TB Modelling and Analysis Consortium

TB Modelling and Analysis Consortium (TB-Mac)

Optimising TB control in high HIV prevalence settings; Modelling and quantitative research priorities

Johannesburg, South Africa

28-29 September 2012

Meeting Report

www.tb-mac.org

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TB Modelling and Analysis Consortium

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3	A priori 'straw man' of modelling research priorities and coverage by published modelling
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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. TB-Mac's first objective is to identify high priority research questions to optimise TB control that would benefit from modelling or other quantitative research. At the first TB-Mac meeting held in September in Johannesburg, the aim was to identify modelling questions to optimise TB control in high HIV prevalence settings.

In preparation for the discussions an a priori list of modelling research priorities was constructed based on a review of existing research agenda documents. A systematic review of the TB-HIV modelling literature was also conducted to give an indication of the existing level of coverage of each research priority.

The meeting was structured in four sessions; 1) Case finding and treatment of active TB, 2) Screening and treatment of latent TB, 3) TB vaccines and 4) Economics of TB control. During these sessions the a priori list was discussed, updated and prioritised, resulting in a final ranked shortlist of high priority TB-HIV modelling questions.

This TB-HIV modelling research agenda is being used to engage with TB modellers to promote work on these TB-HIV modelling questions over the coming months. Funding from the Gates Foundation is likely to be available for some modelling activities in the research agenda and requests for proposals will follow early next year. The TB-HIV modelling research agenda will also be disseminated to key stakeholders and via publication.

1.1

TB Modelling and Analysis Consortium (TB-Mac)

Background

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

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

This led to critical research gaps and conflicting policy recommendations which served TB control poorly. Policy making and resource allocation must be based on scientific consensus derived from best analytic inputs, which draw on data and models in epidemiology, economics, demography and related disciplines. The TB Modelling and Analysis Consortium (TB-Mac, www.tb-mac.org) aims to improve the interaction between quantitative researchers, policy makers, TB programmes and donors to improve global control.

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

1.2

TB-Mac meeting 1: Optimising TB Control in high HIV prevalence settings

This report describes the first TB-Mac meeting in Johannesburg, South Africa which covered the work area "Optimising TB control in high HIV prevalence settings".

Meeting objectives

1. Encourage interaction between HIV-TB modellers, empirical scientists, policy makers and funders
2. Identify key modelling research questions to improve TB control in high HIV prevalence settings.
3. Facilitate getting these research questions answered

Scope of meeting

The focus on high HIV prevalence settings effectively meant the meeting discussed TB control in countries in Eastern and Southern Africa. For the purpose of this meeting, mathematical modelling included economic and operational modelling, but excluded structural (e.g. 3D) and statistical modelling as defined by Garnett et al.[1]. As the issue of multi-drug resistance (MDR) will be a key part of future TB-Mac meetings, and is not restricted to high HIV prevalence settings it was not a focus of this meeting. The emphasis of this meeting was on formulating modelling priorities, which would be followed, but not preceded by identification of key data gaps.

Meeting preparation - Review of modelling and research agendas and creation of 'straw-man' list of a-priori research questions

Research priorities were extracted from three recently published WHO/StopTB research agendas[2][3][4]. These were used because they employed a structured consultation process of a wide range of experts and policy makers, providing the required broad foundation. These priorities were selected because they applied to high HIV prevalence settings and could benefit from mathematical modelling. The extracted priorities are listed in Appendix 2. These were then grouped within each session into broad themes and specific questions (see Appendix 3, first 3 columns).

To get an overview of existing TB modelling work, and to what extent the extracted research questions had already been addressed by modelling work, a systematic literature review was conducted of all TB mathematical modelling papers that applied to settings with high HIV prevalence. In addition to searching Pubmed, we scanned personal reference libraries from the TB-Mac committee members, mathematical biology journals and references from relevant papers. This yielded 75 relevant papers which were matched to the research questions from the priorities review (see Appendix 3, final column). The 'straw-man' list of a priori modelling research questions was

[1] Garnett et al. Lancet *(**2011**)*; 378: 515–25
[2] An international roadmap for tuberculosis research, *(**2011**) Stop TB partnership*
[3] Priorities in operational research to improve tuberculosis care and control, *(**2011**) Stop TB Partnership*
[4] Priority research questions for tuberculosis/human immunodeficiency virus (TB/HIV) in HIV-prevalent and resource-limited settings, *(**2010**) World Health Organisation*

created for discussion in the sessions, by comparing the extracted research questions to the modelling work identified in the systematic review of the modelling literature.

Structure and process of meeting

The meeting was structured in 4 sessions (see agenda in Appendix 1):

1. Case finding and treatment of active TB
2. Screening and treatment of latent TB
3. TB vaccines
4. Economics of TB

To initiate the discussion in each session, and to identify and rank high priority TB-HIV modelling research questions, an a priori list of research priorities was presented to guide discussions. This 'straw man' list was created by comparing research priorities in TB/HIV indentified from existing research agendas that would benefit from modelling, with existing published TB modelling publications (see 'meeting preparation' section for details).

Each session consisted of a presentation on the 'straw man' list of research priorities, followed by three presentations on selected quantitative and modelling research in the area. The modelling research questions were then discussed, updated and ranked (see next section for lists). Attendees were asked to identify questions that 1) required modelling to provide the answers, 2) could be addressed with existing or accessible data and would therefore 3) be achievable short term (within the next 2 years). After consolidating the outcomes of the brainstorm sessions, the attendees then ranked the questions.

1.3

MEETING DISCUSSIONS AND RESULTS

DAY 1

1.3.1

Session 1: How can case finding and treatment of active TB cases be optimised for TB control in high HIV prevalence settings?

This session was chaired by Geoff Garnett (Bill and Melinda Gates Foundation) and the discussant was Mark Nicol (University of Cape Town). The session covered active and passive case finding as well as the new treatment approaches to improve TB control. Its rather broad scope was reflected in the long list of 'straw man' research questions included in this work area (see Appendix 3). It also showed a paucity of existing operational modelling work in this area.

Katharina Kranzer (London School of Hygiene and Tropical Medicine) presented an overview of the current empirical data on active vs. passive case finding, followed by a presentation by David Dowdy

(Johns Hopkins Bloomberg School of Public Health) and Pete Dodd (London School of Hygiene and Tropical Medicine) on modelling methods used to study the relative impact of active, enhanced and passive case finding. Finally Philip Glaziou (World Health Organisation) reported on models to better interpret the limited data on TB related mortality in populations.

The research priorities identified in this session ranged from the highly practical (Q6 – estimating the impact of reducing initial default), to comparing 'hidden' model assumptions (Q10 – the assumed proportion of TB due to recent infection), and for the potential use of models a tool for National TB programme managers and policy makers (Q4 and Q7) (see table 1).

1.3.2

Session 2: How can screening and treatment of latent *M.tuberculosis* (Mtb) infection be optimised for TB control in high HIV prevalence settings?

Gavin Churchyard (The Aurum Institute) chaired this session and Rueben Granich (UNAIDS) led the discussions. The a priori 'straw man' (Appendix 3) showed that the main areas in need of modelling were the individual level benefit of isoniazid preventive therapy (IPT) and ART, as well as the duration of protection offered.

During the session Amitabh Suthar (World Health Organisation) and Alison Grant (London School of Hygiene and Tropical Medicine) reviewed the evidence on the extent and duration of protection IPT and ART offer HIV positive individuals against developing TB disease. Brian Williams (South African Centre for Epidemiological Modelling and Analysis) presented on the relationship between ART, CD4 count and risk of TB disease. Emilia Vynnycky (London School of Hygiene and Tropical Medicine) then presented on modelling IPT for TB control.

The discussions focussed on how various TB prevention approaches could be combined to maximise impact, and how modelling could explore the additive effect of each intervention when other approaches were already in place and functioning well.

The resulting research questions were combined with those from session 1 (see table 1) for ranking by the attendees.

1.3.3

Ranking of questions Day 1

There was considerable overlap between research questions from both sessions on day 1 and therefore they were consolidated before ranking. Table 1 shows the ten (2x5) questions from day 1.

Table 1. High priority modelling questions on screening and treatment of active and latent TB

Rank	Priority modelling question
1	Can a more complicated model estimate the impact of a range of combination TB prevention strategies?
2	What is the most (cost-)effective case finding strategy, (outbreak control/targeted/mass treatment/multi-disease)?
3	Can models help us understand the duration of (I)PT protection in different settings?
4	Can a simple algorithm be defined to guide optimal case finding approaches for national programme staff and policy makers based on the following epidemiological data (ARI; Case Notification Rate; HIV prevalence)?
5	Can models be used to quantify uncertainties in the natural history of Mtb that are relevant for decision making, and make recommendations for how to prioritise data collection activities?
6	What is the impact of reducing initial default and improving cure rates?
7	Would a highly simplified, user friendly model for TB still be useful for policy makers?
8	What is the (cost-)effectiveness of new point of care diagnostic tests and algorithms?
9	Can we use models to define proxy measure of intervention impact?
10	Should we do a formal model comparison on the proportion of TB due to recent infection and the estimated ARI?

1.3.4

DAY 2

Session 3: How could TB vaccines be optimised for TB control in high HIV prevalence settings?

Willem Hanekom (South African Tuberculosis Vaccine Initiative) chaired this session and the discussions were led by Jacqui Shea (Oxford-Emergent Tuberculosis Consortium). The 'straw man' (Appendix 3) used to start discussions showed an overall paucity of modelling activity on vaccines mechanisms and impact in high HIV prevalence settings, reflecting the complexity of TB immunology which is further clouded by the presence of HIV.

Laura Rodrigues (London School of Hygiene and Tropical Medicine) discussed how lessons learned from the current BCG vaccine can inform work on future vaccines. Suzanne Verver (KNCV Tuberculosis Foundation) then presented an overview of epidemiological issues surrounding the introduction of vaccines. Finally Ted Cohen (Brigham and Women's Hospital / Harvard School of Public Health) illustrated the additional complexities involved in modelling the impact of a vaccine on TB control.

After discussion and ranking, the high priority modelling questions (table 2), covered the basic evaluation of the potential impact of specific vaccines or new markers/diagnostic tests (Q1, Q4, Q5a) as well as applied models to aid vaccine candidate selection, and models to elucidate the impact of Mtb strain variability on vaccine efficacy (Q5b).

Table 2: High priority modelling questions on TB vaccines

Rank	Priority modelling question
1	Which vaccine strategy (pre-exposure, post-exposure or therapeutic) and in which target populations (infants, adolescents/young adults, HIV-infected), would have the most impact on the TB epidemic in varying TB/HIV/MDR settings and at community, country and global level, over the next 5, 10 or 15 years?
2	How do we best select vaccine candidates from the current pipeline for progression to efficacy evaluation in Phase IIb/Phase III trials?
3	How can we improve the design of vaccine clinical trials to take into account changing epidemiology, point of intervention, new biomarkers and combination with other TB/HIV interventions?
4	How will new biomarkers impact on the choice of populations to vaccinate and the development of new TB vaccines?
5a*	How would a new highly specific diagnostic test to detect recent infections/latency affect vaccine development and implementation?
5b*	How does TB strain variability affect vaccine development and efficacy?

**During the ranking by the meeting attendees 2 questions tied for fifth place*

1.3.5

Session 4: How can economics help us optimise TB control in high HIV prevalence settings?

This session was chaired by Anna Vassall (London School of Hygiene and Tropical Medicine) with the discussions led by David Dowdy. Initial work on the 'straw man' (Appendix 3) had highlighted that most work had been done on cost-effectiveness of (new) interventions, and little work on programmatic impacts and operational research. During the meeting it became clear that there is a lack of detailed data required to populate such models, as well as the lack of TB specific knowledge in operational research modelling techniques are the main limiting factors for widespread use of these models.

The session explicitly looked beyond cost-effectiveness studies, and report on the broader issues surrounding the financing of TB control measures by countries. This was highlighted in the presentation by Christopher Fitzpatrick (World Health Organisation), who discussed the financial constraints for expanding TB/HIV services. Nick Menzies (Harvard University) highlighted the importance of incorporating full and long term ART costs in models for TB prevention, as well as considering TB related and HIV related health effects together, despite the complexity it adds. In his presentation, Till Bärnighausen (Africa Centre) gave an overview of lessons that could be learned from economic modelling for HIV, in particular when considering a combination of interventions.

During the discussions, 4 economic modelling research priorities were identified as shown in table 3.

Table 3: High priority modelling questions on the economics of TB control

Rank	Priority modelling question
1	What is the most cost-effective combination of existing TB control interventions in high HIV prevalence settings? Consider in particular: - All types of intervention - detection, diagnosis, treatment, prevention, structural or social - That models need to be generalisable and account for time, the intervention needs to be feasible as well as practical and specific - This requires an initial evaluation of economies of scale – what is the reduction of costs per unit (e.g. confirmed diagnosis) if intervention is implemented widely?
2	Develop models to study operational processes or that would allow combined operational-economic evaluation
3	Apply operational modelling to efficiency/value-for-money of various systems
4	Macroeconomic modelling to examine funding needs & gaps by country or region, and in short/long term
5	*Not specified*

1.4

OUTPUTS AND NEXT STEPS

By identifying key priorities for TB modelling in high HIV prevalence settings the meeting achieved the first objective of TB-Mac. The consortium is already engaging with TB modellers to stimulate work on the high priority questions formulated here (objective 2). Dissemination of the results (objective 3) will happen through this report (available for download from the TB-Mac website (http://www.tb-mac.org/WorkAreas/WorkArea/1), a newsletter for which we will invite the wider TB community to sign up (http://www.tb-mac.org/Home/SignUp) and a peer reviewed publication summarising the key research needs. We will also engage with national programme managers and policy makers to ask for their ranking of these questions.

The meeting was a successful first step in bringing the TB modelling community closer together. In future TB-Mac will build on this solid start and will look to expand the TB modelling community, by including more TB modellers, and attracting modellers from other fields to the exciting field of TB. Finally the research priorities formulated here can serve as motivation with funders to increase their funding for TB modelling.

APPENDICES

1. Meeting agenda
2. Full list of extracted research priorities
3. A priori ‘straw man’ of modelling research priorities and coverage by published modelling
4. Participant list

APPENDIX 1: AGENDA

TB Modelling and Analysis Consortium

BILL & MELINDA GATES foundation

Optimising TB control in high HIV prevalence settings - Modelling and quantitative research priorities

28-29th Sept 2012, Nina Room, Hyatt Regency, Johannesburg, South Africa

richard.white@lshtm.ac.uk or dyec@who.int

Please keep presentations within time. All times include time for discussion and clarification (ie 15 minute slot => 10 minutes presentation, 5 minutes discussion)

Thur 27th			
18:00+	*Optional pre-meeting reception (Jabulani Room)*	All present welcome	
Fri 28th	**Introductions and overview**	**Speaker**	**Chair**
08:45 - 09:15	*Welcome Refreshments (outside Nina room)*		
09:15 - 09:25	**Welcome**	**Michael Kimerling (BMGF)**	**Gavin Churchyard (Aurum)**
09:25 - 09:40	TB-Mac and meeting aims	Richard White (LSHTM)	
09:40 - 09:55	Key policy/practical questions for TB control in high HIV prevalence settings	Lindiwe Mvusi (SA MoH)	
09:55 - 10:10	Key empirical uncertainties in TB/HIV epidemiology for control	Liz Corbett (MLW/LSHTM)	
10:10 - 10:35	A-priori *'straw-man'* list of modelling TB/HIV research priorities	Rein Houben (LSHTM)	
	Question 1: How can case finding and treatment of active TB cases be optimised for TB control in high HIV prevalence settings?		**Geoff Garnett (BMGF) (TBC)**
10:35 - 10:40	Overview	Richard White (LSHTM)	
10:40 - 10:55	Review of data on passive vs. active/enhanced case finding studies	Katharina Kranzer (UCT)	
10:55 - 11:10	Modelling of improved passive case finding vs. enhanced vs. active case finding	Pete Dodd (LSHTM) & David Dowdy (JHSPH)	
11:10 - 11:25	Measuring and modelling TB-HIV mortality	P Glaziou (WHO)	
11:25 - 11:55	*Refreshments (outside Nina room)*		
11:55 - 13:25	Discussion (Refining list of modelling research priorities)	Mark Nicol (UCT)	
13:25 - 14:40	*Lunch (outside Nina room)*		
	Question 2: How can screening and treatment of LTBI be optimised for TB control in high HIV prevalence settings?		**Gavin Churchyard (Aurum)**
14:40 - 14:45	Overview	Richard White (LSHTM)	
14:45 - 15:00	Review of data on ART and IPT for TB control	ART: Amitabh Suthar (WHO) IPT: Alison Grant (LSHTM)	
15:00 - 15:15	Modelling ART for TB control	Brian Williams (SACEMA)	
15:15 - 15:30	Modelling IPT for TB control	Emilia Vynnycky (LSHTM)	
15:30 - 16:00	*Refreshments (outside Nina room)*		
16:00 - 17:30	Discussion (Refining list of modelling research priorities)	Reuben Granich (WHO)	
18:30 +	*Consortium meal (Jabulani Room)*		

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28-29th Sept 2012, Nina Room, Hyatt Regency, Johannesburg, South Africa

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Sat 29th		Speaker	Chair
09:00 - 09:45	Discussion of day one questions	Brian Williams	**W Hanekom (UCT)**
	Question 3: How could TB vaccines be optimised for TB control in high HIV prevalence settings?		**W Hanekom (UCT)**
09:45 - 09:50	Overview	Richard White (LSHTM)	
09:50 - 10:05	Lessons from BCG mode of action & implications for investigating impact of new vaccines	Laura Rodrigues (LSHTM)	
10:05 - 10:20	Epidemiological background to vaccine introduction	Suzanne Verver (KNCV)	
10:20 - 10:35	Modelled impact of TB vaccines versus other TB control strategies	Ted Cohen (Harvard)	
10:35 - 11:05	*Refreshments (outside Nina room)*		
11:05 - 12:05	Discussion (List and rank modelling research priorities)	Jacqui Shea (Oxford Emergent)	
	Question 4: How can economics help us optimise TB control in high HIV prevalence settings?		**Anna Vassal (AIGHD/ LSHTM)**
12:05 - 12:10	Overview	Anna Vassal (AIGHD/ LSHTM)	
12:10 - 12:25	Financing for TB control: what are the constraints for the expansion of TB/HIV services?:	Christopher Fitzpatrick (Stop TB/ WHO)	
12:25 - 12:40	Incorporating ART costs into TB economic evaluations	Nick Menzies (Harvard)	
12:40 - 12:55	Cost-effectiveness analysis of combined interventions: treatment of prevention in South Africa	Salal Humar (Harvard)	
12:55 - 13:55	*Lunch*		
13:55 - 14:55	Discussion (List and rank modelling research priorities)	David Dowdy (JHSPH)	
14:55 - 15:25	*Refreshments (outside Nina room)*		
	Overall discussion		**Richard White (LSHTM)**
15:25 - 17:00	Final discussion of modelling research priorities	Brian Williams (SACEMA)	

APPENDIX 2: FULL LIST OF EXTRACTED RESEARCH PRIORITIES

(A)CF and Active TB research questions		Proposed model type		
#	Research Priority	1	2	Source
A1	Project a number of suitable options of diagnostic approaches or packages for potential implementation, to identify new programmatic approaches, to improve access, screening and diagnosis of TB.	1 Epi - Dyn trans	5 OR	1 WHO OpRes
A2	Optimize implementation of a new diagnostic tool/packages, to improve access, screening and diagnosis of TB	1 Epi - Dyn trans	5 OR	1 WHO OpRes
A3	Forecast operational requirements including costs and impact on transmission, by modelling expected impact and implications of scale-up, to evaluate the impact of scale-up of a new test or new package of tests, to improve access, screening and diagnosis of TB.	1 Epi - Dyn trans	5 OR	1 WHO OpRes
A4	How early to start antiretroviral therapy (i.e. at what CD4 count level) among HIV-infected TB patients, to achieve maximum reduction in the risk of developing TB?	2 Epi - cohort		2 WHO TB-HIV
A5	What are the best infection control interventions that effectively reduce M. tuberculosis transmission (both drug susceptible and resistant) in health-care settings, at home and in the community?	1 Epi - Dyn trans		2 WHO TB-HIV
A6	What are the best operational models to assess the impact of infection control measures in reducing the spread of M. tuberculosis to HIV-infected adults and children?	1 Epi - Dyn trans	5 OR	2 WHO TB-HIV
A7	What are the definition, true prevalence, natural history and importance of subclinical TB, particularly for people living with HIV?	1 Epi - Dyn trans		2 WHO TB-HIV
A8	What is the best model to eliminate diagnostic delay and hasten treatment initiation for TB using existing tools, including the efficacy of the revised WHO algorithm for smear-negative TB on mortality among HIV-infected patients with suspected TB?	2 Epi - cohort	1 Epi - Dyn trans	2 WHO TB-HIV
A9	What is the optimal timing and frequency of systematic TB screening among people living with HIV?	2 Epi - cohort	1 Epi - Dyn trans	2 WHO TB-HIV
A10	What is the programmatic impact of the most promising diagnostic tools currently available for rapid TB diagnosis, including diagnosis of drug resistance and of smear-negative patients identified through large-scale evaluation studies?	1 Epi - Dyn trans	5 OR	2 WHO TB-HIV
A11	What is the role of contact tracing in intensified TB (and HIV) case-finding at the population level?	1 Epi - Dyn trans		2 WHO TB-HIV
A12	What is the simple and rapid point-of-care "TB dipstick test" to diagnose all types (smear-positive and negative pulmonary, extrapulmonary drug susceptible and drug resistant) of TB in all patients, including children and people living with HIV?	2 Epi - cohort		2 WHO TB-HIV
A13	What are the best first and second-line antiretroviral therapy regimens in terms of safety, efficacy, tolerability, optimal dosage of drugs and drug interactions, to use in combination with a rifampicin-based TB regimen?	3 W/in host		2 WHO TB-HIV
A14	What are the optimal length and dosage of rifampicin-based TB treatment in adults and children living with HIV?	3 W/in host		2 WHO TB-HIV
A15	What are the safety, efficacy and pharmacokinetic parameters of new and novel drugs that could replace rifampicin and shorten TB treatment, to cure susceptible and drug-resistant TB in people living with HIV, with or without antiretroviral therapy (either first or second-line antiretroviral therapy)?	3 W/in host		2 WHO TB-HIV
A16	What are the safety, efficacy, optimal dosage and drug interactions of rifabutin in curing active TB, preventing TB relapse and preventing acquired rifamycin resistant failures in people living with HIV on antiretroviral therapy, possibly including integrase inhibitor based regimens?	3 W/in host	2 Epi - cohort	2 WHO TB-HIV
A17	What are the programmatic impact and benefit to individual treatment outcomes of line probe assays and other non-culture-based assays for diagnosis of drug-resistant TB at the peripheral level of care?	2 Epi - cohort	5 OR	2 WHO TB-HIV

(A)CF and Active TB research questions		Proposed model type		
#	Research Priority	1	2	Source
A18	What are the surveillance or clinical criteria that allow facility-based MDR-TB and XDR-TB outbreaks to be identified and responded to rapidly?	1 Epi - Dyn trans		2 WHO TB-HIV
A19	What are the true burden, predictors and transmission dynamics of MDR-TB and XDR-TB in high HIV prevalence and resource-limited settings?	1 Epi - Dyn trans		2 WHO TB-HIV
A20	What is the impact of concurrent HIV infection on transmission, acquisition and progression of drug resistant TB in people living with HIV with or without antiretroviral therapy?	1 Epi - Dyn trans		2 WHO TB-HIV
A21	What are the global and regional burden and dynamics of childhood TB and the impact of HIV?	1 Epi - Dyn trans		2 WHO TB-HIV
A22	What are the safety, tolerability, pharmacokinetic parameters and drug interactions of new and novel anti-TB drugs in pregnant women and nursing mothers?	3 W/in host		2 WHO TB-HIV
A23	What is the efficacy, feasibility and acceptability of community-based models for MDR-TB treatment and management, and what are the implications on M. tuberculosis transmission, particularly among people living with HIV, and on resource allocation	1 Epi - Dyn trans	4 CE/Decision	2 WHO TB-HIV
A24	What are the best models of delivery of collaborative TB/HIV interventions to most-at-risk and special populations in all settings with different TB and HIV epidemiology and epidemic states?	1 Epi - Dyn trans	5 OR	2 WHO TB-HIV
A25	What are the best operational models to increase and scale-up laboratory capacity, including implementing new TB diagnostic techniques and drug-susceptibility testing, and improve diagnosis of TB at all levels of care?	1 Epi - Dyn trans	5 OR	2 WHO TB-HIV
A26	What are the best strategies and optimal models to integrate and deliver joint TB/HIV interventions, including antiretroviral therapy, at community and health sector levels to HIV-infected TB adults, children and families?	1 Epi - Dyn trans	5 OR	2 WHO TB-HIV
A27	What are the best strategies to promote and scale-up of integrated screening of HIV infection and TB infection and disease among household contacts of HIV-infected TB patients?	1 Epi - Dyn trans	5 OR	2 WHO TB-HIV
A28	What is the cost-effectiveness of joint TB/HIV interventions delivered through a community approach and through health facilities?	1 Epi - Dyn trans	4 CE/Decision	2 WHO TB-HIV
A29	What is the efficacy, feasibility and acceptability of community-wide or targeted community interventions for TB and HIV prevention and care in HIV-prevalent settings?	1 Epi - Dyn trans		2 WHO TB-HIV
A30	What is the relative contribution of community versus health facility transmission of susceptible and drug-resistant TB?	1 Epi - Dyn trans		2 WHO TB-HIV
A31	What are the best models of community participation (i.e. effective, feasible, acceptable and sustainable) for enhanced TB case-finding and early HIV detection, to reduce delay in initiation of TB and HIV care, and their impact on reducing TB and HIV transmission?	1 Epi - Dyn trans		2 WHO TB-HIV
A32	What are the predictors of infectiousness of HIV-infected TB patients, particularly those with drug-resistant TB?	3 W/in host		3 WHO R_Map
A33	What are the relative contributions of the various foci of TB transmission (e.g. household, community, nosocomial transmission) at the population level, and what are the roles of the various demographic and social factors in specifi c settings?	1 Epi - Dyn trans		3 WHO R_Map
A34	What are the social determinants of M. tuberculosis transmission in populations, what is their contribution to the risk of TB, and how could these be targeted in control programmes? (from the Disease Reference Group)	1 Epi - Dyn trans		3 WHO R_Map

(A)CF and Active TB research questions		Proposed model type		
#	Research Priority	1	2	Source
A35	What is the best programmatic model for surveillance in TB control in terms of epidemiology and management?	1 Epi - Dyn trans	5 OR	3 WHO R_Map
A36	What is the impact of DOTS implementation on the burden of disease?	1 Epi - Dyn trans	4 CE/Decision	3 WHO R_Map
A37	How can the existing diagnostic tests be most effi ciently combined to optimize detection of drug sensitive and drug-resistant TB in different population settings (children, people living with HIV) and at all health-care levels so as to minimize morbidity, mortality and transmission of TB?	1 Epi - Dyn trans	4 CE/Decision	3 WHO R_Map
A38	What are the cost-effectiveness, the human resource implications, the outcomes of patients with suspected TB and the benefits to patients (including improved cure rates, proportion of patients completing therapy and reduction in treatment failure) of introducing the novel diagnostic test or combination of tests?	4 CE/Decision	5 OR	3 WHO R_Map
A39	What does 'impact' mean? What important outcomes with respect to patients, populations, health systems and epidemiology should be measured to assess the impact of improved diagnostic products? Which preliminary data are required to allow analysis and prediction of the impact?	1 Epi - Dyn trans	5 OR	3 WHO R_Map
A40	What programmatic impact does the introduction of novel diagnostic tools or a combination of existing and novel diagnostic tools have on the detection of smear-negative TB (implementation, feasibility, equitable access by all patients, cost-effectiveness, patient outcomes and diagnostic delay in routine settings)?	5 OR	4 CE/Decision	3 WHO R_Map
A41	What will be the role of simplifi ed nucleic acid amplifi cation tests in the diagnosis of TB in resourcelimited settings, and what are the implications for replacement of smear microscopy? What is their performance in high HIV prevalence settings, in the diagnosis of active TB in children of various ages and in the diagnosis of extrapulmonary TB?	5 OR		3 WHO R_Map
A42	What are the optimal dosage, safety and effi cacy of novel TB drugs (in all populations, including children and HIV-infected people)? How can existing and novel TB drugs be optimally combined into safe, well-tolerated multidrug regimens that minimize drug–drug interactions and ensure an effective (i.e. relapse-free) cure?	2 Epi - cohort		3 WHO R_Map
A43	What are the safety, effi cacy and optimal dosage of rifabutin? What are its drug interactions in TB treatment? How can we best prevent acquired rifamycin-resistant failure in HIV-infected people receiving ART?	3 W/in host		3 WHO R_Map
A44	What is the interaction between existing second-line TB drugs and antiretroviral drugs, and how can adverse events be best recognized and managed?	3 W/in host		3 WHO R_Map
A45	What are the optimal length and dosage of rifamycin-based TB treatment in children and in people living with HIV? Are the currently recommended doses too low? How can the sterilizing activity be maximized, and what would be the effect of higher dosages on safety, toxicity and interactions with other TB drugs or ART?	3 W/in host		3 WHO R_Map
A46	What are the feasibility, impact and cost-effectiveness of automated, cartridge-based nucleic acid amplifi cation tests if used at the point of care?	1 Epi - Dyn trans	4 CE/Decision	3 WHO R_Map
A47	How can diagnostic services be brought nearer to the community (e.g. decentralization, active case-finding, mobile systems)? How effective are these methods, and how can they be integrated into the general health system, including HIV and maternal and child health programmes?	1 Epi - Dyn trans	5 OR	3 WHO R_Map
A48	What are the best operational models for enhanced TB case-fi nding among HIV-infected patients in HIV service facilities and at community level, in settings with high and low HIV prevalence?	1 Epi - Dyn trans	5 OR	3 WHO R_Map

(A)CF and Active TB research questions		Proposed model type		
#	Research Priority	1	2	Source
A49	Which high-risk populations should be screened for drug-susceptible, MDR- and XDR-TB; when should they be screened, and for what should they be screened?	1 Epi - Dyn trans	4 CE/Decision	3 WHO R_Map

Latent TB research questions		Proposed model type		
#	Research Priority	1	2	Source
L1	Prevention and treatment of TB in persons living with HIV: Models to improve adherence to IPT: Identifying operational requirements	5 OR		1 WHO OpRes
L2	What are the operational models to scale-up isoniazid preventive therapy in HIV care settings, including frequency of symptom screening, monitoring tools and measures to maintain high adherence among health workers?	5 OR		2 WHO TB-HIV
L3	What is the best administration schedule of preventive TB therapy in HIV-infected patients (repeated courses or lifelong preventive therapy)?	2 Epi - cohort	5 OR	2 WHO TB-HIV
L4	What is the durability of effect of different combination of preventive TB therapy (isoniazid preventive therapy and other multidrug short course regimens)?	2 Epi - cohort		2 WHO TB-HIV
L5	What is the effect of isoniazid preventive therapy on the emergence of drug resistance (especially on isoniazid and rifampicin)?	1 Epi - Dyn trans		2 WHO TB-HIV
L6	What is the optimal duration, safety, efficacy and cost-effectiveness of isoniazid preventive therapy alone or added with antiretroviral therapy in reducing the risk of active TB compared to antiretroviral therapy alone among people living with HIV, particularly under programme conditions?	4 CE/Decision		2 WHO TB-HIV
L7	What is the optimal TB preventive therapy regimen in terms of efficacy, safety, tolerability and duration of protection to be used in HIV-infected adults and children, and other special populations, such as pregnant women and people with underlying liver disease?	2 Epi - cohort		2 WHO TB-HIV
L8	What is the impact of an early start of antiretroviral therapy (in terms of CD4 count) on clinical outcomes and on transmission of drug-resistant TB?	2 Epi - cohort	1 Epi - Dyn trans	2 WHO TB-HIV
L9	What is the safety, efficacy, tolerability and optimal dosage of a single drug or combination of drugs to treat contacts of MDR-TB patients to prevent TB, including children, people living with HIV and pregnant women?	3 W/in host		2 WHO TB-HIV
L10	What is the effect of antiretroviral therapy in preventing TB in children?	2 Epi - cohort	1 Epi - Dyn trans	2 WHO TB-HIV
L11	What is the impact of antiretroviral therapy to prevent mother-to-child transmission of HIV on maternal and child TB transmission and epidemiology?	1 Epi - Dyn trans		2 WHO TB-HIV
L12	What is the optimal timing for preventive therapy in pregnant women and nursing mothers (antenatal vs. postnatal)?	1 Epi - Dyn trans		2 WHO TB-HIV
L13	How can the organization and provision of TB treatment and ART be optimally combined in health centres, TB programmes and HIV programmes for better TB and HIV control (including screening for TB, initiation of isoniazid preventive therapy, early start of ART and infection control)?	1 Epi - Dyn trans	5 OR	2 WHO TB-HIV
L14	What would be the probable epidemiological impact of widespread latent tuberculosis infection diagnosis and treatment on TB transmission in high-burden countries?	1 Epi - Dyn trans		3 WHO R_Map
L15	What is the optimal TB preventive therapy in terms of effi cacy, safety, tolerability and duration of protection that can be used in HIV-infected adults and children, particularly those receiving ART?	2 Epi - cohort		3 WHO R_Map
L16	Can novel drugs rapidly kill latent or persisting bacilli in people with latent TB infection? If so, how should they be optimally combined to introduce a safer, shorter, more effi cacious preventive drug regimen for adults and children (including HIV-infected people and patients receiving ART)?	3 W/in host		3 WHO R_Map

Latent TB research questions		Proposed model type		
#	Research Priority	1	2	Source
L17	What are the optimal drug combinations in terms of tolerability, effi cacy, safety and adherence for contacts of patients with MDR-TB, including children and HIV-infected people?	2 Epi - cohort	1 Epi - Dyn trans	3 WHO R_Map

TB Vaccines and immunology research questions		Proposed model type		
#	Research Priority	1	2	Source
V1	What are the clinical and immunological dual effects of HIV and TB on mother-to-child transmission of HIV and TB, and maternal and perinatal outcomes?	1 Epi - Dyn trans		2 WHO TB-HIV
V2	What is the role and best strategy to improve BCG vaccine efficacy and safety in HIV-infected infants and children, including deferring BCG until HIV-infection status is known?	2 Epi - cohort		2 WHO TB-HIV
V3	What is the role of BCG in prevention of TB in HIV-infected infants?	2 Epi - cohort		2 WHO TB-HIV
V4	Can an immune response to the pathogen or a vaccine prevent infection, i.e. Block adherence to or invasion of M. tuberculosis in lung cells and tissues (mucosal immunity)?	3 W/in host		3 WHO R_Map
V5	How does M. tuberculosis interact with the immune system during the various phases of progression from infection to disease?	3 W/in host		3 WHO R_Map
V6	What components of the immune system and what components of the pathogen are responsible for elimination of M. tuberculosis or for preventing reactivation of latent TB infection?	3 W/in host		3 WHO R_Map
V7	What marks the transition between the key stages of human TB along the infection–disease spectrum, and what are the bacterial or host markers that indicate where an individual is placed along the spectrum and predict which individuals will progress from one phase of the spectrum to the next and why?	3 W/in host		3 WHO R_Map
V8	Which biomarker or combinations of biomarkers will help distinguish the various stages of the spectrum of TB infection (from sterilizing immunity to active disease) and will allow accurate identifi cation of patients at each level, including detection of latently infected people who are at highest risk for progression to disease? Which specific platform and which human samples (e.g. sputum, blood or urine) will be most useful?	3 W/in host		3 WHO R_Map
V9	Why and how, in some individuals, does M. tuberculosis subvert the immune response, to induce a chronic infl ammatory state with ineffective elimination of bacteria?	3 W/in host		3 WHO R_Map
V10	How can the defi nition of clinical end-points for vaccine trials be improved, particularly for infants and HIV-infected individuals?	2 Epi - cohort		3 WHO R_Map
V11	How can we better understand the immune responses in various populations (HIV-infected and uninfected; various ages, from infancy to adolescence and adulthood) so as to devise optimal strategies for vaccination?	3 W/in host		3 WHO R_Map

TB Modelling and Analysis Consortium

APPENDIX 3: A PRIORI 'STRAW MAN' OF MODELLING RESEARCH PRIORITIES

1. **Meeting session 1: (A) CF and Active TB**
2. **Meeting session 2: Latent Mtb infection**
3. **Meeting session 3: Vaccines and Immunology**
4. **Meeting session 4: Economics and Operational Research**

Research themes for modelling

Meeting session 1: (A)CF and Active TB

Theme	Broader question	Research questions (see 'Full list' document)	Modelling papers addressing qu.	
(A)CF, diagnosis of TB	New (combinations of) diagnostic tools	A1, A2, A3, A8, A10, A12, A17, A25, A37, A38, A39, A40, A41, A46, A47	**Basu, 2007**	*Prevention of nosocomial transmission of extensively drug-resistant tu*
			Currie, 2005	*Cost, affordability and cost-effectiveness of strategies to control tub*
			Dowdy, 2006	*The potential impact of enhanced diagnostic techniques for tubercu*
			Dowdy, 2008	*Impact of enhanced tuberculosis diagnosis in South Africa: a mathe*
			Dye, 2000	*Criteria for the control of drug-resistant tuberculosis*
			Lin, 2011	*A modelling framework to support the selection and implementation of*
			Sanchez, 2008	*Impact of HIV on novel therapies for tuberculosis control*
	Xpert remit (i.e. NAAT or integrated DR testing)	A17, A25, A37, A41, A46	**Abimbola, 2012**	*Cost-Effectiveness of Tuberculosis Diagnostic Strategies to Redu*
			Andrews, 2012	*The cost-effectiveness of routine tuberculosis screening with Xper*
			Meyer-Rath, 2012	*The Impact and Cost of Scaling up GeneXpert MTB/RIF in So*
			Vassall, 2011	*Rapid diagnosis of tuberculosis with the Xpert MTB/RIF assay in hi*
	Who to screen for TB	A11, A27, A49, A31	**Basu, 2007**	*Prevention of nosocomial transmission of extensively drug-resistant tu*
			Basu, 2011	*Addressing institutional amplifiers in the dynamics and control of tube*
			Dowdy, 2006	*The potential impact of enhanced diagnostic techniques for tubercu*
			Lin, 2011	*A modelling framework to support the selection and implementation of*
			Mellor, 2011	*Incorporating household structure into a discrete-event simulation m*
	ACF vs PCF: Timing, frequency of screening	A9, A48	**Dodd, 2011**	*Periodic active case finding for TB: when to look?*
			Dowdy, 2006	*The potential impact of enhanced diagnostic techniques for tubercu*
			Mellor, 2011	*Incorporating household structure into a discrete-event simulation m*
			Sanchez, 2008	*Impact of HIV on novel therapies for tuberculosis control*
Optimising TB Rx regimens	with regard to safety, outcome and interaction with ART	A4, A13, A14, A15, A16, A22, A42, A43, A44, A45	**Basu, 2007**	*Prevention of nosocomial transmission of extensively drug-resistant tu*
			Currie, 2005	*Cost, affordability and cost-effectiveness of strategies to control tub*
			Jonsson, 2011	*Population pharmacokinetics of ethambutol in South African tuber*
			Manabe, 2012	*Rifampicin for continuation phase tuberculosis treatment in Ugand*
			Peloquin, 1997	*Population pharmacokinetic modeling of isoniazid, rifampin, and*
			Sanchez, 2008	*Impact of HIV on novel therapies for tuberculosis control*

Theme	Broader question	Research questions (see 'Full list' document)	Modelling papers addressing qu.
			Srivastava, 2011 *Multidrug-resistant tuberculosis not due to noncompliance but t*
			Wilkins, 2008 *Population pharmacokinetics of rifampin in pulmonary tuberculosi*
Optimising infection control	What are the best infection control measures	A5, A6	**Basu, 2007** *Prevention of nosocomial transmission of extensively drug-resistant tu*
			Basu, 2009 *Averting epidemics of extensively drug-resistant tuberculosis*
Burden and transmission of TB	… of active (i.e. with clinical signs) TB?	A30, A33, A34	**Bermejo, 1992** *Tuberculosis incidence in developing countries with high prevalen*
			Bhunu, 2009 *Modeling HIV/AIDS and tuberculosis coinfection*
			Currie, 2003 *Tuberculosis epidemics driven by HIV: is prevention better than cur*
			Dolin, 1994 *Global tuberculosis incidence and mortality during 1990-2000*
			Dye, 1998 *Prospects for worldwide tuberculosis control under the WHO DOTS sti*
			Dye, 2000 *Criteria for the control of drug-resistant tuberculosis*
			Escombe, 2008 *The infectiousness of tuberculosis patients coinfected with HIV*
			Hughes, 2006 *Modeling tuberculosis in areas of high HIV prevalence*
			Massad, 1993 *Modeling the interaction between aids and tuberculosis*
			Murray 2002 *Determinants of cluster distribution in the molecular epidemiology*
			Naresh, 2009 *Modelling the effect of tuberculosis on the spread of HIV infection i*
			Porco, 2001 *Amplification dynamics: predicting the effect of HIV on tuberculosis*
			Raimundo, 2002 *The Attracting Basins And The Assessment Of The Transmission*
			Roeger, 2009 *Modeling TB and HIV co-infections*
			Sanchez, 2009 *Incongruent HIV and tuberculosis co-dynamics in Kenya: interacti*
			Schinazi 2002 *On the role of social clusters in the transmission of infectious disea*
			Schulzer, 1992 *An estimate of the future size of the tuberculosis problem in sub-Sa*
			Schulzer, 1994 *A mathematical model for the prediction of the impact of HIV infe*
			Sharomi, 2008 *Mathematical analysis of the transmission dynamics of HIV/TB co*
			Uys, 2011 *Transmission elasticity in communities hyperendemic for tuberculosis*
			Williams, 2005 *The impact of HIV/AIDS on the control of tuberculosis in India*
			Wood, 2010 *Tuberculosis transmission to young children in a South African comm*
	… of subclinical TB?	A7	**Dowdy, 2006** *The potential impact of enhanced diagnostic techniques for tubercu*
	… of (M)DR TB	A19, A20, A23, A30	**Basu, 2009** *Averting epidemics of extensively drug-resistant tuberculosis*
			Blower, 2004 *Modeling the emergence of the 'hot zones': tuberculosis and the amp*

Theme	Broader question	Research questions (see 'Full list' document)	Modelling papers addressing qu.
			Dye, 2000 *Criteria for the control of drug-resistant tuberculosis*
			Escombe, 2008 *The infectiousness of tuberculosis patients coinfected with HIV*
			Sergeev, 2012 *Modeling the dynamic relationship between HIV and the risk of dru*
	… of childhood TB	A21	**Dye, 1998** *Prospects for worldwide tuberculosis control under the WHO DOTS sti*
			Schulzer, 1992 *An estimate of the future size of the tuberculosis problem in sub-S*
			Sharomi, 2008 *Mathematical analysis of the transmission dynamics of HIV/TB co*
			Wood, 2010 *Tuberculosis transmission to young children in a South African comm*
Integration of TB/HIV care		A24, A26, A28, A47 L13	**Bachmann 2006** *Effectiveness and cost effectiveness of early and late prevention*
Best methods of surveillance		A18, A35	-
Cost-effectiveness research for ACF/Active TB*	Diagnostics	A28, A37, A38, A39, A40, A49 Xpert remit: A46	*
	Rx	A23, A36	*
	Integrated TB/HIV services	A28	*
Operational Research for ACF/Active TB	Diagnostics	A2, A3, A10, A17, A25, A37, A38, A39, A40	**Lin, 2011** *A modelling framework to support the selection and implementation of*
			Millen, 2008 *The effect of diagnostic delays on the drop-out rate and the total del*
		Xpert remit: A41	-
	Infection Control	A6	-
	Rx	A23	**Sharomi, 2008** *Mathematical analysis of the transmission dynamics of HIV/TB co*
	Burden of TB	A35	-
	Integrated TB/HIV services	A1, A24, A26, A27, A47, A48, L13	**Sharomi, 2008** *Mathematical analysis of the transmission dynamics of HIV/TB co*
Others		A29, A32	-

* Cost-effectiveness papers shown in Session 4 only (for brevity)

Research themes for modelling

Meeting session 2: Latent Mtb infection

Theme	Broader Question	Research questions (see 'Full list' document)	Modelling papers addressing qu.
Duration of protection	What is the duration of protection offered by different combinations of preventive TB therapies?	L4, L6, L15, L16	-
Population impact of IPT	What is the population impact of IPT for HIV–infected on Mtb transmission (DS and DR) in the general population?	L5, L14	**Bacaer, 2008** *Modeling the joint epidemics of TB and HIV in a South African townshi* **Basu, 2009** *Primary and secondary tuberculosis preventive treatment in HIV clinics: s* **Bell, 1999** *Tuberculosis preventive therapy for HIV-infected people in sub-Saharan Af* **Bhunu, 2009** *Modeling HIV/AIDS and tuberculosis coinfection* **Brewer, 1996** *Evaluation of tuberculosis control policies using computer simulation* **Cohen, 2006** *Beneficial and perverse effects of isoniazid preventive therapy for latent* **Currie, 2003** *Tuberculosis epidemics driven by HIV: is prevention better than cure?* **Currie, 2005** *Cost, affordability and cost-effectiveness of strategies to control tubercu* **Foster, 1997** *Modelling the economic benefits of tuberculosis preventive therapy for p* **Guwatudde, 2004** *A re-examination of the potential impact of preventive therapy on t* **Heymann 1993** *Modelling the efficacy of prophylactic and curative therapies for prev* **Maheswaran, 2012** *Intensive Case Finding and Isoniazid Preventative Therapy in HI* **Masobe, 1995** *Isoniazid prophylactic therapy for tuberculosis in HIV-seropositive pat* **Mills, 2011** *Modelling the performance of isoniazid preventive therapy for reducing tu* **Murray 2002** *Determinants of cluster distribution in the molecular epidemiology of tu* **Pho, 2012** *The cost-effectiveness of tuberculosis preventive therapy for HIV-infected i*
Population impact of ART	On clinical outcomes and transmission of DR TB, and child TB transmission	L8, L11	**Atun, 2007** *High coverage with HAART is required to substantially reduce the numbe* **Bacaer, 2008** *Modeling the joint epidemics of TB and HIV in a South African townshi* **Basu, 2007** *Prevention of nosocomial transmission of extensively drug-resistant tuber* **Basu, 2009** *Primary and secondary tuberculosis preventive treatment in HIV clinics: s* **Bhunu, 2009** *Modeling HIV/AIDS and tuberculosis coinfection*

Theme	Broader Question	Research questions (see 'Full list' document)	Modelling papers addressing qu.
			Cohen, 2006 *Beneficial and perverse effects of isoniazid preventive therapy for latent*
			Currie, 2003 *Tuberculosis epidemics driven by HIV: is prevention better than cure?*
			Currie, 2005 *Cost, affordability and cost-effectiveness of strategies to control tubercu*
			Dowdy, 2006 *The potential impact of enhanced diagnostic techniques for tuberculosis*
			Pho, 2012 *The cost-effectiveness of tuberculosis preventive therapy for HIV-infected i*
			Sharomi, 2008 *Mathematical analysis of the transmission dynamics of HIV/TB coinfe*
			Williams, 2003 *Antiretroviral drugs for tuberculosis control in the era of HIV/AIDS*
			Williams, 2010 *Antiretroviral therapy for tuberculosis control in nine African countri*
Patient benefit of preventive therapy	What is the patient benefit of receiving preventive therapy, and what does it add to ART?	L3, L6, L7, L12, L15, L17	**Bachmann 2006** *Effectiveness and cost effectiveness of early and late prevention of H*
			Bell, 1999 *Tuberculosis preventive therapy for HIV-infected people in sub-Saharan Af*
			Foster, 1997 *Modelling the economic benefits of tuberculosis preventive therapy for p*
Patient benefit of ART in children		L10	-
Cost-effectiveness research for IPT*		L6	*****
Operational Research for IPT	How can IPT be made accessible to all those in need & how can it best be combined with ART	L1, L2, L3, L13	-

* Cost-effectiveness papers shown in Session 4 only (for brevity)

Research themes for modelling

Meeting session 3: Vaccines and Immunology

Theme	Broader Question	Research questions (see 'Full list' document)	Modelling papers addressing qu.
Understanding within–host immunological processes	What are the immunologically distinctive processes involved in the pathway from Mtb infection to active disease (e.g. *potential vaccine targets, or diagnostic targets*)	V1, V4, V5, V6, V7, V8, V9, V11	**Basu, 2008** *The theoretical influence of immunity between strain groups on the prog* **Kirschner 1999** *Dynamics of co-infection with M. Tuberculosis and HIV-1* **Magombedze, 2006** *Modelling the human immune response mechanisms to mycoba* **Magombedze, 2008** *In-Vivo Mathematical Study Of Co-Infection Dynamics Of Hiv-* **Murray 2002** *Determinants of cluster distribution in the molecular epidemiology of* **Raimundo, 2002** *The Attracting Basins And The Assessment Of The Transmission C*
BCG	How can the current BGC vaccine be improved	V2, V3	**Tseng, 2011** *Cost-effectiveness of novel vaccines for tuberculosis control: a decision*
Vaccine trial design	How can the definition of clinical end–points for vaccine trials be improved for HIV–infected individuals?	V10	-

Research themes for modelling

Meeting session 4: Economics and Operational Research

Theme	Broader Question	Research questions (see 'Full list' document)	Modelling papers addressing qu.
Cost effectiveness			
Cost–effectiveness of interventions for TB control	Diagnostics	A28, A37, A38, A39, A40, A49	**Baltussen, 2005** *Cost effectiveness analysis of strategies for tuberculosis control in developing*
			Bonnet, 2010 *Added value of bleach sedimentation microscopy for diagnosis of tuberculosis: c*
			Currie, 2005 *Cost, affordability and cost-effectiveness of strategies to control tuberculosis in c*
			Dodd, 2011 *Periodic active case finding for TB: when to look?*
			Dowdy, 2008 *Cost-effectiveness of novel diagnostic tools for the diagnosis of tuberculosis*
			Dowdy, 2008 *Impact and cost-effectiveness of culture for diagnosis of tuberculosis in HIV-infe*
			Maheswaran, 2012 *Intensive Case Finding and Isoniazid Preventative Therapy in HIV Infecte*
			Abimbola, 2012 *Cost-Effectiveness of Tuberculosis Diagnostic Strategies to Reduce Early Mo*
		Xpert specific: A46	**Andrews, 2012** *The cost-effectiveness of routine tuberculosis screening with Xpert MTB/RIF p*
			Meyer-Rath, 2012 *The Impact and Cost of Scaling up GeneXpert MTB/RIF in South Africa*
			Vassall, 2011 *Rapid diagnosis of tuberculosis with the Xpert MTB/RIF assay in high burden c*
	IPT	L6	**Bachmann 2006** *Effectiveness and cost effectiveness of early and late prevention of HIV/AIDS*
			Bell, 1999 *Tuberculosis preventive therapy for HIV-infected people in sub-Saharan Africa is c*
			Currie, 2005 *Cost, affordability and cost-effectiveness of strategies to control tuberculosis in c*
			Foster, 1997 *Modelling the economic benefits of tuberculosis preventive therapy for people wi*
			Maheswaran, 2012 *Intensive Case Finding and Isoniazid Preventative Therapy in HIV Infecte*
			Masobe, 1995 *Isoniazid prophylactic therapy for tuberculosis in HIV-seropositive patients--a*
			Pho, 2012 *The cost-effectiveness of tuberculosis preventive therapy for HIV-infected individua*
			Samandari, 2011 *Costs and consequences of additional chest x-ray in a tuberculosis preventi*
			Shrestha, 2007 *Cost-utility of tuberculosis prevention among HIV-infected adults in Kampala,*
	Rx	A23, A36	**Baltussen, 2005** *Cost effectiveness analysis of strategies for tuberculosis control in developing*
			Dowdy, 2009 *The persistence of tuberculosis in the age of DOTS: reassessing the effect of cas*
			Jacquet, 2006 *Impact of DOTS expansion on tuberculosis related outcomes and costs in Haiti*
			Laxminarayan, 2009 *Global investments in TB control: economic benefits*

Theme	Broader Question	Research questions (see 'Full list' document)	Modelling papers addressing qu.
			Maheswaran, 2012 *Intensive Case Finding and Isoniazid Preventative Therapy in HIV Infecte*
			Manabe, 2012 *Rifampicin for continuation phase tuberculosis treatment in Uganda: a cost-ef*
			Porco, 2001 *Amplification dynamics: predicting the effect of HIV on tuberculosis outbreaks*
			Wilton, 2001 *Directly observed treatment for multidrug-resistant tuberculosis: an economic e*
	Integrated TB/HIV	A28	**Bachmann 2006** *Effectiveness and cost effectiveness of early and late prevention of HIV/AIDS*
			Currie, 2005 *Cost, affordability and cost-effectiveness of strategies to control tuberculosis in*
Operational Research			
Programmatic impact new interventions	Diagnostics	A2, A3, A10, A17, A25, A37, A38, A39, A40	**Lin, 2011** *A modelling framework to support the selection and implementation of new tubercu*
			Millen, 2008 *The effect of diagnostic delays on the drop-out rate and the total delay to diagno*
		Xpert specific: A41	-
	Rx	A23	**Sharomi, 2008** *Mathematical analysis of the transmission dynamics of HIV/TB coinfection in*
Best operational model for	… integrated TB/HIV services	A1, A24, A26, A27, A47, A48 L1, L2, L3, L13	**Sharomi, 2008** *Mathematical analysis of the transmission dynamics of HIV/TB coinfection in*
	…Mtb infection control	A6 L13	-
	… TB surveillance	A35	-

APPENDIX 4: LIST OF MEETING ATTENDEES

TB Modelling and Analysis Consortium Meeting 1
Optimising TB control in high HIV prevalence settings - Modelling and quantitative research priorities

Participant Name	Organisation
Richard White	London School of Hygiene and Tropical Medicine
Chris Dye (skype)	World Health Organization
Michael Kimerling	Bill and Melinda Gates Foundation
Geoff Garnett	Bill and Melinda Gates Foundation
Philip Eckhoff	IV-Global Good
David Dowdy	Johns Hopkins Bloomberg School of Public Health
Ted Cohen	Brigham and Women's Hospital/Harvard School of Public Health
Anna Vassall	London School of Hygiene and Tropical Medicine
Rein Houben	London School of Hygiene and Tropical Medicine
Emilia Vynnycky	London School of Hygiene and Tropical Medicine
Liz Corbett	London School of Hygiene and Tropical Medicine and MLW-Malawi
Katharina Kranzer	London School of Hygiene and Tropical Medicine
Pete Dodd	London School of Hygiene and Tropical Medicine
Mark Nicol	University of Cape Town

TB Modelling and Analysis Consortium Meeting 1
Optimising TB control in high HIV prevalence settings - Modelling and quantitative research priorities

Amitabh Suthar	World Health Organization
Alison Grant	London School of Hygiene and Tropical Medicine
Brian Williams	South African Centre for Epidemiological Modelling and Analysis
Suzanne Verver	KNCV Tuberculosis Foundation
Laura Rodrigues	London School of Hygiene and Tropical Medicine
Jacqueline Shea	Oxford-Emergent Tuberculosis Consortium
Christopher Fitzpatrick	World Health Organization
Nick Menzies	Harvard University
Willem Hanekom	South African Tuberculosis Vaccine Initiative, University of Cape Town
Gavin Churchyard	The Aurum Institute
Timothy Hallett	Imperial College London
Reuben Granich	World Health Organization
Angeline Nanni	Aeras
Dermot Maher	The Wellcome Trust

TB Modelling and Analysis Consortium Meeting 1
Optimising TB control in high HIV prevalence settings - Modelling and quantitative research priorities

Katherine Fielding	London School of Hygiene and Tropical Medicine
Gabriela Gomez	Amsterdam Institute for Global Health and Development
Nicola Foster	Health Economics Unit
Christine Sizemore (skype)	National Institute of Allergy and Infectious Diseases
Philippe Glaziou (skype)	World Health Organization
Till Barnighausen	Africa Centre
Mark Bletcher	South African Ministry of Health
Carel Pretorius	Futures Institute
Piotr Hippner	The Aurum Institute
Kavi Velen	The Aurum Institute

Meeting Co-ordinator: Olivia Ross-Hurst, London School of Hygiene and Tropical Medicine