

The session was rounded off with a presentation and discussion on the evidence available for programmatic activities to impact lead by Richard White and Madeleine Clarkson. This outlined the gap between activities and evidence of their impact, as well as a proposed framework to begin to fill that gap and a case study doing so for community active case finding. This was followed by a general discussion.

The following morning's session was chaired again by Michael Kimerling. Nick Menzies provided a summary of the previous day's discussions, before those present were separated into six assigned discussion groups. Four groups discussed one area of the benchmarks each, one group discussed the proposed reporting and review templates, and a final group discussed the proposed framework linking activities to impact. Each group was tasked with proposing concrete next steps for TB MAC to take towards the activities ongoing in their area of discussion. The second half of the morning was dedicated to presenting feedback

from the groups to the wider audience. The country-level modelling benchmarking, reporting, review and data gaps sessions were ended by a wrap-up and discussion of next steps from Nick Menzies.

1.3.4 Outcomes and next steps

Responses from the group to the presentations included a universal acceptance of the need for the BRR activities, along with many useful suggestions to ensure that the approach fitted into country-level modelling applications. In particular, it was noted that the review process required additional development in order to be of most use to the funders, as well as to allow for both internal and external review. Importantly, there was a strong demand for piloting of the BRR approach, which will be taken forward through further discussions with the TB Modelling Roadmap Steering Committee. The BRR working group will undertake to edit individual documents to reflect the discussions held, which will then be used in the piloting process. Feedback from this process will be used to further refine and develop the BRR.

The discussions on the framework for data gaps linking activities to impact resulted in clarity on the problem, identification of what the TB community needs to do, and what TB's initial role could be. The discussions with the TB Modelling Roadmap Committee to fill data gaps linking activities to epi impact have started, and should conclude during the Union conference. Initial discussion have concluded that TB MAC should identify those activities that it could absorb without further funding, and those that would require additional support required, in time for the RSC meeting Oct Union conference. New activities that could be absorbed by TB MAC, may include using a list TB of intervention activities previously created by the GHCC to develop and maintain a structured database to link these to coverage increases, and to populate this with evidence collated by modellers during modelling applications. Lit review of data to populate the database is likely to need to be a separately funded activity.

1.4 Country-level modelling and economics (DAY 2)

1.4.1 Background

In addition to supporting TB MAC's initiative to promote benchmarking, transparent reporting, and the establishment of an external review process for country-level modelling, we continued both leading economic activities within TB MAC and strengthening links with other external economic initiatives relevant to TB MAC's efforts to improve the use of economic methods and information in TB modelling. Our external links prioritised initiatives aiming to close the data gaps in TB costs and cost effectiveness as highlighted by the TB Modelling Roadmap Steering Committee: 1) the Global Health Cost Consortium and efforts to improve future cost data quality and ensure accessibility to up to date cost data, 2) the WHO Global TB Programme's cost data collection efforts both from programmatic and patient perspectives, 3) the Center for the Evaluation of Value and Risk in Health (CEVR) at Tufts University compilation of information on "cost-per-DALY averted" metric to measure the efficacy of health interventions to improve decision making. Our main economic activity this year was a workshop co-convened with the International Decision Support Initiative (iDSI) to discuss methods and approaches to improve the inclusion of equity considerations in model-based economic evaluations to inform priority setting. The aim of this session was to discuss these activities and discuss future directions.

1.4.2 Aims and objectives

Objective 1: present & get feedback on tools and resources from the Global Health Cost Consortium.
Objective 2: update on data collection activities led by WHO's Global TB programme.
Objective 3: share content and promote discussion around Equity in Transmission Modelling workshop.
Objective 4: introduce and establish a link with the Global Health Cost Effectiveness Analysis (GHCEA) Registry, Gates-funded initiative led by the CERV at Tufts.

1.4.3 Summary

After an overview of the background and objectives for this afternoon session, we started with an update and discussion of GHCC's tools and resources. Anna Vassall first introduced the GHCC's reference case for estimating the costs of global health services and interventions, both the development process and the tool. The goal of this reference case is to improve the quality of cost estimates through improved consistency and transparency of methods, assumptions, and reporting. During her presentation, Anna highlighted principles and (forthcoming) tools relevant for TB modellers. The discussion during Anna's talk focused mainly on the availability of reporting checklists. Previous ones have been tested and found reasonable but are quite long and more work will be done on it and made available through the GHCC website. There is also a complete list of TB costs agreed on by the Global Fund and WHO GTP. The updated version is available upon request, a working version up on the website. GHCC is also developing series of reference case compatible costing tools - currently being piloted.

Lori Bollinger then introduced the newly-launched unit cost study repository (UCSR). This is a comprehensive and standardised database containing detailed unit cost data for all HIV and TB interventions, from both a patient and provider perspective. It was launched at the IAS in Amsterdam (July 2018) and will be updated through June 2019. The idea of this repository came out of a need for centralized TB and HIV cost data that has been quality assessed and standardised. In her presentation, Lori encouraged meeting participants to explore the tool and give feedback to GHCC on ways to improve and further develop it.

There was interest in knowing more about the database: understanding the difference between provider and patient perspectives and how these generalise across settings, and where these may overlap; how are currency and inflation variations being handled (at the moment, everything is in 2017 US dollars; eventually the currency reported in each study will be included (ex. France 1994)). This discussion highlighted the need to expand the UCSR supporting material. A second discussion point was around accessibility of the data and whether analysts can download the full dataset. Currently you can only download at the intervention level, although eventually there will be a download all for a country (this functionality now exists). If an analyst needs the whole database, it could be made accessible upon request. Another suggestion is for GHCC to send updates to analysts expressing interest in knowing about when updates to data occur. There were questions about the sustainability of this resource and the quality assessment of estimates (currently the GHCC is creating a quality index with 4 elements: biased up, biased down, precision, and reporting standards that needs to be vetted by the advisory groups)

The work of GHCC in TB is aligned with the activities of WHO Global TB Programme. The presentation by Sedona Sweeney aimed to describe the data available in UCSR from a patient perspective and get feedback on planned activities to explore the transferability of existing data from settings with studies to other settings without any data. She also presented an exploration of methods to pool subnational studies data into a nationally representative estimate to answer the question: Can we use the GHCC resources to inform patient costs estimates for those countries where there will not be a national survey led by WHO-GTP? The discussion that followed Sedona's presentation reflected on uncertainty around current data and the need better/more standardized data on cost of care and income measurement.

The second part of the session started with a presentation by Andrew Siroka updating the audience on progress made by WHO GTP's catastrophic cost surveys. He also described the kind of data that is becoming available and presented an opportunity to add more broadly on what other data could be collected by WHO from the health service perspective. Further questions about data ownership and availability: the data is owned by the countries, not by WHO, but long-term goal is to set up repository with de-identified data. Currently best approach to access patient cost data would be to get in touch with Andrew. The GTB Finance database reported yearly since 2006 by NTPs and reviewed by GTB to ensure data quality will be publicly available after this year.

For the next presentation, Gabriela Gomez reported back to the audience on a workshop held in March co convened by TB MAC and IDSI. This was a multidisciplinary discussion on

opportunities to introduce equity considerations in model based economic evaluations. The meeting report was shared with the participants. Shufang (GFATM) noted that equity is one of the founding pillars of the Global Fund's strategy and the aim is to bring equity into the modelling work supported rapidly - this is even more pressing in HIV than in TB (or malaria) and there is a need for a quick piloting of methods. The Optima group are doing equity analysis, by choosing sub-populations in TB models that are marginalized / low-income. However, breaking down sub-populations even further to truly add equity would lead to poor data and there is a need to engage in country to define what equity means and then equity indicators could be added.

Finally, David Kim introduced the Global Health CEA registry. This registry is the first comprehensive database to compile articles utilizing the "cost-per-DALY averted" metric to measure the efficacy of health interventions. The Center for the Evaluation of Value and Risk in Health (CEVR) created this systematic summary of articles, organized by article, ratios, and disability weights. The registry is available for downloading online. CEA registry has published 620 cost per DALY analyses (44 on TB). This group has also developed DALY calculation tools that may be of use to modellers, if expanded to include age categories.

1.4.4 Outcomes and next steps

Next year's activities are being planned around health systems constraints into modelling through the completion of an ongoing review. We will continue BRR work and will be interested in furthering equity work by looking at case studies. We are open to further ideas on health systems or equity work, please contact Anna and Gaby if you have ideas about this.

1.5 TB prevention (DAYS 3-4)

1.5.1 Background

The meeting took place over the third and fourth days of the overall meeting, and focused on 5 overarching questions/themes around TB prevention. Day 3 was dedicated to the first 3 overarching questions: (1) *What new insights from immunology and natural history should be investigated or incorporated into models of TB prevention?*; (2) *What are the most important modeling considerations for TB drugs and drug development in TB prevention?*; and (3) *What are the implications of global targets and epidemic trends for models of TB prevention?* Day 4 was dedicated to the remaining 2 questions: (4) *How should models consider the role of social determinants, comorbidities, nutrition, and the environment in prevention of TB?*; and (5) *Implementing TB prevention: what aspects of implementation should models improve upon?*

1.5.2 Aims and objectives

Objective 1: To update stakeholders on methods and evidence to address five "big" questions in modeling of TB prevention.
Objective 2: To identify tangible next steps (manuscripts, training programs, communications, etc.) that can lead to better models of TB prevention in the future.
Objective 3: To increase networking and sharing of knowledge between modelers, epidemiologists and other stakeholders in TB prevention.
Objective 4: To promote the opportunity to access $100k funding (shared across TB prevention, diagnostics and vaccines).

1.5.3 Summary

Day 3 Summary
Session 1
This session was centered around the question: "What new insights from immunology and natural history should be investigated or incorporated into models of TB prevention?"
The session started with a presentation from Louis Joslyn. He presented recent and ongoing work at Kirshner lab at University of Michigan on pairing data and insights from *in vivo* models to build computational models of TB granulomas, and how this approach can inform future experimental and clinical work. In his talk focused on the role of sub-clinical TB, Paul Drain (University of Washington) highlighted priority questions for research/modeling (such as understanding the transmissibility of TB during the subclinical stage) and diagnosis of subclinical TB (such as point-of-care screening and diagnostic tests for incipient and subclinical TB). Hanif Esmail from Oxford University was tasked with presenting the role of the infectious host. Drawing on historical data on the kinetics of disease progression, he emphasized the importance of investing in detecting early disease (given that many people who present late for diagnosis/treatment of TB may be infectious earlier in the disease course). The session concluded with a presentation by Florian Marx from the Desmond Tutu TB Center: he argued that individuals previously treated with TB can be an important target

population for TB control in high burden settings, given that they continue to be at higher risk of TB (via reinfection) even after successfully completing treatment.

Session 2

This session aimed to delve into the question: “What are the most important modeling considerations for TB drugs and drug development in TB prevention?” The first presenter in this session was Robert Horsburgh from Boston University School of Public Health. Drawing on several recent epidemiological studies, he emphasized the role of preventive therapy, particularly among HIV-positive individuals. Emily Kendall of Johns Hopkins University used mathematical models to argue that estimating the population-level impact of TB drugs could help set priorities for drug development, including the development of preventive therapy. Amber Kunkel from Institut Pasteur highlighted the need for local data to account for existing resistance and the probability of future events when considering the emergence of drug resistance in development of novel drug regimens. The session concluded with a presentation from Gabriela Gomez of the London School of Hygiene and Tropical Medicine. She emphasized the importance of carefully and transparently constructing baseline comparators when making economic considerations for novel regimens of TB.

Session 3

Presentations and discussion in this session focused around the question: “What are the implications of global targets and epidemic trends for models of TB prevention?” Marieke van der Werf from the European Center for Disease Prevention and Control started the session. She argued that better understanding the cascade of TB prevention (including identifying risk populations and assessment of quality and coverage of implementation) was critical for TB prevention in the European Union and other regions targeting pre-elimination. Joaquin Sanz at University of Chicago presented on the importance of incorporating realistic demographic dynamics in models of TB projections and evaluating the impact of TB interventions. Anete Trajman from Federal University of Rio de Janerio spoke about the role of treatment for LTBI in changing global landscape and highlighted the challenges faced in settings like Brazil, including the very low levels of enrollment for LTBI treatment. Hassan Haghparast Bidgoli from the UCL Center for Global Health Economics discussed the importance of including patient costs in economic evaluation of TB prevention programs, in the context of broader socio-economic and epidemiological goals.

Day 3 concluded with a keynote presentation by Dick Menzies of McGill University that focused on key issues to consider for modeling latent TB. The presentation delved into various aspects of LTBI treatment, including the challenges associated with diagnosis of LTBI, safety and efficacy of new regimens, ability to enroll and retain individuals during treatment regimens, and risks of reinfection and resurgence.

Day 4 Summary

Session 4

Session 4 aimed to advance discussion around the question: “How should models consider the role of social determinants, comorbidities, nutrition, and the environment in prevention of TB?” The first speaker in this session was Rein Houben from the London School of Hygiene and Tropical Medicine, who presented on the modeling of socio-economic drivers and

consequences for TB. He argued for more modeling work in this area, along with data strengthening and consideration of broader socioeconomic outcomes (such as catastrophic costs) when evaluating TB prevention efforts. Olivia Oxlade from McGill University, while speaking about TB in the context of changing social determinants, argued that accounting for "general health" of the population may be important, as this may capture important social determinants that contribute to TB epidemiology and have implications for TB control efforts. Stephane Verguet of the Harvard School of Public Health presented the framework of extended cost-effectiveness analysis to assess equity and poverty reduction benefits of TB control, including highlighting key data gaps (e.g. out-of-pocket spending for TB patients). Tom Wingfield of the University of Liverpool presented on the implications for models when considering catastrophic costs at the patient level: he emphasized the need for considering wider implications on health and wellbeing (and the data, methods and collaborations that support these considerations).

Session 5
The final session focused on the question: "Implementing TB prevention: what aspects of implementation should models improve upon?" Sandip Mandal of the Public Health Foundation of India started the session with a presentation on modeling TB interventions in high burden settings, showing that uncertainties regarding latency and the effectiveness of preventive therapy can lead to large variations in model projections of TB interventions in countries constituting WHO's SEARO region. Hamidah Hussain from Interactive Research and Development described the challenges of implementing TB prevention in South Asian megacities (Karachi and Dhaka) and questions that local NTP officials face including how to identify priority populations for preventative therapy and how to balance the cost of therapy against the risk of disease. The final speaker in the session was Chongguang Yang of Yale University. He presented recent and ongoing work characterizing the role of internal migration on transmission of TB in China, emphasizing the importance of considering this demographic group for TB control in urban areas.

1.5.4 Outcomes and next steps

At the end of Day 3, participants were asked to discuss within small groups and suggest questions or topics they would like to advance toward a tangible research product. These suggestions were collated and synthesized by the coordinators overnight, and via open vote on Day 4, finalized into three broad topics. Participants were asked to self assort into these three groups based on their preferences, and each topic was discussed within the self-selected groups. The groups were also asked to discuss what tangible output they envisioned would come out of this discussion, and to identify a contact person. The three topics were as follows: (1) Reframing the paradigm of TB (including discussions around what constitutes a case of active TB and the contribution of individuals with subclinical TB disease to transmission, including implications for models); (2) Modeling LTBI treatment (including comparing different strategies of prioritizing screening, and role of new tests); and (3) Projecting the emergence of drug resistance with various LTBI regimens (focused on HIV+ and household contacts).
Finally, the Request for Applications (RFA) closing date is October 31, 2018. We encouraged participants to take the ideas from this meeting and craft them into proposals for the RFA.

In summary, the TB Modeling Research Group meeting met all of its objectives. A broad variety of stakeholders were updated on the latest evidence and methods to address five “big questions” in the realm of TB prevention; three tangible products were identified for advancing models of TB prevention (with specific groups taking each product forward); networking and sharing of information between modelers, epidemiologists, and other stakeholders was promoted; and participants were given the opportunity to develop specific proposals for the RFA. This meeting not only succeeded in bringing together a diverse group of individuals - including experienced TB modelers, policymakers and other stakeholders, and people with expertise in related fields (e.g., health systems) - but we also have a clear path forward from this meeting, in terms of how to realistically improve models of TB prevention in the year to come.

1.6 TB Vaccines (DAY 5)

1.6.1 Background

Quantitative modelling is a useful tool for decision makers. There has not been much focus on the use of quantitative modelling for the development of TB vaccines. A literature review in 2016 found only 23 papers had used quantitative modelling to explore the impact of potential new TB vaccines (Harris et al 2016), and 5 publications have appeared since (Liu et al 2017, Arregui et al 2017, Shrestha et al 2016, Shrestha et al 2017 and Fu et al 2018). Even fewer within host/immunological vaccine modeling papers have been published.

In 2017, the Bill and Melinda Gates Foundation kindly allocated funding in the TB MAC grant to support a meeting to bring together vaccine modellers, immunologists, epidemiologists, decision makers and others to identify ways to maximise the utility of quant modelling to support TB vaccine candidate development and implementation.

1.6.2 Aims and objectives

Aim: Identify ways to maximise the utility of quant modelling to support TB vaccine candidate development and implementation

Objective 1: Update vaccine modellers/ immunologists/ epidemiologists/ etc on new preclinical/ clinical/ modelling results + upcoming data
Objective 2: Create framework for the use of quantitative modelling to accelerate TB vaccine development
Objective 3: Summarise key problems/actions to improve utility of quantitative TB modelling for a) Vaccine dose/regimen selection, b) TB vaccine Target Product Profiles (TPPs)/ Preferred Product Characteristics (PPCs) and implementation
Objective 4: Increase networking amongst and sharing of knowledge between vaccine modellers/ immunologists/ epidemiologists/ etc)
Objective 5: Make available $100k funding opportunity call (shared across TB prevention, diagnostic, & vaccines)

1.6.3 Summary

The purpose of session 1 was to discuss a framework for the use of quantitative modelling to accelerate TB vaccine development, chaired by Richard White. Session 1 started with an overview of TB MAC from Richard White followed by the rationale for this meeting. He highlighted that the aim of the meeting was to maximise the utility of quantitative modelling to support TB vaccine candidate development and implementation. Willem Hanekom gave a plenary talk with updates of the latest TB vaccine data, including the encouraging Bacillus Calmette–Guérin (BCG) revaccination efficacy result, details on intravenously administered BCG and an overview of the development of safer and more efficacious whole-cell vaccines

(of which there are two in phase 2a, one in phase 2b and three in phase 3). He briefly touched on Cytomegalovirus-based vaccines, where the prevention of disease data has shown promise in Nonhuman Primates (NHPs). This presentation preceded publication of the M72 results.

The second part of session 1 included a discussion between consumers and producers of modelling evidence in vaccine development. Identifying a correlate, or correlates, of protection (CoP) was a critical aim identified by participants now we have protection information from the Phase IIb trials, although it was highlighted that we don't know if a CoP might be specific to a particular candidate or group of candidates. It was suggested that math modelling may be able to help cross-translate known CoPs between candidates. Population differences were also a key topic of discussion and many highlighted the need for modelling to investigate differences in efficacy between subpopulations, such as latently infected and HIV infected, and the impact this would have on cost of implementation. However, it was questioned whether population vaccine targeting would be used in practice. As a last remark to the discussion, Tom Evans suggested that it would be very useful for modellers need to tell clinical scientists what data is needed to parameterise and improve models.

Session 1 concluded with group work, where each group was asked to draft ideas for how modelling could accelerate vaccine development at different stages in the pathway. Specifically, what questions needed modelling evidence? What quantitative methods could be used to address them? And what modelling groups were using these methods already? Ideas that were identified included validating dose-response and animal models with new efficacy data; modelling to help design new experimental and Ph1 dose-finding studies; exploring the interaction between antigen and delivery system; translating methods from other vaccines to inform trial design; modelling to assess impact of population heterogeneity and simulated trial design to potentially shorten trial duration.

The aim of session 2 was to discuss issues in using quantitative models for TB vaccine dose/regimen selection and focus on how to move forward. It was chaired by Willem Hanekom. As a consumer of modelling evidence for TB vaccine dose/regimen selection, Tom Evans gave a talk on the need for modelling for vaccine dose finding. He started by drawing the comparison between vaccine and drug development. Modelling is commonly used to define optimal drug dose, but these methods have not been used in vaccine development until recently. He stated that we usually don't check if vaccine dose is "right" so we aren't aware if there are problems with our dose choice, but there is now emerging evidence dose selection has been suboptimal. As a solution, he suggested pharmacokinetic/ pharmacodynamic (PK/PD) -style modelling taking results from animals to generate a model, use allometric scaling to choose doses in man, and doing adaptive studies in which doses are chosen during the ongoing study. Finally, he highlighted plans to apply these methods to adenovirus and TB vaccine data.

Three producers of modelling evidence for vaccine dose/regimen were then presented. First was Rada Savic, a PK/PD modeller who argued that similar problems, and solutions, exist in both drug and vaccine development and it is possible to translate the quantitative methods

from drugs to vaccines. She highlighted the main quantitative methods used for drugs development, that have accelerated drug candidates. She suggested that data sharing, standardisation, and collation will be key in integrating modelling into vaccine development.

Louis Joslyn spoke about the successful development of a pre-infection vaccination framework using a systems biology approach that integrated NHP and human data. Using the framework, he was able to show that prior BCG vaccination similarly impacts NHPs and humans response to Hybrid-56 (a subunit vaccine currently in development by Statens Serum Institut, Denmark). He highlighted that the timing of BCG vaccination must be considered further to support this result, however he acknowledged that there were difficulties matching historical BCG vaccination in adults, to macaques in a laboratory. His modelling analysis predicted that the 3rd H56 vaccination dose in humans was not associated with positive changes in memory cells across time, and could have been omitted; a prediction that has recently been validated in an empirical clinical dose-ranging trial.

Finally, Sophie Rhodes gave a talk on her work on the use of a mechanistic model to optimise TB vaccine dose selection. She outlined how by giving mice multiple doses of H56 TB vaccine and making an assumption on the allometric scaling factor between mouse and human, her modelling predicted that a lower dose than had used in the H56 clinical trials, would have been as immunogenic. This result was also recently been validated in an empirical clinical dose-ranging trial. The importance of the assumption on the allometric scaling factor was highlighted, and it was agreed that more work should be conducted to establish how vaccine dose scales across species and how the type of vaccine (live, subunit, etc.) affects the allometric factor.

Session 2 concluded with group work, where each group was asked a series of questions relating to moving forward with modelling to improve vaccine dose decision making. Specifically, participants we asked to identify blocks to the integration of quantitative modelling to vaccine development and actions to remove these blocks. There was strong support amongst the groups that improved understand of the basic science, correlates of protection, and link between animal models and humans responses would allow modellers to calibrate predictive models, and calculating return on investment from previous dose errors. The groups also agreed that model-based experiment and early phase 1 clinical trial designs could also allow us to generate more informative dose-response and regimen data. Finally, cross-disease modelling and pooling data were proposed by two groups to rapidly improve dose prediction.

The third session was chaired by Jeff Barrett and started with presentations by Willem Hanekom, Johan Vekemans and Derek Tate. Johan Vekemans presented the perspective of the WHO Initiative for Vaccine Research regarding tuberculosis. This highlighted key areas for consideration in population level TB vaccine models. These included identifying a clear use case for proposed vaccines, with models incorporating epidemiologic heterogeneity, drug resistance, HIV and consideration for targeting. Johan also reiterated the need to present a Full Value Proposition to decision makers, which includes wider socioeconomic considerations at earlier stages in the development process. Derek Tate described key gaps

which must be addressed when developing implementation strategy, including identifying acceptable dosing regimes and adapting TPPs to differing geographic contexts.

Next, Rebecca Harris, Joaquin Sanz and Sourya Shrestha presented work on modelling to inform vaccine TPPs, natural history parameterisation and implementation strategy respectively. Rebecca Harris highlighted the role of modelling to investigate vaccine efficacy, duration of protection and host status required for vaccine efficacy by varying epidemiologic contexts, and the contribution of this work towards TPP development. Joaquin Sanz presented work to underscore the complexities of distinguishing the specific *effect* of vaccination (e.g. preventing transmission, vs delaying disease) and a modelling framework to aid in isolating these effects among trial data. Lastly, Sourya Shrestha presented work to highlight the incorporation of geospatial heterogeneity into vaccine impact modelling, with a discussion focusing on selecting risk groups.

Session 3 concluded with group work, where each group was asked a series of question surrounding the use of quantitative models in informing vaccine characteristics in target product profiles, identifying target populations and developing implementation strategy. Groups were asked to identify impediments to using quantitative models and actions to overcome these blocks. Multiple groups commented on the need for improve quantity and quality of epidemiologic and health systems data to facilitate modelling, emphasizing the need to understand heterogeneity in said data and compatibility between data sources. The need for uniform set of definitions for infection and disease, with standardised language and assays was also discussed. Finally, groups highlighted issues in generalising small scale modelling studies to the national level and the impact of enriching for high risk groups in estimates of general population vaccine efficacy. Groups also suggested that revisiting BCG trial data to better evidence critical model assumptions, modelling to help guide new Ph3 trial designs and vaccine implementation planning, modelling the impact of BCG revaccination or the use of multiple vaccines, modelling age and risk groups, and prevention of recurrence

1.6.4 Outcomes and next steps

All stated outcomes were met. Attendees were updated on recent results and there was time to network and share knowledge. About 10 more individuals, primarily from South Africa, the UK or Belgium, joined online. Information was collated on the framework for the use of quantitative modelling to accelerate TB vaccine development, and problems/actions to improve the utility of quantitative TB modelling for a) vaccine dose/regimen selection, and b) TB vaccine TPPs/PPCs and implementation, were identified. A Request for Funding Applications is open for individuals to submit vaccine-related funding applications.

A draft list of next steps has been drawn up. These include communication activities to prepare a paper based on information gathered during the meeting, and a list of key research questions to address, including validating dose-response and animal models with new efficacy data, modelling to help design new experimental and Ph1 dose-finding studies, revisiting BCG trial data to better evidence critical model assumptions, calculating return on investment from previous dose errors, modelling to help guide new Ph3 trial designs and vaccine implementation planning, modelling the impact of BCG revaccination or the use of multiple vaccines, and modelling age and risk groups, and prevention of recurrence.

1.7 TB diagnostics (DAY 5)

1.7.1 Background

The meeting took place over a day and focused on 4 overarching themes around TB diagnostics, including a TB survivor perspective and a keynote presentation. The 4 overarching themes were as follows: (1) Modeling Diagnosis of Latent/Incipient/Subclinical TB; (2) Modeling Diagnosis of Adult Pulmonary TB (including “triage” testing); and (3) Advancing the Modeling of Diagnostic Testing in Key Populations: Children and People Living with HIV; and (4) Modeling the Diagnosis of TB Drug Resistance

1.7.2 Aims and objectives

Objective 1: To update stakeholders on methods and evidence related to incorporation of diagnostic tests into models of TB prevention.
Objective 2: To increase networking and sharing of knowledge between modelers, epidemiologists and other stakeholders in the field of TB diagnostics for prevention.
Objective 3: To publicize and facilitate responses to a $100k funding opportunity (shared across TB prevention, diagnostics and vaccines).

1.7.3 Summary

Day 5 Summary

The meeting started with a brief introduction by Sourya Shrestha, followed by a TB survivor perspective by Tisile Phumeza from Cape Town, South Africa. She shared her experience of having to endure and fight through a bout of drug resistant TB disease. Madhukar Pai from McGill University was the keynote speaker. In his talk titled “Global Health Tech: Still searching for silver bullets & killer apps?”, Dr. Pai argued for the need to be more circumspect about unreasonably raising expectations of the impact of novel interventions, and also of using meaningful outcomes (and closely related surrogate endpoints) to assess the impact of these interventions.

Session 1

This session was coordinated to facilitate discussions around modeling diagnosis of latent, incipient and subclinical TB. The first speaker in the session was Shuyi Ma from the Center for Infectious Disease Research. In her presentation, she highlighted the profound heterogeneity across individual human hosts with respect to susceptibility to infection, disease progression, and reinfection; differences across bacterial populations were also discussed. Saskia Ricks from Imperial College presented ongoing modeling work that explores the epidemiological impact and cost considerations of novel tests to detect incipient TB: her work showed substantial potential impact of such tests and also suggested that the cost of testing could be an important cost-driving component of any treatment regimen for incipient TB. Eleanor Click from the Centers for Disease Control and Prevention, through her work in Kenya, highlighted the challenges of diagnosing TB in children and explored the role of using minimally invasive specimens in potentially closing this diagnostic gap. Ricardo Steffen from Universidade do Estado do Rio de Janerio presented on the topic of economic

considerations for models of diagnostic testing for latent, incipient, and subclinical TB, paying particular attention to sources of variability in such models.

Session 2

The discussions in this session were focused around modeling diagnosis of adult pulmonary TB. The first speaker in this session was Liesl Page-Shipp from IRD Global, and she presented on challenges in implementing TB diagnostic testing in high burden settings. Apart from highlighting challenges driven by the subjectivity of certain diagnostic tests (for example, chest X-rays), she also emphasized the roles of modeling in tailoring TB intervention programs and in advocating for the importance of such interventions. Alice Zwerling of the University of Ottawa discussed the economic implications of implementing novel diagnostic testing in vulnerable populations. Based on her work in vulnerable populations in Cambodia and the Canadian Arctic, she emphasized the need to consider social justice and equity issues along with monetary cost. Christina Yoon of the University of California, San Francisco presented key epidemiologic and economic considerations when evaluating C-reactive protein (CRP) as an example of a potential TB 'triage' test, and argued that point-of-care CRP could improve efficiency and reduce the cost of intensive case-finding. Hojoon Sohn from the Johns Hopkins Bloomberg School of Public Health presented on the topic of modeling patient care-seeking behavior, highlighting that care-seeking behavior can have important implications for the cost-effectiveness of rapid diagnostics in settings like India, where many patients seek healthcare from private and informal health providers.

Session 3

The theme of this session was advancing the modeling of diagnostic testing in key populations, specifically children and people living with HIV. Leonardo Martinez of Stanford University presented on modeling pediatric tuberculosis. His presentation highlighted how data and insights from existing studies can be utilized to support modeling of pediatric TB, and where critical knowledge gaps exist. Courtney Yuen of Harvard Medical School, speaking on what role modeling can play in advancing pediatric TB interventions, emphasized the synergistic relationship between modeling and implementation science: implementers can provide data (and help assess their reliability and generalizability) for models, and modeling work can inform programmatic and implementation choices. Patrick Cudahy from the Yale School of Medicine presented on modeling the diagnosis of HIV-associated TB, and pointed out that the best use of TB diagnostic tools in this population may vary across a range of immunosuppression levels; he also discussed the importance of deploying resources to those at the highest risk of failing treatment. Chris Whalen of the University of Georgia, speaking about diagnosis of TB in endemic settings, argued for the importance of meaningfully incorporating local/spatial information into models and highlighted the need to better understand the factors that contribute to the infectious period – including interventions that might effectively shorten that infectious period.

Session 4

Presentations in this session were focused on modeling the diagnosis of TB drug resistance. Philippe Glaziou of the World Health Organization, joining virtually from Geneva, presented on the global burden of drug-resistant TB. Dr. Glaziou not only presented new estimates for

drug resistance across the globe, but also pointed out the importance of better understanding the dynamics of rifampicin resistant TB (e.g., primary vs. acquired, drivers of future projections). Grant Theron of Stellenbosch University presented on whether better diagnosis of TB drug resistance translates into better clinical outcomes, emphasizing the importance of evaluating the role of diagnostic tests in the context of the broader health system. Emily Kendall from the Johns Hopkins University presented on modeling the epidemiological impact and cost-effectiveness of improved diagnostic testing for drug-resistant TB. She argued that modeling diagnosis of TB drug resistance can address several important questions, including how to value the importance of DST for novel drugs, and when and how to expand DST based on the setting and the population.

1.7.4 Outcomes and next steps

This meeting ultimately succeeded in meeting its stated goals. First, stakeholders (including modelers, decision-makers, discovery scientists, diagnostic test developers, and epidemiologists) left the meeting with a better understanding of the current best methods and evidence related to incorporating diagnostic testing (for incipient/subclinical TB, of active pulmonary TB, among key populations, and drug susceptibility testing) into models of TB prevention. Second, this meeting provided a unique forum (small, diverse group of discussants) for rich discussions and networking among individuals in these different fields. Third, participants were encouraged to take the ideas from this meeting and craft them into proposals for the RFA, taking advantage of new links of communication and collaboration forged within the meeting. Next steps will include specific proposals to the RFA (closing date: October 31, 2018), as well as additional grant proposals for transdisciplinary work linking models with unique sources of laboratory, epidemiological, and policy-level data; these proposals are already being discussed among specific invitees.

APPENDICES

2.1 Participant List
2.2 Meeting Agenda

Appendix 2.1 Participant List (face to face)

Name	Organisation
Alice Anne Zwerling	University of Ottawa
Amber Kunkel	Institut Pasteur (Paris)
Andrew Siroka	World Health Organisation
Anete Trajman	Federal University of Rio de Janeiro
Anna Vassall	London School of Hygiene & Tropical Medicine
Bob Horsburgh	Boston University
Brad Wagner	Institute for Disease Modeling
Brittany Hagedorn	Institute for Disease Modeling
Carel Pretorius	Avenir Health
Chanchala Kaddi	Bill & Melinda Gates Medical Research Institute
Chathika Weerasuriya	London School of Hygiene & Tropical Medicine
Chongguang Yang	Yale School of Public Health
Christina Yoon	University of California, San Francisco
Christopher Whalen	University of Georgia
Courtney Yuen	Harvard Medical School
Daniel Chin	Bill & Melinda Gates Foundation
David Collier	White Ox Ltd.
David Dowdy	Johns Hopkins Bloomberg School of Public Health
David Kim	Tufts Medical Center
Dereck Tait	Aeras
Dick Menzies	McGill University
Eleanor Click	Centers for Disease Control and Prevention

Emily Kendall	Johns Hopkins University
Ewan Tomeny	Liverpool School of Tropical Medicine
Finn McQuaid	London School of Hygiene & Tropical Medicine
Florian Marx	Stellenbosch University South Africa
Frank Cobelens	Amsterdam Institute for Global Health and Development
Gaby Gomez	London School of Hygiene & Tropical Medicine
Grant Theron	Stellenbosch University
Hamidah Hussain	IRD Global
Hanif Esmail	Nuffield Division of Clinical Laboratory Sciences, University of Oxford
Hannah Priyadarshini Gideon	University of Pittsburgh School of Medicine
Hassan Haghparast-Bidgoli	University College London
Hojoon Sohn	Johns Hopkins University
Jacob Creswell	Stop TB Partnership
Jeff Barrett	Bill & Melinda Gates Medical Research Institute
Jennifer Flood	California Department of Public Health
Joanna Emerson	Center for the Evaluation of Value and Risk in Health, Tufts Medical Center
Joaquin Sanz Remon	University of Chicago
Johan Vekemans	World Health Organisation
Jolene Skordis	UCL Institute for Global Health
Karen Elkins	Center for Biologics Evaluation and Research - FDA
Karim Azer	Bill & Melinda Gates Medical Research Institute
Katherine Floyd	World Health Organisation
Leander Grode	Vakzine Project Management
Leonardo Martinez	Stanford University, School of Medicine
Liesl Page-shipp	IRD Global
Lori Bollinger	Avenir Health
Louis Joslyn	University of Michigan

Madeleine Clarkson	London School of Hygiene & Tropical Medicine
Madhu Pai	McGill University
Marcel Behr	University of Montreal
Marieke van der Werf	European Centre for Disease Prevention and Control
Meghan Bellerose	Harvard T.H. Chan School of Public Health
Michael Kimerling	KNCV Tuberculosis Foundation
Nick Menzies	Harvard T.H. Chan School of Public Health
Olivia Oxlade	McGill University
Patrick Cudahy	Yale School of Medicine
Paul Drain	University of Washington
Philippe Glaziou	World Health Organisation
Phumeza Tisile	TB Proof, University of Cape Town
Rada Savic	University of California, San Francisco
Rebecca Harris	London School of Hygiene & Tropical Medicine
Rein Houben	London School of Hygiene & Tropical Medicine
Ricardo Steffen	Universidade do Estado do Rio de Janeiro (UERJ)
Richard White	London School of Hygiene & Tropical Medicine
Robin Mogg	Bill & Melinda Gates Medical Research Institute
Romain Ragonnet	University of Melbourne
Sandip Mandal	Public Health Foundation of India
Saskia Ricks	Imperial College London
Sedona Sweeney	London School of Hygiene & Tropical Medicine
Shufang Zhang	The Global Fund
Shuyi Ma	Center for Infectious Disease Research
Sophie Rhodes	London School of Hygiene & Tropical Medicine
Sourya Shrestha	Johns Hopkins University
Stephane Verguet	Harvard T.H. Chan School of Public Health
Ted Cohen	Yale University

Tina Sachs	London School of Hygiene & Tropical Medicine
Tom Evans	Vaccitech
Tom Wingfield	University of Liverpool
Willem Hanekom	Bill and Melinda Gates Foundation
Zhaoling Meng	Bill & Melinda Gates Medical Research Institute

Remote attendees

Alison Grant	London School of Hygiene and Tropical Medicine
Anna Bershteyn	Institute for Disease Modeling
Chanchala Kaddi	Bill and Melinda Gates Foundation
Christy Hansen	Bill and Melinda Gates Foundation
Elisa Nemes	University of Cape Town
Esse Ifebi Herve Akpo	GlaxoSmithKline
Helen McShane	University of Oxford
Hongbin Guo	University of Ottawa
Jennifer Flood	California Department of Public Health
Joshua Havumaki	University of Michigan
Marie-Ange Demoitie	GlaxoSmithKline
Nadia Ouaked	GlaxoSmithKline
Nobu Nishikiori	World Health Organisation
Philippe Glaziou	World Health Organisation
Raj Bandaru	Bill and Melinda Gates Foundation
Sourabhi Pandey	
Tom Scriba	University of Cape Town
Thomas Yates	University College London
Youngji Jo	

Appendix 2.2 Meeting Agenda

TB MAC/WHO Annual Meeting
10 - 14th September
World Bank offices, Washington DC

Agenda
COUNTRY-LEVEL MODELLING SESSION
Monday, 10th September

BENCHMARKING, REPORTING & REVIEW, EVIDENCE GAPS			
Time	**Content as**	**Speaker**	**Chair**
0830-0900	**Registration**		
0900-0920	**Welcome, context & overall meeting objectives** ***TB MAC and the TB Modelling Roadmap***	**Richard White** **Daniel Chin**	**Michael Kimmerling**
0920-0950	**Overview of planned BRR activities** ***Motivation, efforts to date, session objectives***	**Nick Menzies**	
0950-1010	**The stakeholder's perspective** ***Need for these activities, wider context***	**Daniel Chin** **Shufang Zhang**	
1010-1030	**Tea break**		
1030-1110	**Presentation of proposed modelling benchmarks and discussion** ***General benchmarks (not country-specific)***	**Nick Menzies**	
1110-1150	***Country-specific epidemiological benchmarks***	**Andrew Siroka**	
1150-1230	***Country-specific economic benchmarks***	**Anna Vassall**	
1230-1300	***Additional standard outputs***	**Ted Cohen**	
1300-1400	**Lunch break**		

1400-1440	**Presentation of proposed reporting approach and discussion**	**Finn McQuaid**	**Frank Cobelens**
1440-1500	**Presentation of proposed approach for external review and discussion**	**David Dowdy**	
1500-1525	**Tea break**		
1525-1615	**Activity->Impact evidence gaps for country level resource allocation**	**Richard White**	
1615-1645	**Discussion**	**All**	
1645-1700	**Wrap up of the day, assignments for group work**	**Nick Menzies Richard White**	

Agenda
COUNTRY-LEVEL MODELLING SESSION
Tuesday, 11th September

BENCHMARKING, REPORTING & REVIEW, EVIDENCE GAPS			
Time	**Content as**	**Speaker**	**Chair**
0900-0920	**Summary of the previous day, group work assignments and objectives**	**Nick Menzies**	**Michael Kimmerling**
0920-1045	**Small group work to suggest revisions** **B1 - General benchmarks** **B2 - Country-specific epi benchmarks** **B3 - Country-specific econ benchmarks** **B4 - Additional standard outputs** **RR - Reporting/Review** **EG - Act>Imp evidence gaps**	**Nick Menzies** **Andrew Siroka** **Anna Vassall** **Ted Cohen** **Finn McQuaid** **Richard White**	
1045-1115	**Tea break**		
1115-1245	**Feedback and discussion (15 min/group)** **B1 - General benchmarks** **B2 - Country-specific epi benchmarks** **B3 - Country-specific econ benchmarks** **B4 - Additional standard outputs** **RR - Reporting/Review** **EG - Act>Imp evidence gaps**	**Nick Menzies** **Andrew Siroka** **Anna Vassall** **Ted Cohen** **Finn McQuaid** **Richard White**	
1245-1300	**Wrap up from morning & next steps**	**Nick Menzies** **Finn McQuaid**	
1300-1400	**Lunch break**		
ECONOMICS IN TB MAC: ACTIVITIES AND EXTERNAL LINKS			
1400-1410	**Session overview and objectives**	**Gabriela Gomez**	**Gabriela Gomez**
1410-1430	**GHCC: Reference case and reporting tools**	**Anna Vassall**	
1430-1500	**GHCC: Update on Unit Cost Study Repository**	**Lori Bollinger**	

1500-1530	**GHCC: Patient-incurred costs and catastrophic expenditures**	**Sedona Sweeney**	
1530-1600	**Tea break**		
1600-1620	**WHO: Update catastrophic costs surveys**	**Andrew Siroka**	**Anna Vassall**
1620-1640	**TB MAC/IDSI: Feedback from Equity workshop**	**Gabriela Gomez**	
1640-1700	**Global Health CEA registry and DALYs**	**David Kim**	
1700-1715	**Discussion and activities for next year**	**Anna Vassall**	
1715-1730	**Wrap up of the TB MAC / WHO Task Force meeting**	**Richard White**	

Agenda
TB PREVENTION SESSION
Wednesday, 12th September

KEY CONSIDERATIONS FOR MODELLING OF TB PREVENTION		
Time	**Content as**	**Speaker**
0830-0900	Introductions and scope/goals of the meeting	David Dowdy
Session 1: What new insights from immunology and natural history should be investigated or incorporated into models of TB prevention?		
0900–1000	Immunology of TB: insights from in vivo models and implications for prevention	Louis Joslyn
	Role of subclinical TB - can we model prevention of TB in the subclinical stages?	Paul Drain
	Thinking of TB from the perspective of the infectious host	Hanif Esmail
	TB prevention among individual previously treated with TB	Florian Marx
1000-1030	Questions & Discussion	All
1030-1045	Tea break	
Session 2: What are the most important modelling considerations for TB drugs and drug development in TB prevention		
1045-1145	Shorter and novel regimens for TB prevention: what are the most important epidemiological considerations?	Robert Horsburgh
	Considering population level impact in prioritising profile of novel TB drugs	Emily Kendall
	Considering emergence of drug resistance in development of novel drug regimens	Amber Kunkel
	Costs and economic considerations for novel regimens of TB prevention	Gabriela Gomez
1145-1215	Questions & Discussion	All
1215-1315	Lunch break	

Session 3: What are the implications of global targets and epidemic trends for models of TB prevention?		
1315-1415	The role of TB prevention in countries and regions targeting pre-elimination	Marieke van der Werf
	Modeling TB epidemics in the face of evolving global demography	Joaquin Sanz Remon
	What is the role of treatment for LTBI in the changing global landscape?	Anete Trajman
	Patient costs in models of TB prevention: an increasingly important consideration?	Hassan Haghparast-Bidgoli
1415-1515	Questions & Discussion	All
1515-1530	Tea break	
1530-1615	Keynote and group discussion	Dick Menzies
1615-1650	Group discussion	All
1650-1700	Wrap up & Summary	David Dowdy

Agenda
TB PREVENTION SESSION
Thursday, 13th September

Time	Content as	Speaker
0830-0845	Recap of previous day	David Dowdy
0845-0900	Introduction to the day	Sourya Shrestha
Session 4:How should models consider the role of social determinants, comorbidities, nutrition and the environment in prevention of TB?		
0900-1000	Outside the biomedical -- modelling the socio-economic drivers and consequences of TB	Rein Houben
	TB in the context of changing social determinants	Olivia Oxlade
	Is it worth it? Economic and ethical considerations of targeting social-level factors to prevent TB	Stephane Verguet
	Catastrophic costs at the patient level and implications for models	Tom Wingfield
1000-1030	Questions & Discussion	All
1030-1045	Tea break	
Session 5: Implementing TB prevention:what aspects of implementation should models approve upon?		
1045-1145	Modeling TB interventions in high burden settings: what are the gaps in evidence?	Sandip Mandal
	Challenges associated with implementation of TB prevention at large megacities	Hamidah Hussain
	Internal migration and Transmission of Tuberculosis in China: Socio-demographic factors in TB prevention	Chongguang Yang
	TB interventions in high burden settings: what role can models play?	
1145-1215	Questions & Discussion	All

1215-1315	**Lunch break**	
1315-1415	**Small group discussions**	**Break into three small groups**
1415-1430	**5 minute summary**	**Group representatives**
1430-1515	**Group discussion (specific to today)**	**All**
1515-1600	**Next steps & closing: Group discussion about next steps and areas for further methods development**	**All**

Agenda
VACCINES SESSION
Friday, 14th September

Overarching theme

- Maximising the utility of quant modelling to support TB vaccine candidate development and implementation

Goals

- Update vaccine modellers/ immunologists/ epidemiologists/ etc on new preclinical/ clinical/ modelling results + upcoming data
- Framework for the use of quantitative modelling to accelerate TB vaccine development
    - Potential manuscript submission on Framework
- Summary of key problems/actions to improve utility of quantitative TB modelling for
    - Vaccine dose/regimen selection
    - TB vaccine TPPs/PPCs and implementation
- Increased networking amongst and sharing of knowledge between vaccine modellers/ immunologists/ epidemiologists/ etc)
- $100k funding opportunity call (shared across TB prevention, diagnostic, & vaccines)

TB VACCINE QUANTITATIVE MODELLING MEETING			
Time		**Speaker**	**Chair**
0800-0830	**Registration**		**Richard White**
0830-0840	**Welcome and aims for the day**	**Richard White**	
0840-0910	**Plenary - Update on new discovery, preclinical, clinical, modelling TB vaccine results + expected upcoming data**	**Willem Hanekom**	
Session 1: Framework for the use of quantitative modelling to accelerate TB vaccine development			
0910-0925	**Consumers #1: Development need statement - how would we like to use quant modelling to accelerate vaccine development, and draft framework**	**Jeff Barrett**	
0925-1010	• **Consumers #2+: Input from other stakeholders (1 min each)**	**Decision makers** **Modellers**	

	• Producers: Input from producers of modelling evidence (1 min each) • General discussion	All	
1010-1030	Tea break		
1030-1115	Group work - Flesh out Framework	Jeff Barrett Sophie Rhodes Rebecca Harris Louis Joslyn Tom Evans Richard White (with remotes)	
1115-1145	Feedback from group work (4 mins each)	Group rapporteurs	
1145-1235	Lunch break		
Session 2: Issues in using quant models for TB vaccine dose/regimen selection			
1235-1250	Consumer: Need statement - how do we want quant modelling to improve TB vaccine dose/regimen selection?	Tom Evans	Willem Hanekom
1250-1305	Producer #1: Bridging knowledge and methods used in drug development to vaccine development	Rada Savic	
1305-1320	Producer #2: Integrating NHP, human, and modeling to determine the influence of BCG timing on H56 vaccine outcomes	Louis Joslyn	
1320-1335	Producer #3: Modelling for vaccine dose/regimen selection	Sophie Rhodes	
1335-1420	Group work	Jeff Barrett Sophie Rhodes Rebecca Harris Louis Joslyn Tom Evans Richard White (with remotes)	
1420-1450	Feedback from groups (4m each)	Group rapporteurs	

1450-1510	**Tea break**		
Session 3: Issues in using quant models for informing vaccine characteristics in TPP/PPCs, target-population-informed development, and implementation strategy			
1510-1525	**Consumers: Needs statement for informing vaccine characteristics in TPP/PPCs and target-population-informed development and for informing implementation strategy (eg BCG revac RCTs/roll out)**	**Willem Hanekom Johan Vekemans Dereck Tait**	**Helen Fletcher**
1525-1540	**Producer #1: Modelling for informing TB vaccine TPPs and PPCs**	**Rebecca Harris**	
1540-1555	**Producer #2: Importance of/issues in natural history parameterisation and vaccine characteristic assumptions**	**Joaquin Sanz**	
1555-1610	**Producer #3: Importance of implementation strategy (age, spatial, risk groups ...) in TB Vaccine impact modelling**	**Sourya Shrestha**	
1610-1655	**Group work**	**Jeff Barrett Sophie Rhodes Rebecca Harris Louis Joslyn Tom Evans Richard White (with remotes)**	
1655-1725	**Feedback from groups (4m each)**	**Group rapporteurs**	
1725-1730	**Wrap up and next steps**	**Richard White**	

Agenda
DIAGNOSTICS SESSION
Friday, 14th September

TB MAC DIAGNOSTICS MEETING: Across the Disease Spectrum: The Future of Modeling TB Diagnostic Testing		
Time	**Content as**	**Speaker**
0830-0845	Introductions and scope/goals of the meeting	David Dowdy
0845-0900	TB survivor perspective	Phumela Tisile
Session 1: Modeling Diagnosis of Latent/Incipient/Subclinical/Clinical TB		
0900-1000	The biology of incipient and subclinical TB: considerations for modelers	Shuyi Ma
	Using models to advance the diagnosis of incipient and subclinical TB	Saskia Ricks
	Closing the gap in TB diagnosis in children	Eleanor Click
	Economic considerations for models of diagnostic testing for latent, incipient, and subclinical TB	Ricardo Steffen
1000-1030	Questions & Discussion	All
1030-1045	Tea break	
Session 2: Modeling Diagnosis of Adult Pulmonary TB (including "triage" testing)		
1045-1145	Implementing TB diagnostic testing in high burden settings: challenges and the role of models	Liesl PageShipp
	Cost considerations for implementing novel diagnostic testing in vulnerable populations	Alice Zwerling
	CRP as a potential "triage" test for TB: epidemiological and economic considerations for modelers	Christina Yoon

	Evaluating epidemiological and economic implications of improving TB diagnosis	**Hojoon Sohn**
1145-1215	**Questions & Discussion**	**All Participants**
1215-1315	**Lunch break**	
1315-1345	**Keynote: Global health technologies: are we still searching for silver bullets and killer apps?**	**Madhukar Pai**
Session 3: Advancing the Modeling of Diagnostic Testing in Key Populations: Children and People Living with HIV		
1345-1445	**Modeling Pediatric Tuberculosis: how can we improve?**	**Leonardo Martinez**
	What role can modeling play in advancing pediatric TB interventions?	**Courtney Yuen**
	Modeling the diagnosis of HIV-associated TB: key research questions and data gaps	**Patrick Cudahy**
	Epidemiological considerations for models of TB diagnosis in HIV-endemic settings	**Chris Whalen**
1445-1515	**Questions & Discussions**	**All**
1515-1530	**Tea break**	
Session 4: Modeling the Diagnosis of TB Drug Resistance		
1530-1630	**The global epidemiology of TB drug resistance and key questions for modelers**	**Matteo Zignol Andrew Siroka**
	How will better diagnosis of TB drug resistance translate into better clinical outcomes?	**Grant Theron**
	Modeling the epidemiological impact and cost-effectiveness of improved diagnostic testing for drug-resistant TB	**Emily Kendall**
1630-1700	**Questions & Discussion**	**All**