TB Modelling and Analysis Consortium

TB Modelling and Analysis Consortium (TB MAC)

Impact and Cost-Effectiveness of Current and Future Diagnostics for TB

Amsterdam, The Netherlands

24-25 April 2013

Meeting Report

www.tb-mac.org

BILL & MELINDA GATES foundation

TB Modelling and Analysis Consortium

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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 second meeting, held April 2013 in Amsterdam, the aim was to bring together experts in the field of TB diagnostics to improve the contribution of modelling to the development, deployment and evaluation of novel TB diagnostics. Work focussed on 4 specific areas of research, or workstreams:

1) Informing scale-up strategies for Xpert MTB/RIF

2) Developing and selecting target product profiles (TPPs) for novel TB assays

3) Understanding the role of drug susceptibility testing (DST) in existing and novel TB drug regimens

4) Describing analytic and modelling needs for better models of TB diagnostics

In preparation for the meeting, a systematic literature review of existing modelling papers on TB diagnostics was carried out, to provide an overview of existing modelling work, the research questions explored and methods used.

During the meeting each workstream met and discussed their area of research, with regular input from the complete group, and worked toward specific deliverables. These were: identifying modelling research questions for Xpert scale and target product profiles for novel TB assays that will form research funding applications; progression of a modelling work package to use modelling to help understand the role of drug susceptibility testing (DST) in existing and novel TB drug regimens, and identifying critical analytic and TB diagnostic modelling needs.

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 (September 2012, 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 2: Impact and Cost-Effectiveness of Current and Future Diagnostics for TB

This report describes the second TB MAC meeting in Amsterdam, The Netherlands which covered the research area "Impact and Cost-Effectiveness of Current and Future Diagnostics for TB".

Meeting objectives

1. Informing scale-up strategies for Xpert MTB/RIF
2. Developing and selecting target product profiles (TPPs) for novel TB assays
3. Understanding the role of drug susceptibility testing (DST) in existing and novel TB drug regimens
4. Describing analytic and modelling needs for better models of TB diagnostics

Scope of meeting

To focus our efforts, the meeting's discussions were restricted to diagnostics for active TB disease. With numerous new diagnostic tests of active TB developed, recommended, implemented, and scaled-up over the last decade, there is a wide array of urgent questions that require modelling. The emphasis of this meeting was to make progress on several key research areas which required immediate modelling input.

Meeting preparation - workstream communication and systematic review

Participants were grouped into the workstreams according to preference, and conducted at least one pre-meeting phone conference to discuss the meeting aims and deliverables. A systematic review of TB diagnostic modelling was done. Detailed methods, definitions and results can be found in appendix 2, but in short this built on an existing collection of all TB modelling papers (see www.tb-mac.org/Resources). Within this resource, those papers examining novel diagnostics for active TB, or the diagnostic process were selected, and data describing their scope, methods and outcomes were extracted.

Pre-meeting modelling workshop

Before the meeting, a two-day workshop was organised for 15 participants whose experience with TB (transmission) modelling was limited. Led by David Dowdy and Pete Dodd, participants were given didactic lectures on the theory behind TB modelling, as well as some experience answering a modelling question with a user friendly model (FlexDx-TB). 70% of respondents stated they would likely use the model in their research or practice after the workshop.

Structure and process of meeting

The meeting was structured with a mix of plenary and workstream specific sessions, as can be seen in the meeting agenda (appendix 1). After a plenary session on day 1, workstream groups discussed

their respective remits in breakout sessions. Results from these initial discussions were reported during the plenary session on the morning of day 1, during which each workstream received input from the wider group. Taking these comments into account, the workstreams then prepared final reports on their objectives, and the way forward, which were presented during the final plenary meeting.

1.3

Meeting discussion and results

1.3.1 Report on plenary presentations (day 1)

After introductory remarks by the meeting organiser (David Dowdy, JHU) and Richard White (chair, TB Modelling and Analysis Consortium), Frank Cobelens (AIGHD) delivered an overview of the field of TB diagnostics. He discussed how modelling can contribute to understanding the (potential) impact and cost-effectiveness of new tools, product profiles of diagnostics in the development pipeline, and identifying operational pathways to optimal implementation of novel diagnostics.

This was followed by plenary presentations for each of the 4 workstreams.

1. Informing scale-up strategies for Xpert MTB/RIF (chair: Ted Cohen, BWH/Harvard University)

   Betina Durovni (DoH, Rio de Janeiro) gave a summary of how the roll-out of Xpert in Brazil would be evaluated, after which Gavin Churchyard (The Aurum Institute) described the patient cohort enrolled in the XTEND study and Allison Grant discussed the use of Xpert in the context of the XPHACTOR study. Edina Sinanovic (University of Cape Town) and Nicola Foster (University of Cape Town) gave an impression of the model being developed to evaluate the cost-effectiveness of Xpert roll-out in South Africa, after which Nick Menzies (Harvard University) showed preliminary work on evaluating different Xpert roll-out scenarios for the 22 high TB burden countries. These presentations served as a basis of subsequent discussion of current efforts to scale-up use of Xpert as a replacement for smear microscopy and expanded use of Xpert for other uses (e.g. to be used as a test to rule-out TB in advance of provided IPT). The discussions provided a summary of current (and planned) areas of modelling and economic analysis and highlighted the importance of new models for predicting the impact and costs associated with different approaches for Xpert use in different epidemiological settings other than those are currently being considered.

2. Developing and selecting target product profiles (TPPs) for novel TB assays (chair: Madhukar Pai, McGill University)

   Madhukar Pai gave a summary describing target product profiles (TPPs) and their relevance, and discussed why the term ‘point-of-care’ is so inconsistently used. He suggested that modelling can inform TPP development by: 1) helping to come up with a sharper definition of what POC testing is; 2) prioritising between TPPs to identify those that can have the biggest impact on TB control; and 3) refining elements within a TPP to identify attributes of greatest relevance. Because most people equate POC with an instrument-free, inexpensive dipstick, the dominant view is that there is no POCT for TB. In reality, what we care about is rapid completion of the test

and treat loop within the same clinical encounter. A POCT program requires technology but also an enabling healthcare system that allows 'test and treat on the same day'. Also, POCT is a spectrum that can happen in several settings and thus opens the possibility of several TPPs. Anja van't Hoog (AMC Department of Global Health and AIGHD) presented considerations for a TPP for triage testing, and discussed how to explore these into a model. Following this, Amanda Sun (JHU) showed results from a model that evaluated the impact of introducing novel diagnostic tests in the Southeast Asia epidemic and Adithya Cattamanchi (University of California San Francisco) reported on a model that compared the impact of same-day microscopy, Xpert as a replacement of standard microscopy, and same day Xpert.

3. Understanding the role of drug susceptibility testing (DST) in existing and novel TB drug regimens (chair: Frank Cobelens, AMC/AIGHD)

   William Wells (TB Alliance) presented the current pipeline of TB drugs, and discussed how introducing these drugs would change the required DST algorithms. While the ultimate goal would be to have regimens consisting entirely of new drugs, the new regimens currently under evaluation contain existing or repurposed TB drugs (notably moxifloxacin (M) and pyrazinamide (Z), against which resistance does exist), while sufficiently accurate rapid DST is not available. Wayne van Gemert (WHO) presented an update on the global surveillance of TB drug resistance, showing considerable gaps in the data on M and Z, both geographically, as well as with specific groups of TB patients. Finally David Dowdy presented a preliminary model outline for evaluating the impact of DST following the introduction of novel drug regimens, highlighting the challenges to keep model structure manageable in the face of many different treatment permutations. The discussions subsequently focused on the type of modelling needed. There is a need for understanding the long-term impact on incidences of drug-resistant (e.g. pre-XDR, XDR) TB of these new regimens and the various ways of deploying rapid resistance assays in different populations (e.g. low/high MDR) to guide global policy decisions as well as investments in assay development. However, there is also need for predicting the short-term programmatic impacts and cost-effectiveness of various DST algorithms in combination with new regimens. While the first requires a transmission model framework, a decision-analytical cohort model framework would be more suitable for the latter.

4. Describing analytic and modelling needs for better models of TB diagnostics (chairs: Richard White and Anna Vassal, LSHTM)

   In this workstream Henrik Salje (JHU) described his work on modelling the diagnostic process in India, highlighting the need to better understand how patients shift between different health care providers, and the complications it brings to modelling this process. Jason Andrews (Massachusetts General Hospital) focussed on 3 key parameters in TB models (mortality, transmission and diagnosis), highlighting gaps in the parameterisation of these. Jason highlighted that data on the number of secondary infections by time since infection was a critical, but poorly-known determinant of the impact of diagnostics. This was supported in subsequent discussions in this workstream. Pete Dodd (LSHTM) then described the role and requirements of user-friendly models of TB diagnostics, after which Andrea Pantoja gave an overview of the challenges involved when parameterising cost and expenditure models. In respect of gaps in the cost data, it was suggested that although considerable gaps existed, the emphasis should be first on collecting unit costs from a limited number of settings that could be considered representative regionally, as well as for countries with different income levels. The presentation also highlighted a need for guidance on methods to extrapolate unit cost data from one setting to other country settings.

1.3.2 **Outcome from discussions (day 2)**

The short-term (meeting) deliverables for each group were met and are outlined below, along with the plans for achieving the long-term deliverables.

Workstream 1: Informing scale-up strategies for Xpert MTB/RIF (chair: Ted Cohen)

Outcome: At the final plenary meeting, Ted Cohen reported on the model requirements to inform scale-up, including a policy-maker focus, and model outcomes should also include timing of needs as well as budget impact. Models should explore 3 different settings as defined by their TB, HIV and MDR prevalence status (high TB - high HIV, high TB, low HIV, high MDR, low HIV), answer questions around deployment of Xpert, and targeting of populations, and consider the effect of scaling up Xpert on other TB services (e.g. the availability of MDR treatment) as well as other health services (e.g. HIV programmes).

Way forward: These considerations will be translated into a Request for Proposals, which will invite TB modellers to apply for funding from TB MAC to address these questions. The gaps identified in this workstream will also be written up in the meeting manuscript, to be submitted before November 2013.

Workstream 2: Developing and selecting target product profiles (TPPs) for novel TB assays (chair: Madhukar Pai)

Outcome: Madhukar Pai summarised the discussions, starting with a goal oriented definition of POCT, developed by the workstream members: "Testing that will result in a clear, actionable, management decision (e.g. referral, initiation of confirmatory test, start of treatment), within the same clinical encounter (e.g. day)." He also provided a list of attributes that should be included in all TPPs for TB diagnostics, including the clinical purpose (e.g. triage or diagnose pulmonary TB), desired outcome (e.g. start treatment that day), the target population (e.g. children) and level of implementation (e.g. ART clinic), as well as its range of users. After creating a list of 11 potential TPPs to develop, the following three were considered high priority:

a. Community based triage and referral test to be used by first-contact providers (e.g. community health workers, informal providers) for identifying individuals who require confirmatory testing for pulmonary TB

b. Clinic or health centre based test for diagnosis of pulmonary TB that will result in same-day treatment ["test and treat today (TTT)"]

c. Centralized rapid DST test for DST testing (existing and new TB drugs) in known active TB patients or those with increased risk of resistance (retreatment cases)

Of these, it was decided that modelling around the first TPP (triage and referral test) will be the first activity for the workstream.

Way forward: An application has been made to TB MAC to co-fund work on this model. This application focuses on exploring the feasibility of digital CXR/computer assisted reading and C-reactive protein lateral flow assays as a TB triage test for identifying individuals who require confirmatory testing for pulmonary TB. The objectives are to define currently available case studies (e.g. digital chest X-ray, C-reactive protein) and assess conditions (cost, volume, sensitivity,

specificity) under which these tests could result in cost saving (or more cases found); improve available decision analysis model to include an additional level of care where triage test is implemented (i.e. community level, informal provider); and expand costing to include patient perspective.

Workstream 3: Understanding the role of drug susceptibility testing (DST) in existing and novel TB drug regimens (chair: Frank Cobelens)

Outcome: These discussions focussed on strategies to triage the potential DST algorithms using both transmission and cohort modelling. With regard to the transmission modelling, the workstream discussed questions about the existing model outline made by David Dowdy, in particular regarding model inputs (e.g. appropriate parameter ranges for resistance amplification, fitness costs and which DST algorithms should be included) and model outputs (e.g. the appropriate time horizon of the model). The cohort model would be integrated with the transmission model to estimate near and medium term market size.

As for timing, since a cohort model could also help triage potential DST algorithms before implementation in the more complex model, this work should ideally precede the transmission model work. The workstream also highlighted key parameters to be investigated by the models, including baseline drug resistance level, patient populations who receive the DST (with varying coverage), DST algorithm, and sensitivity/specificity of the DST.

Way forward: An initial literature review of necessary input parameters for transmission modelling will be conducted in the next few weeks/months. The group will strive to have initial model results for a September meeting at WHO.

Workstream 4: Describing analytic and modelling needs for better models of TB diagnostics (chairs: Richard White and Anna Vassall)

Outcome: Participants in this workstream identified key data gaps (Table 1), the level of detail at which these could ideally be defined (resolution), and how feasible it would be to acquire these data. With regard to modelling development, the most urgent needs for investment were identified to be the expansion of health system modelling, linking these to transmission and costing (cohort) models, and the expansion of developing user-friendly models that are accessible to policy- makers on the (sub)national level.

Way forward: As with Workstream 1, gaps identified in this workstream will be written up in the meeting manuscript, to be submitted before November 2013.

Table 1: Data gaps identified by workstream 4

Data gaps	Resolution	Feasibility
Data/estimates on when in disease course do secondary cases occur versus timing diagnosis (whether active or passive), treatment initiation and		Perhaps analysis spatial patterns of cases. Transmission to HH contact in low incidence settings. Transmission from untreated MDR/XDR cases.

treatment completion, including losses to follow up. - Infectiousness and symptoms - Contacts	By co-morbidities, e.g. HIV, MDR Setting dependent	By HIV, possible. By other co-morbidities probably less feasible Some data available
Number, quality and timing of interaction with HS (and losses to f/up) (from start of disease course) - Public and private	Country type (income, public/private/informal, pop density)	Can gather drop out in pragmatic RCTs. Patient interviews. Ideal: nationwide electronic databases linked to identification numbers Demonstration data from countries, then extrapolated.
Resource and patient costs with each of these interactions - Health system spend (affordability)	Regional, income level	Within limited number of RCTs. Diagnostic cost update Treatment costs update (ongoing) New ideas for expenditure data

1.4

Outputs and next steps

These outcomes of workstreams 1 and 4 will be consolidated into an academic paper and submitted by November 2013. Work identified by streams 1 and 2 will be eligible for funding from TB MAC to support work on these modelling questions. The funding call will be made by the end of June, 2013. The output of stream 3 (development of a "bridging model" to evaluate different algorithms for DST) will be funded though either the Foundation or the TB Alliance, and aligned with the plans to advance NIH-funded Diagnostics Forum modelling work over the next 12 months.

The libraries for the systematic literature review are available now on the TB MAC website (www.tb-mac.org/Resources).

The meeting consolidated the ongoing process of activating and expanding the field of the TB modelling community. The wide participation and presence of young scientists starting in TB modelling shows that this process is already underway. In future, TB MAC will continue to bring together new and experienced TB modellers, along with data experts around specific topics to share novel research and experiences, and to provide new focus and energy to the field.

APPENDICES

2.1 Meeting agenda + participant list

2.2 Systematic review of modelling papers on TB diagnostics

2.1 Agenda and Participant List

TB MAC Meeting #2
Impact and Cost-Effectiveness of Current and Future Diagnostics for TB
Draft Objectives/Deliverables, Agenda, and Participant List
Amsterdam, April 24-25

Introduction/Overview:
Development, deployment, and evaluation of novel TB diagnostics is a rapidly-moving field of research, with numerous new diagnostic tests developed, recommended, implemented, and scaled-up over the last decade. However, the contribution of modelling to these decision-making processes has been limited. There are now at least four areas of research that have risen high on the agenda for TB modelling:

(1) Informing scale-up strategies for Xpert MTB/RIF
(2) Developing and selecting target product profiles (TPPs) for novel TB assays
(3) Understanding the role of drug susceptibility testing (DST) in existing and novel TB drug regimens
(4) Describing analytic and modelling needs for better models of TB diagnostics

While other important questions regarding modelling of TB diagnostics certainly exist, these four "work streams" are all in immediate need of input from TB MAC. Therefore, in contrast to the first TB MAC meeting (where the focus was more broad and focused on priority-setting), this meeting will be focused and results-oriented.

Workstreams and Objectives/Deliverables

1. Informing scale-up strategies for Xpert MTB/RIF

Xpert MTB/RIF has been implemented nationwide in South Africa and is being scaled-up rapidly in Brazil, Indonesia, India, and other countries. Recent modelling analyses have also suggested that, in HIV-endemic regions at least, Xpert may be cost-effective but might not have major impact on incidence. However, the most appropriate way to implement Xpert remains uncertain. For example, are centralized or more point-of-care strategies preferred? What is the most appropriate algorithm for Xpert use, in areas of very limited resources or lower HIV prevalence? How much of Xpert's benefit derives from case detection, prevention of mortality, or detection of drug resistance? These and many other questions remain unanswered; data to inform such models are likely to be emerging soon.

Chair: Ted Cohen

Objectives/Deliverables:

a. Summary of existing (published and ongoing) modelling work related to Xpert scale-up
b. List of 3-5 most important modelling questions related to Xpert scale-up that are likely to remain unanswered by early 2014 without input from TB MAC
c. Manuscript (in conjunction with Stream 4, see final page)

2. Developing and selecting target product profiles (TPPs) for novel TB assays

Although many TB diagnostic assays are already in development, other diagnostic niches remain unfilled. A critical question in seeking to either develop new assays or adapt existing ones to fill these niches is to outline "target product profiles" that describe the characteristics of ideal tests that would meet an important existing diagnostic need. While certain aspects of TPP development (e.g., technical specifications) are not modelling priorities, understanding the potential population-level impact and economic considerations of tests that meet different TPPs (or the "ideal" versus "acceptable" TPP) is a very important consideration in TPP development.

Chair: Madhu Pai

Objectives/Deliverables:

a. List of 3-5 assay characteristics of TPPs that should be included in a comparative model
   - May have more than one list (e.g., a list of TPPs to compare, and within key TPPs, a list of assay characteristics to compare)
b. Policy-relevant, publishable model that compares the items on one list
   - By the end of the meeting: outline and plan/timelines for model construction
   - Fall 2013: initial results available
   - Funding: Existing BMGF grant to Madhu for TPP development

3. Understanding the role of DST in existing and novel TB drug regimens

As novel drug regimens become available, rifampin resistance and/or MDR-TB may no longer be the primary consideration related to TB drug resistance. Specifically, resistance to pyrazinamide (PZA), fluoroquinolones, and novel agents (e.g., PA-824) may be equally important to consider. However, drug susceptibility testing (DST) for these agents is not widely available at this time. Furthermore, if/when such DST assays become available, it is not clear how they should best be deployed, in terms of optimizing the population-level dynamics of drug-resistant TB and maintaining economic efficiency. The TB Diagnostics Forum, co-founded by the Bill and Melinda Gates Foundation and the U.S. National Institutes of Health, has prioritized these questions. A modelling subgroup has been formed and plans to conduct a two-stage modelling strategy, with the first stage exploring the relevant parameter space from a theoretical perspective and the second stage describing the deployment of novel regimens into paradigmatic populations. The first stage has just started; input and participation in the second-stage model will be welcomed.

Chair: Frank Cobelens

Objectives/Deliverables:

a. List of 3-5 key scenarios (populations, DST strategies, regimens) that should be included in a comparative model

b. "Second-stage" model(s) that uses results from the "first-stage" model to describe deployment of novel regimens into key populations with different DST strategies

- By the end of the meeting: outline and plan/timelines for model construction
- Fall 2013: initial results available

4. Describing analytical and modelling needs for better models of TB diagnostics

Current models of TB diagnostics have only a limited set of preceding work from which to draw. These existing models are limited in their handling of key variables, including the amount of transmission that occurs before patients with active TB begin to seek diagnosis, the general time course of TB transmission, interaction of diagnostic tests with diagnostic systems (e.g., public/private sector diagnosis), "smear status" over time, outcomes/transmission from TB patients who are lost to follow-up, and "initial default" rates. Many of these structural uncertainties could be addressed by new data analysis or changing the structure of our models, but we currently lack a framework for thinking effectively about how best to model TB diagnostics.

Co-Chairs: Richard White, Anna Vassall

Objectives/Deliverables:

a. Summary of existing (published and ongoing) modelling work relating to population level impact/transmission, health systems and cost effectiveness.

b. List of 3-5 key improvements to TB diagnostic models that, if implemented, would improve our TB diagnostics/diagnosis model predictions

c. Manuscript (in conjunction with Stream 1, see final page)

MEETING AGENDA

April 22-23, (Garden II)
Pre-Conference Modelling Workshop
10-15 participants drawn from those with less modelling experience
Led by David Dowdy & Pete Dodd

Day 1: April 24 (Cairo / Melbourne)

8.45-9.30 Welcome & introductions (Richard White & David Dowdy)

9.30-10.30 Keynote/introductory address (Frank Cobelens)

How Should Modelers Think of Diagnostic Tests, and What is the Landscape of TB Diagnostics?
40 minute presentation followed by 20 minutes of discussion

10.30-10.45 Break

Presentations & discussion: **Xpert lessons & scale-up** (Ted Cohen, Workstream Chair)

10.45 – 11.00 Betina Durovni: *Evaluating the scale-up of Xpert in Brazil*

11.00 – 11.15 Gavin Churchyard: *XTEND: self reported HIV prevalence, mortality and health seeking behavior*

11.15 – 11.30 Edina Sinanovic & Nicola Foster: *Evaluating the cost-effectiveness of Xpert scale-up in South Africa*

11.30 – 11.45 Nick Menzies: *Modelling the impact and cost-effectiveness of Xpert in the 22 high-burden countries*

Presentations & discussion: **TPPs/new assay development** (Madhukar Pai, Workstream Chair)

11.45 – 12.10 Madhukar Pai: *Target product profiles: which attributes will increase impact?*

12.10 – 12.20 Anja van't Hoog: *Modelling TPPs for a triage test to rule out active TB*

12.20 – 12.30 Amanda Sun: *Modelling tradeoffs between sensitivity and deployability in TB diagnostics for Southeast Asia*

12.30 – 12.40 Adithya Cattamanchi: *Population-level impact of same-day microscopy and Xpert MTB/RIF*

12:45-1:30 Lunch (Beijing Lounge)

Presentations & discussion: **Diagnostics and drug resistance/DST** (Frank Cobelens, Workstream Chair)

1.30 – 1.45 William Wells: *New regimens for TB therapy and the consequences for drug susceptibility testing*

1.45 – 2.00 Wayne van Gemert: *Global surveillance of TB drug resistance: an update*

2.00 – 2.15 David Dowdy: *Modelling the impact of DST for novel TB drug regimens: an exploratory model*

2.15 – 2.30 *Discussion*

Presentations & discussion: **Analytic and modelling needs** (Richard White & Anna Vassall, Workstream Co-Chairs)

2.30 – 2.45 Henrik Salje: *Modelling the deployment of TB diagnostics within the Indian healthcare system*

2.45 – 3.00 Jason Andrews: *Data needs and future projections for tuberculosis*

3.00 – 3.15 Pete Dodd: *User-friendly models of TB diagnostics: what is the appropriate role?*

3.15 – 3.30 Andrea Pantoja: *Availability of cost and expenditure data on TB diagnostics - a brief guide*

3.30 – 4.00 Break

4.00 – 6.00 Breakout sessions (Garden I and II)

Each of the 4 workgroups meets to discuss how they will meet their designated objectives/ deliverables. Workgroups continue working until they have reached a stopping point.

6.00 – 6.30 Workstreams 1 / 4 writing committee meeting

6.30 – 7.00 Meeting of workstream chairs to coordinate Day 2

****Evening Activity: TB MAC Dinner****

Day 2: April 25 (Cairo / Melbourne)

Each AM "workstream session" consists of a 15-minute presentation by the workstream chair, followed by 30 minutes of input from the entire consortium. Focus is on engaging people who could not be at each workstream simultaneously, and on how best to meet deliverables/objectives.

8:30-8:45 Introduction to the day (David Dowdy)
8:45-9:30 Workstream 1 Session: Xpert lessons and scale-up
9:30-10:15 Workstream 2 Session: TPPs/new assay development

10:15-10:30 Break

10:30-11:15 Workstream 3 Session: Diagnostics and drug resistance/DST
11:15-12:00 Workstream 4 Session: Modelling the diagnostic process

12:00-1:00 Lunch (Beijing Lounge)

1:00-3:00 Breakout sessions (Garden I and II)
Each of the 4 workstreams meets to develop a final plan for meeting their objective, after getting feedback from the entire team. All workstreams should plan to provide a five-slide summary that includes their short-term objectives and a plan for meeting their longer-term objective.

3:00-3:15 Break

3:15-4:45 Workstream reports
Each workstream gets 20 min. to present its summary and obtain final feedback from the full group, by way of developing a final plan for their long-term objectives.

4:45-5:15 Meeting summary and next steps (David Dowdy)

Manuscript deliverables (lead by workstreams 1 and 4)

Manuscript summary manuscript describing the potential contribution of mathematical modelling to the impact and cost-effectiveness of current and future TB diagnostics.

- Based primarily on lit review and outputs of workstream 1 and 4
- By the end of the meeting: outline paper and have list of potential responsibilities/co-authors

Fall 2013: manuscript submitted

Participant List

Richard White	LSHTM (TB MAC Director)
David Dowdy	JHSPH (TB MAC Committee member, Meeting Organizer)
Chris Dye	WHO (TB MAC Committee Chair)
Michael Kimerling	Bill and Melinda Gates Foundation (TB MAC Committee member)
Geoff Garnett	Bill and Melinda Gates Foundation (TB MAC Committee member)
Ted Cohen	BWH / Harvard (TB MAC Committee member)
Philip Eckhoff	Intellectual Ventures (TB MAC Committee member)
Anna Vassall	LSHTM (TB MAC Committee member)
Rein Houben	LSHTM (TB MAC Epidemiologist)
Olivia Ross-Hurst	TB MAC / LSHTM (TB MAC Coordinator)
DJ Lisondra	Bill and Melinda Gates Foundation (BMGF Coordinator)
Betina Durovni	CREATE
Gavin Churchyard	Aurum Institute
Edina Sinanovic	UCT
Nick Menzies	Harvard
Sanne van Kampen	KNCV
Adithya Cattamanchi	UCSF
Susan van den Hof	KNCV
Ivor Langley	Liverpool
Maunank Shah	JHU
Wayne van Gemeert	WHO
Gaby Gomez	AIGHD
Alison Grant	LSHTM
Anja van't Hoog	AIGHD
Claudia Denkinger	McGill University
Sandra Kik	McGill University
Bachti Alisjahbana	Indonesia National TB Program
Jennifer Gardiner	Bill and Melinda Gates Foundation
Amanda Sun	JHU
Madhukar Pai	McGill University
Marco Schito	NIAID
Catharina Boehme	Find Diagnostics
Frank Cobelens	AIGHD
William Wells	TB Alliance
Jason Andrews	Massachusetts General Hospital
Gwen Knight	LSHTM
Grace Huynh	Intellectual Ventures
Daniel Chin	Bill and Melinda Gates Foundation
Nicola Foster	UCT
Henrik Salje	JHSPH
Pete Dodd	LSHTM
Andrew Azman	JHSPH

Olivia Oxlade	McGill University
Arne von Delft	TB-PROOF
Andrea Pantoja	Independent
Bertie Squires	Liverpool
Molebogeng Rangaka	LSHTM
Alice Zwerling	JHSPH
David Collins	MSH
Liz Corbett	LSHTM
Peter Small	Bill and Melinda Gates Foundation
Nim Pathy	Princeton (via teleconference)

2.2 Results from systematic literature review

Contents

Review methods & structure of document

Review methods

1. Updated the existing collection of all TB modelling papers, see http://www.tb-mac.org/Resources/Resource/4 for methods and downloadable file. Within this collection of papers a free text search for diag* was done
2. Scope: Models that evaluated novel tools to diagnose active TB. Not models that explore impact of screening new populations (e.g. Active versus Passive Case Finding). Review focuses on the models comparing diagnostic tool or methods of TB diagnostic modelling, not populations to diagnose.
3. Inclusion/Exclusion criteria
    a. Exclude if:
        i. Focus on diagnosing latent TB disease to fit with scope of meeting
        ii. Published before 2000 so to reflect current modelling practices and reasonably novel diagnostic methods
        iii. Used only diagnostic tools that fall within existing standards of care at the time of analysis. Note: Xpert not considered standard of care for this review
    b. Include cost-effectiveness paper only if reported use of decision or markov model in analysis
4. Paper selection and data extraction done by 2 reviewers (Alice Zwerling, Rein Houben)
5. From 436 records we selected 92 papers for full-text review, of which 31 papers were included for data extraction

Structure of document

As agreed in calls before the meeting, papers were grouped to match the three main areas for discussions in Workstream 4: 1) Population level impact/transmission, defined as models including a transmission component or measure population wide impact, 2) Health Systems, defined as models including compartments that represent points of interactions between patient and health care providers or institutions and 3) Cost-effectiveness, defined as models which include a cost component.

Definitions of variables and key abbreviations

Variable definitions

General overview

Primary research question: What was the main objective of the model?
Population: What was the population the model represents?
Setting: What epidemiological setting did the model parameters seek to represent?
Baseline diagnostic pathway: When a novel diagnostic tool or algorithm was investigated, what was the current standard of diagnostic that served as comparison?
Main comparison: What novel diagnostic tool(s) or algorithm(s) did the model consider?
Outcome: What outcome variable(s) were generated to address the question?
Time Horizon: Over what time period was the outcome assessed?
Conclusion: The main conclusion of the paper regarding the primary research question

Diagnostics modelled and model scope

Novel diagnostic: Was a novel diagnostic tool modelled and if so, what was it?
Model method: Did the model explore an aspect or method of TB diagnostic modelling and if so, what was it?
Diagnostic tools explicitly modelled: Did the model include a parameter, compartment or node to represent this diagnostic?
Stage of tech: Did the model consider a product profile of a novel diagnostic, an existing novel test with known performance characteristics, or scale-up of such a test
Health sys scope: What part of the health system was taken into consideration – only the diagnostic pathway (Dx), diagnosis and treatment factors (Dx Rx), or other health services such as HIV?

Modelling methods

Model type(s): What modelling approach was taken to address the question – epidemiological dynamics (transmission), decision, markov, queuing, discrete event simulation or combination of these?
Health system: Did the model include compartments (this excluded decision models) that represent points of interactions between patient and health care providers or institutions?
Data fit: Did the authors implement a procedure (manual adjustment or automated calibration of parameters) to the model output to historical epidemiological data? Not collected for decision analytic models, as such fitting is not currently part of this methodology.
Sensitivity: Was a sensitivity analysis conducted and if so, was this done one-way or two way only (i.e at most one or two parameters allowed to vary at the same time) or was a multivariate approach taken. This covers both methods to acquire a range of likely values around point estimates of the main outcomes, as well as examinations of model's sensitivity to particular assumptions.
Pre-diag inf: Did the model explicitly include transmission that occurs between start of infectiousness and TB diagnosis?
FP/FN: Did the model consider the impact on model outcomes of TB cases that received a false positive or negative TB diagnosis?

Repeat entry: Did a model allow patients that received a false negative diagnosis to re-enter the diagnostic pathway during the same TB episode?
Drug Susc: Did the model stratify part of the diagnostic pathway and performance or treatment outcome based on the drug susceptibility status of the TB case?
HIV: Did the model stratify part of the diagnostic pathway and performance or treatment outcome based on the HIV status of the TB case?
Previous Rx: Did the model stratify part of the diagnostic pathway and performance or treatment outcome based on the TB treatment history of the TB case?

Cost effectiveness analysis specific variables

CE included: Was a cost-effectiveness measure included?
CE measure: How was cost-effectiveness calculated (costs/outcome measure)
ICER: Was an Incremental Cost-Effectiveness Ratio (ICER) calculated. This requires a formal comparison between diagnostic strategies on the difference in cost and outcome units (e.g. DALYs)
Costing perspective: What type of costs were included? Were provider costs calculated from the health system or TB programme perspective, were costs made by the patient or family considered and were societal costs (e.g. lost productivity) considered?
Costing source: How was the costing data acquired - primarily empirical: authors collected cost data as part of study or used empirically collected cost data from another study done in the same setting and time period; primarily non-empirical: cost data mainly acquired through expert opinion, market prices, meta-analyses or pooled extrapolated estimates (e.g. WHO CHOICE); Combo: empirical and non-empirical costs estimates both made up a substantial proportion of all costs.
Costing scope: Within provider costs, what level costs were included? Partial site: only includes primarily test and treatment costs; full site: includes salaries, overheads, facilities, capital costs, maintenance, etc...; above service level costs: also include higher level costs, such as implementation and program managerial costs.

Abbreviations

TB	Active TB disease
Dx	Diagnosis
Rx	Treatment
N/A	Not applicable
XDR	Extensively Drug Resistant
CE	Cost-effectiveness
DST	Drug sensitivity test;
MMR	Mass Miniature Radiography
HYPO = Hypothetical test	
NAAT = Nucleic acid amplification test	
MTD: *Mycobacterium tuberculosis* Direct	

Part 1: Population impact/transmission models (n=14)

Table 1.1: General overview

Ref	Primary research question	Population	Setting	Baseline diagnostic pathway	Main comparison	Outcome	Time horizon	Conclusion
Abu-Raddad PNAS 2009	Potential impact of novel vaccine, drugs and diagnostics	General pop'n	Southeast Asia (not China)	*Assumed standard DOTS (Sputum smear & Xray for smear negative)*	LED, NAAT, dipstick test	TB inc, mortality	35 yrs	NAAT prevents equal number of deaths as LED, but prevents twice as many cases
Basu 2009 PNAS	Evaluating transmission dynamics of XDR-TB in South Africa	General pop'n	KwaZulu-Natal (South Africa)	Clinical Dx of DR	Rapid DST for all new TB cases (turnover reduced from 6 wks to <1 wk)	Transmission, mortality	5 yrs	Early community based DST could help reduce ongoing transmission of DR TB
Dowdy 2006 AIDS	Impact of improved diagnostics on TB incidence in high HIV prevalence settings	General pop'n	High HIV prevalence	Current standard Dx: sens: 80% SSpos, 25% SSneg	1) Rapid molecular testing 2) culture	Mortality & TB Inc/Prev	16-32 yrs	Improved Dx may have substantial impact on TB morbidity and mortality in HIV-endemic regions
Dowdy 2008 PNAS	Impact of enhanced TB diagnostics on the TB epidemic in RSA	General pop'n	South Africa	Culture without DST performed in 5% of new suspects and with DST in 37% suspects with previous Rx	Culture in all suspects, DST in 37% of new suspects, 85% of retreatment suspects & Hypothetical test	Mortality, MDR/XDR TB incidence	10 yrs	Rapid expansion of culture and DST reduces overall mortality (17%) and MDR mortality (47%), but does not prevent XDR incidence
Dowdy 2013 AJRCCM	Estimate pop'n level impact of TB case-finding strategies in presence of subclinical prediagnostic disease	General pop'n	Low, medium and high burden	*Assumed standard DOTS (Sputum smear & Xray for smear negative)*	Increased sensitivity during the clinical phase	TB inc	10 yrs	Pre-diagnostic infectious period important to include when evaluating diagnostic and case finding strategies
Dye 2012 IJMR	Explore potential impact of new TB diagnostic tests on TB epidemic	General pop'n	India	N/A	Dx pathway that halves diagnostic delay	TB inc	40 yrs	New diagnostic test will most reduce diagnostic delay when applied by all providers (public and private)
Langley 2012 HCMS	Explore how discrete event simulation can inform implementation decisions around novel Dx	General pop'n	Tanzania	Sputum smear & DST in reference lab	1) full implementation of NAAT (Xpert) 2) LED optimized microscopy	Costs, patients cured	Lifetime, 10 yrs	Linked operational and transmission model highly useful to inform policy decisions on TB diagnostics
Lin 2011 IJTLD	Potential of integrating operational and dynamic transmission model	General pop'n	Low- and middle-income	Sputum smear	Hypothetical faster and more sensitive test	TB inc	10 yrs	Linked operational and transmission model useful to inform impact of alternative diagnostic pathways
Lin 2012 BullWHO	Estimate impact of new diagnostic tool in detailed model of diagnostic pathway	General pop'n	Tanzania	Sputum smear & Xray for smear negative	Hypothetical first line test 100/70% sensitivity for SSpos/SSneg TB	TB inc, prev	10 yrs	Models of diagnostic impact should include operational context

Ref	Primary research question	Population	Setting	Baseline diagnostic pathway	Main comparison	Outcome	Time horizon	Conclusion
Menzies 2012 PlosMed	Population impact and CE of Xpert for TB diagnosis	General pop'n	Botswana, Lesotho, Namibia, South Africa, Swaziland	Sputum smear, culture if - on smear & strong suspicion of TB or hx of TB Rx	Xpert as first line test	TB inc, prev	10 & 20 yrs	Introduction of Xpert would lower incidence, prevalence and mortality within 10 yrs, but will increase costs for HIV care and MDR Rx.
Millen 2008 PLosONE	Impact of test sensitivity on diagnostic delay and drop out	TB Cases	Parameters based on South Africa (Western Cape)	Sputum smear & Xray for smear negative, culture centralised	One stop test with 60% sensitivity	Diagnostic delay	Diagnostic pathway	Test sensitivity is key determinant of diagnostic delay
Uys 2007 PlosONE	Impact of diagnostic delay on transmission	General pop'n	South Africa (Western Cape)	N/A	Reduction in diagnostic delay that decreases rate of infection of personal contacts by 20%	Transmission	~15 wks	Average time to diagnosis needs to be below a threshold, otherwise an epidemic will escalate
Uys 2009 JCM	Impact of delayed diagnosis of DR in TB patients	General pop'n	Western Cape (South Africa)	Culture for DST (turnover of 40 days)	MTBDRplus (2 day turnover)	TB inc (DR TB)	20 yrs	Current strategies have long delays and will not halt the spread of MDR TB, rapid Dx of DR in the community is needed
Winetsky 2012 PLosMed	Evaluate CE of Xpert and other Dx strategies in prison populations in Russia and Eastern Europe	Prison pop'n with high MDR prevalence	Tajikistan, Russia, Latvia	No screening	Annual mass screen with Xpert or MMR	TB and MDR prev, costs	10 yrs, lifetime	Annual screening with Xpert is more effective than MMR and is cost effective

Table 1.2: What was modelled (diagnostics and scope of model)

Ref	Novel diagnostic		Model method		Diagnostic tools explicitly modelled							Stage of tech	Health sys scope
					Symp	Sput Smear	Xray	Xpert	Other NAAT	Culture	Other		
Abu-Raddad PNAS 2009	Y	HYPO*: LED, NAAT, Dipstick	N	N/A	N	Y (LED)	N	N	Non-specific	N	HYPO: dipstick	Scale-up/ Product profile	Dx Rx
Basu 2009 PNAS	Y	HYPO: Rapid DST	N	N/A	Y	Y	Y	N	N	N	HYPO: Rapid POC test for XDR	Product profile	Dx Rx
Dowdy 2006 AIDS	Y	Rapid molecular testing, culture	N	N/A	N	Y	N	N	Non-specific	Y	N/A	Product profile	Other services (HIV)
Dowdy 2008 PNAS	Y	Expanded culture and DST	N	N/A	N	Y	Y	N	N	Y	HYPO: 100% sensitivity, immediate result, 1m drug resistance result	Scale up/ Product profile	Dx Rx
Dowdy 2013 AJRCCM	Y	HYPO: 3 Dx tests	Y	Pre-Dx transmission	N	N	N	N	N	N	HYPO: 20% increase in in sens (similar to Xpert)	Product profile	Dx Rx
Dye 2012 IJMR	Y	HYPO	Y	Include interactions between patient and provider	N	N	N	N	N	N	HYPO: improved test	Product profile	Dx Rx
Langley 2012 HCMS	Y	Xpert	Y	Link operational and transmission model	Y	Y (ZN & LED)	Y	Y	N	Solid	N/A	Existing test	Dx Rx
Lin 2011 IJTLD	N	N/A	Y	Link operational and transmission model	N	N	N	N	N	N	HYPO: 1 sample 1 day test	Product profile	Dx Rx
Lin 2012 BullWHO	Y	HYPO	Y	More detail of diagnostic pathway	N	Y	Y	N	N	N	HYPO: 100% sens for smear + 70% smear	Product profile	Dx Rx
Menzies 2012 PlosMed	Y	Xpert	N	N/A	Y	Y	Y	Y	N	Y	N/A	Existing test / Scale-up	other services (HIV)
Millen 2008 PLosONE	N	N/A	Y	Diagnostic delay	N	Y	Y	N	N	Solid	N/A	Product profile	Dx
Uys 2007 PlosONE	N	N/A	Y	Diagnostic delay	N	N	N	N	N	N	N/A	Product profile	Dx
Uys 2009 JCM	Y	MTBDRplus	N	N/A	N	N	N	N	MTBDRplus	N	N/A	Existing test	Dx Rx
Winetsky 2012 PLoS Med	Y	Xpert, mass miniature radiography (MMR)	N	N/A	Y	N	Y (MMR)	Y	N	Liquid & Solid	N/A	Existing test	Dx Rx
SUMMARY				50%	29%	57%	50%	50% explicitly include NAAT, 4 additonal product profiles resemble Xpert		43%			All models looked beyond diagnosis

Table 1.3: Modelling methods

Ref	Model type(s)	Health Sys	Data fit	Sensitivity		Pre-diag inf	FP	FN	Repeat entry		Drug Susc	HIV	Previous Rx
Abu-Raddad PNAS 2009	Transmission	N	Y	Y	one-way	Y	N	N	N	N/A	Y	N	N
Basu 2009 PNAS	Transmission & queuing	Y	N	Y	unclear	Y	N	N	N	N/A	Y	Y	Y
Dowdy 2006 AIDS	Transmission	N	N	Y	one-way	Y	N	N	N	N/A	N	Y	N
Dowdy 2008 PNAS	Transmission	N	Y	Y	multi[a]	Y	N	Y	Y	Identical	Y	Y	Y
Dowdy 2013 AJRCCM	Transmission	N	N	Y	multi[a]	Y	N	N	N	N/A	N	N	N
Dye 2012 IJMR	Transmission & markov	Y	Y	N	N/A	Y	N	Y	Y	Identical	N	N	N
Langley 2012 HCMS	Transmission & discrete event simulation	Y	N	Y	one-way	Y	Y	Y	Y	Identical	Y	Y	Y
Lin 2011 IJTLD	Transmission & discrete event simulation	Y	N	N	N/A	Y	N	N	N	N/A	N	N	N
Lin 2012 BullWHO	Transmission	Y	Y	Y	multi	Y	N	Y	Y	Identical	N	Y	Y
Menzies 2012 PlosMed	Transmission and CE	N	Y	Y	multi[a]	Y	Y	Y	N	N/A	Y	Y	Y
Millen 2008 PLosONE	Decision analytic	N/A	N/A	Y	one-way	N	N	Y	Y	Identical	N	Y	N
Uys 2007 PlosONE	Transmission (cohort model)	N	N	Y	one-way	Y	N	N	N	N/A	N	N	N
Uys 2009 JCM	Transmission	N	Y	Y	one-way	Y	N	N	N	N/A	Y	N	N
Winetsky 2012 PLosMed	Transmission & markov with CE	N	Y	Y	one-way	Y	Y	N	N	N/A	Y	N	Y
SUMMARY	57% applied mixed methods	36%	54%	86%	33% multivar	86%	21%	43%	43%	100% Identical	50%	50%	43%

a repeated runs with random sampling of parameter space to get uncertainty range around point estimates

Part 2: Health System models (n=5)

Table 2.1: General overview

Ref	Primary research question	Population	Setting	Baseline diagnostic pathway	Main comparison	Outcome	Time horizon	Conclusion
Basu 2009 PNAS	Evaluating transmission dynamics of XDR-TB in South Africa	General pop'n	South Africa (KwaZulu-Natal)	Clinical Dx of DR	Rapid DST for all new TB cases (turnover reduced from 6 wks to <1 wk)	Transmission, mortality	5 yrs	Early community based DST could help reduce ongoing transmission of DR TB
Dye 2012 IJMR	Explore potential impact of new TB diagnostic tests on TB epidemic	General pop'n	India	N/A	Dx pathway that halves diagnostic delay	TB inc	40 yrs	New diagnostic test will most reduce diagnostic delay when applied by all providers (public and private)
Langley 2012 HCMS	Explore how discrete event simulation can inform implementation decisions around novel Dx	General pop'n	Tanzania	Sputum smear & DST in reference lab	1) full implementation of NAAT (Xpert) 2) LED optimized microscopy	Costs, patients cured	Lifetime, 10 yrs	Linked operational and transmission model highly useful to inform policy decisions on TB diagnostics
Lin 2011 IJTLD	Potential of integrating operational and dynamic transmission model	General pop'n	Low- and middle-income	Sputum smear	Hypothetical faster and more sensitive test	TB inc	10 yrs	Linked operational and transmission model useful to inform impact of alternative diagnostic pathways
Lin 2012 BullWHO	Estimate impact of new diagnostic tool in detailed model of diagnostic pathway	General pop'n	Tanzania	Sputum smear & Xray for smear negative	Hypothetical first line test 100/70% sensitivity for SSpos/SSneg TB	TB inc, prev	10 yrs	Models of diagnostic impact should include operational context

Table 2.2: Cost-effectiveness specific considerations

Ref	CE included			Costing perspective			Costing Source	Costing Scope
	Done	CE measure	ICER	Health system vs TB programme	Patient/family	Society		
Basu 2009 PNAS	N	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Dye 2012 IJMR	N	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Langley 2012 HCMS	Y	$/DALY	Y	Health system	N	N	primarily empirical	full site
Lin 2011 IJTLD	N	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lin 2012 BullWHO	N	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 2.3: What was modelled (diagnostics and scope of model)

Ref	Novel diagnostic		Model method		Diagnostic tools explicitly modelled							Stage of tech	Health sys scope
					Symp	Sput Smear	Xray	Xpert	Other NAAT	Culture	Other		
Basu 2009 PNAS	Y	HYPO: Rapid DST	Y	Transmission & queuing	Y	Y	Y	N	N	N	HYPO: Rapid POC test for XDR	Product profile	Dx Rx
Dye 2012 IJMR	Y	HYPO	Y	Transmission & markov	N	N	N	N	N	N	HYPO: improved test	Product profile	Dx Rx
Langley 2012 HCMS	Y	Xpert	Y	Transmission & discrete event simulation	Y	Y (ZN & LED)	Y	Y	N	Solid	N/A	Existing test	Dx Rx
Lin 2011 IJTLD	N	N/A	Y	Transmission & discrete event simulation	N	N	N	N	N	N	HYPO: 1 sample 1 day test	Product profile	Dx Rx
Lin 2012 BullWHO	Y	HYPO	N	N/A	N	Y	Y	N	N	N	HYPO: 100% sens for smear + 70% smear	Product profile	Dx Rx
SUMMARY	80%		80%		40%	60%	60%	20%	0%	20%	Hypothetical tests in 80% health system scope papers		

Table 2.4: Modelling methods (including which mixed methods were applied)

Ref	Model type(s)	Health Sys	Data fit	Sensitivity		Pre-diag inf	FP	FN	Repeat entry		Drug Susc	HIV	Previous Rx
Basu 2009 PNAS	Transmission & queuing	Y	N	Y	unclear	Y	N	N	N	N/A	Y	Y	Y
Dye 2012 IJMR	Transmission & markov	Y	Y	N	N/A	Y	N	Y	Y	Identical	N	N	N
Langley 2012 HCMS	Transmission & discrete event simulation	Y	N	Y	one-way	Y	Y	Y	Y	Identical	Y	Y	Y
Lin 2011 IJTLD	Transmission & discrete event simulation	Y	N	N	N/A	N	N	N	N	N/A	N	N	N
Lin 2012 BullWHO	Transmission	Y	Y	Y	multi	Y	N	Y	Y	Identical	N	Y	Y
SUMMARY		100%	40%	60%		80%	20%	60%	60%	100%	40%	60%	60%

Part 3: Cost-effectiveness models (n=20)

Table 3.1: General overview

Ref	Primary research question	Population	Setting	Baseline diagnostic pathway	Main comparison	Outcome	Time horizon	Conclusion
Abimbola 2012 AIDS	CE of culture or Xpert to reduce early mortality in individuals with advanced HIV initiating ART	HIV positive individuals initiating ART with TB symptoms	Sub-Saharan Africa	Sputum smear microscopy, Xray if SSneg	Xpert as first line test	Mortality, costs	6 months	Culture or Xpert CE at reducing early mortality during first 6 months of ART compared with sputum smear & Xray
Acuna CID 2008	CE of DST including rapid (FASTPlaque) or conventional methods	TB Cases (SSpos PTB)	Peru (middle income)	No DST, MDR Rx based on failure with first line Rx	FASTPlaque-Response, INNO-LiPA, direct LJ, MIT assay indirect LJ	Mortality, costs	Lifetime	All alternative DST methods are CE, solid culture is most cost-effective
Albert 2004 IJTLD	CE of incorporating FASTPlaqueTB into Dx algorithm for SS- PTB in South Africa	TB Suspects (SSneg)	Cape Town (South Africa)	Negative sputum smear (2x), Xray + culture if Xray abnormal	FASTPlaque integrated with Dx pathway	Costs, Cases Dx	Diagnostic pathway	FASTPlaqueTB improves case-detection and is cheaper to implement than current NTP algorithm
Andrews 2012 AIDS	CE of Xpert TB screening at ART initiation	HIV positive individuals initiating ART	South Africa	No TB screening	One or two sample Xpert	Survival	Lifetime	All strategies increased life expectancy, at 5100 USD per life year saved with 2 sample Xpert and 2800 USD for sputum smear
Bonnet 2010 IJTLD	CE of sputum smear methods that apply bleach sedimentation	TB Suspects	Kenya (urban health clinic)	Sputum smear	Bleach sedimentation on sputum samples	Costs, case detection rate	Diagnostic pathway	Bleach sedimentation could be CE, but operational barriers complicate roll-out
Dowdy 2003 JCM	CE of GenProbe for rapid exclusion of *Mtb* in smear positive specimens	TB Suspects (SSpos)	Baltimore (USA)	Sputum smear	GenProbe to exclude *Mtb* in positive smears and avoid isolation	Costs	Diagnostic pathway	Gen-Probe not CE for most hospitals in high-income setting
Dowdy 2008 IJTLD	CE of hypothetical new POC test for TB	TB Suspects (for PTB)	South Africa, Brazil, Kenya	No microscopy	Combination of sputum smear, culture, new test with sens = 50-90% and spec = 90-100%	Costs, infections prevented	Lifetime	Novel Dx can be highly CE. Impact highest from highly specific, low-cost tests in setting with poor infrastructure
Dowdy 2008 Plos ONE	CE of TB culture for HIV positive patients	TB Suspects (HIV positive)	Rio de Janeiro (Brazil)	Sputum smear	Sputum smear & culture	Mortality, costs	Lifetime	TB culture is potentially cost-effective diagnostic tool for diagnosis in HIV positive individuals
Dowdy 2011 PLosMed	CE of TB serology tests in India	TB Suspects	India	No microscopy	Sputum smear vs Anda tb (serology Elisa)	Mortality, costs	Lifetime	Sputum smear is more cost-effective than serological tests
Guerra 2008 JCM	CE of specimen dilution algorithms for amplified MTD testing of respiratory specimens	TB suspects (with smear result)	Baltimore (USA)	Conventional undiluted MTD	Various algorithms on diluting sputum samples before MTD	Costs	Diagnostic pathway	Most CE strategy was dilution for SSpos but not SSneg specimens prior to MTD testing

Ref	Primary research question	Population	Setting	Baseline diagnostic pathway	Main comparison	Outcome	Time horizon	Conclusion
Hughes 2012 RespMed	CE of NAAT based strategies for TB diagnosis	TB suspects	UK	Sputum smear and culture	NAAT as first line or as part of algorithm with Sputum smear, culture, NAAT	Costs	Lifetime	NAAT based diagnosis not CE below pre-test TB prevalence of 46%
Langley 2012 HCMS	Explore how discrete event simulation can inform implementation decisions around novel Dx	General pop'n	Tanzania	Sputum smear & DST in reference lab	1) full implementation of NAAT (Xpert) 2) LED optimized microscopy	Costs, patients cured	Lifetime, 10 yrs	Linked operational and transmission model highly useful to inform policy decisions on TB diagnostics
Lim 2000 Resp	CE of empirical versus lab test (including NAAT) driven diagnosis of smear negative TB	TB suspects (SSneg PTB)	Singapore	Clinical signs only	Amplicor and NAAT for BAL	Costs, survival	Lifetime	Compared with clinical signs only, additional testing (Amplicor) provides little improvement in life expectancy.
Menzies 2012 PlosMed	Population impact and CE of Xpert for TB diagnosis	General pop'n	Botswana, Lesotho, Namibia, South Africa, Swaziland	Sputum smear, culture if - on smear & strong suspicion of TB or hx of TB Rx	Xpert as first line test	TB inc, prev	10 & 20 yrs	Introduction of Xpert would lower incidence, prevalence and mortality within 10 yrs, but will increase costs for HIV care and MDR Rx.
Meyer-Rath 2012 PLosONE	Cost and impact of national rollout of Xpert in South Africa	TB suspects	South Africa	Sputum smear, Xray, centralised culture facility	Xpert as first line test	Costs, cases diagnosed,	Diagnostic pathway	In Xpert algorithm, cost per diagnosis increased with 55%, diagnosed 30-37% more cases
Rajalahti 2004 ERJ	Compare standard sputum smear+culture with PCR included strategy	TB Suspects	Finland	Sputum smear & culture	Amplicor standard immediately after first smear and culture	Costs	End of Rx	Routine PCR not cost saving in low prevalence setting
Schnippel 2013 SAMJ	Cost and impact of second Xpert for HIV positive TB supects negative on first Xpert	TB suspects (HIVpos, initial Xpert negative)	South Africa	Culture when negative on initial Xpert	Replace culture with second Xpert	Costs, cases diagnosed	End of Rx	Second Xpert could improve outcomes and generate cost savings
Sun 2013 IJTLD	CE of adding LAM urine test to Dx algorithm for individuals with advanced HIV	TB suspects (HIVpos, CD4<100, 1 TB symptom)	South Africa & Uganda	Standard Dx pathway, 35/99.8% sens/spec	Urine LAM added	Costs, cases diagnosed	Lifetime	Adding urine LAM generated additional Dx and is likely to be CE
Vassall 2011 PLosMed	CE of Xpert in high burden settings	TB Suspects	India, South Africa, Uganda	Sputum Smear (clinical diagnosis for SSneg) and culture based DST for retreatment cases	1) Xpert in addition to smear 2) Xpert replaces smear	Costs	Lifetime	Xpert as a first line test is CE for the diagnosis of TB in low- and middle-income settings, compared smear and clinical signs
Winetsky 2012 PLosMed	Evaluate CE of Xpert and other Dx strategies in prison populations in Russia and Eastern Europe	Prison pop'n with high MDR prevalence	Tajikistan, Russia, Latvia	No screening	Annual mass screen with Xpert or MMR	TB and MDR prev, costs	10 yrs, lifetime	Annual screening with Xpert is more effective than MMR and is cost effective

Table 3.2: Cost-effectiveness specific considerations

Ref	Model method	CE measure	ICER	Costing perspective			Costing Source	Costing Scope
				Health system vs TB programme	Patient/family	Society		
Abimbola 2012 AIDS	Decision	$/death averted	Y	Health system	N	N	primarily non-empirical	full site (ART)
Acuna CID 2008	Decision	$/DALY	N	Health system	N	N	primarily empirical	full site
Albert 2004 IJTLD	Decision	$/SSneg suspect tested	N	Health system	N	N	primarily non-empirical	full site
Andrews 2012 AIDS	Markov	$/YLS	Y	Health system	N	N	combo	full site (HIV costs)
Bonnet 2010 IJTLD	Decision	$/case detected	Y	Health system	Y (transport costs)	N	primarily empirical	full site
Dowdy 2003 JCM	Decision	$/early TB exclusion	N	Health system	N	N	primarily empirical	full site
Dowdy 2008 IJTLD	Decision	$/DALY	Y	TB programme (costs for hospitalizations or physician visits not included)	N	N	primarily non-empirical	partial site
Dowdy 2008 Plos ONE	Decision & Markov	$/DALY	Y	TB programme	N	N	primarily empirical	full site
Dowdy 2011 PLosMed	Decision	$/DALY	Y	TB programme (public and private)	N	N	primarily non-empirical	partial site (but do include some capital costs)
Guerra 2008 JCM	Decision	$/correct PTB Dx	N	TB lab perspective	N	N	primarily empirical	partial site
Hughes 2012 RespMed	Decision	$/QALY	Y	Health system	N	N	primarily non-empirical	partial site
Langley 2012 HCMS	Transmission & discrete event simulation	$/DALY	Y	Health system	N	N	primarily empirical	full site
Lim 2000 Resp	Decision	$/yr added life expectancy	N	Health system	N	N	combo	partial site
Menzies 2012 PlosMed	Transmission and CE	$/DALY	Y	Health system	N	N	primarily non-empirical	above service level (HIV)
Meyer-Rath 2012 PLosONE	Decision	$/case treated & $/suspect	Y	Health system	N	N	combo	full site
Rajalahti 2004 ERJ	Decision	$/pt tested	Y	Health system	N	N	primarily empirical	partial site/full site but doesn't specify salaries, overhead, etc.
Schnippel 2013 SAMJ	Decision	$/TB case initiated on Rx	N	Health system	N	N	primarily non-empirical (uses WHO CHOICE)	partial site
Sun 2013 IJTLD	Decision	$/DALY	Y	TB programme	N	N	primarily non-empirical	partial site
Vassall 2011 PLosMed	Decision	$/DALY	N	Health system	N	N	primarily empirical	full site
Winetsky 2012 PLosMed	Transmission & markov with CE	$/QALY	Y	Health system	N	N	primarily empirical	full site
SUMMARY	15% use Markov		65%	75% Health System (71%)	5%	0%	45% prim empirical	55% full site, 2 of which include HIV

Table 3.3: What was modelled (diagnostics and scope of model)

Ref	Novel diagnostic		Model method		Diagnostic tools explicitly modelled							Stage of tech	Health sys scope
					Symp	Sput Smear	Xray	Xpert	Other NAAT	Culture	Other		
Abimbola 2012 AIDS	Y	Xpert	N	N/A	N	Y	Y	Y	N	Liquid	N/A	Existing test	Other services (HIV)
Acuna CID 2008	Y	FASTPlaque-Response, INNO-LiPA, direct LJ, MIT assay indirect LJ	N	N/A	N	N	N	N	LPA	Solid	FASTPlaque-Response, INNO-LiPA, MTT(colorimetric)	Existing test	Dx Rx
Albert 2004 IJTLD	Y	FASTPlaqueTB	N	N/A	N	Y	Y	N	N	Liquid	FASTPlaqueTB	Existing test	Dx
Andrews 2012 AIDS	Y	Xpert	N	N/A	Y	Y	Y	Y	N	Liquid	HYPO: increased sensitivity and 1 day turn over	Existing test	Other services (HIV)
Bonnet 2010 IJTLD	Y	Bleach sedimentation microscopy	N	N/A	N	Y	N	N	N	N	N/A	Existing test	Dx
Dowdy 2003 JCM	Y	Gen-Probe	N	N/A	N	N	N	N	GenProbe	N	N/A	Existing test	Dx Rx
Dowdy 2008 IJTLD	Y	HYPO: Pont of Care Dx	N	N/A	N	Y	N	N	N	Solid	HYPO: POC test	Product profile	Dx Rx
Dowdy 2008 Plos ONE	Y	Culture as first line	N	N/A	N	Y	N	N	N	Liquid & Solid	N/A	Scale-up	Dx Rx
Dowdy 2011 PLosMed	Y	TB serology tests (anda-tb ELISA)	N	N/A	N	Y	N	N	N	Liquid	Serological tests	Existing test	Dx Rx
Guerra 2008 JCM	Y	Gen-Probe (with sample dilution)	N	N/A	N	Y	N	N	GenProbe	N	N/A	Existing test	Dx
Hughes 2012 RespMed	Y	NAAT	N	N/A	N	Y	N	N	Non-specific	Solid	N/A	Existing test	Dx Rx
Langley 2012 HCMS	Y	Xpert	Y	Operational & transmission	N	Y (ZN, LED)	Y	Y	N	Solid	N/A	Existing test	Dx Rx
Lim 2000 Resp	Y	Amplicor assay (PCR), or CT	N	N/A	N	N	N	N	Amplicor, NAAT on BAL	N	CT	Existing test	Dx Rx
Menzies 2012 PMed	Y	Xpert	N	N/A	N	Y	Y	Y	N	Y	N/A	Existing test / Scale-up	other services (HIV)
Meyer-Rath 2012 PLosONE	Y	Xpert	N	N/A	N	Y	Y	Y	LPA	Liquid	non-specific DST	Scale-up	Dx Rx
Rajalahti 2004 ERJ	Y	Amplicor (PCR)	N	N/A	N	Y	N	N	Amplicor	Liquid	CT	Existing test	Dx Rx
Schnippel 2013 SAMJ	Y	Xpert	N	N/A	N	Y	Y	Y	LPA	Liquid	DST (non-specific)	Existing test	Dx Rx
Sun 2013 IJTLD	Y	Urine LAM	N	N/A	N	N	N	N	N	N	Urine LAM	Existing test	Dx Rx

Ref	Novel diagnostic		Model method		Diagnostic tools explicitly modelled							Stage of tech	Health sys scope
					Symp	Sput Smear	Xray	Xpert	Other NAAT	Culture	Other		
Vassall 2011 PLosMed	Y	Xpert	N	N/A	N	Y	Y	Y	LPA	Liquid & Solid	conventional DST	Existing test	Dx Rx
Winetsky 2012 PLoS Med	Y	Xpert, mass miniature radiography (MMR)	N	N/A	Y	Y	Y (MMR)	Y	Sputum PCR with probes for MDR	Liquid & Solid	N/A	Existing test	Dx Rx
SUMMARY		40% evaluate Xpert			10%	80%	45%	40%	50%	70%		5% product profile, 10% scale up	15% limited to Dx only

HYPO = Hypothetical test;

Table 3.4: Modelling methods

Ref	Data fit	Sensitivity		Pre-diag inf	FP	FN	Repeat entry		Drug Susc	HIV	Previous Rx
Abimbola 2012 AIDS	N	Y	one-way	N	N	N	N	N/A	N	Y	N
Acuna CID 2008	N	Y	multi	N	Y	Y	N	N/A	Y	N	N
Albert 2004 IJTLD	N	Y	one-way	N	Y	Y	N	N/A	N	N	N
Andrews 2012 AIDS	N	Y	two-way	N	Y	Y	N	N/A	Y	Y	Y
Bonnet 2010 IJTLD	N	Y	one-way	N	N	N	N	N/A	N	N	N
Dowdy 2003 JCM	N	Y	multi	N	Y	N	N	N/A	N	N	N
Dowdy 2008 IJTLD	N	Y	multi	N	N	N	N	N/A	N	Y	N
Dowdy 2008 PlosONE	N	Y	multi	N	Y	Y	Y	Same	N	Y	N
Dowdy 2011 PLosMED	N	Y	two-way	N	Y	Y	N	N/A	N	Y	N
Guerra 2008 JCM	N	Y	one-way	N	N	N	N	N/A	N	N	N
Hughes 2012 RespMed	N	Y	one-way	N	Y	Y	N	N/A	Y	N	N
Langley 2012 HCMS	N	Y	one-way	Y	Y	Y	Y	Same	Y	Y	Y
Lim 2000 Resp	N	Y	one-way	N	Y	Y	N	N/A	N	N	N
Menzies 2012 PlosMed	Y	Y	multi	Y	N	N	N	N/A	N	N	N
Meyer-Rath 2012 Plos ONE	N	Y	one-way	N	N	N	N	N/A	Y	Y	Y
Rajalahti 2004 ERJ	N	Y	two-way	N	Y	N	N	N/A	Y	N	N
Schnippel 2013 SAMJ	N	Y	one-way	N	N	Y	N	N/A	Y	Y	N
Sun 2013 IJTLD	N	Y	multi	N	Y	N	N	N/A	N	Y	N
Vassall 2011 PLosMED	N	Y	multi	N	N	Y	N	N/A	Y	Y	Y
Winetsky 2012 PLosMed	Y	Y	multi	Y	N	Y	N	N/A	N	Y	Y
SUMMARY	10%	100%	60% one- or two-way	15%	55%	55%	10%		40%	55%	25%

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