How can mathematical models advance tuberculosis control in high HIV prevalence settings?

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SUMMARY

Existing approaches to tuberculosis (TB) control have been no more than partially successful in areas with high human immunodeficiency virus (HIV) prevalence. In the context of increasingly constrained resources, mathematical modelling can augment understanding and support policy for implementing those strategies that are most likely to bring public health and economic benefits. In this paper, we present an overview of past and recent contributions of TB modelling in this key area, and suggest a way forward through a modelling research agenda that supports a more effective response to the TB-HIV epidemic, based on expert discussions at a meeting convened by the TB Modelling and Analysis Consortium. The research agenda identified high-priority areas for future modelling efforts, including 1) the difficult diagnosis and high mortality of TB-HIV; 2) the high risk of disease progression; 3) TB health systems in high HIV prevalence settings; 4) uncertainty in the natural progression of TB-HIV; and 5) combined interventions for TB-HIV. Efficient and rapid progress towards completion of this modelling agenda will require co-ordination between the modelling community and key stakeholders, including advocates, health policy makers, donors and national or regional finance officials. A continuing dialogue will ensure that new results are effectively communicated and new policy-relevant questions are addressed swiftly.

KEY WORDS: tuberculosis; mathematical modelling; HIV; sub-Saharan Africa; systematic literature review

WHILE *MYCOBACTERIUM TUBERCULOSIS* and the human immunodeficiency virus (HIV) are independently responsible for substantial human suffering and death, in areas where these pathogens dually infect the population, their combined effect has been devastating. HIV-related immunosuppression markedly increases the risk for progression to tuberculosis (TB) disease after *M. tuberculosis* infection,[1] and may increase the risk of initial infection; accordingly, in areas of generalised HIV epidemics, there have been steep increases in TB incidence.[2] During periods of limited success in HIV prevention and control, standard approaches for TB control have been inadequate in these settings; novel strategies are therefore urgently needed.[3]

Mathematical models, defined by Garnet et al. as mechanistic representations for how disease burden is established, are useful tools for projecting the potential public health and economic impact of interventions when population-level empirical data, such as from cluster-randomised trials, are unavailable and too expensive, too time consuming or unethical to acquire.[4] Models can also provide insight by simplifying complex systems into frameworks that are more easily understood. For example, the relationship between the scale-up of antiretroviral

therapy (ART) and the subsequent impact on population-level TB incidence is difficult to predict, but can be understood using a combined model of HIV and TB transmission.[5] In a time of limited resources, mathematical modelling, grounded in available data, can be an important guide for the rational use of resources in TB control, development pipelines of new drugs, vaccines or diagnostics, and highlight what empirical data gaps need to be filled.

Recognising the urgency of TB control in high HIV prevalence settings and the potential contributions of modelling, the TB Modelling and Analysis Consortium (TB MAC, Table 1) convened its first meeting between empirical scientists, policy makers and mathematical modellers in September 2012 in Johannesburg, South Africa. The aim of this meeting was to identify a modelling research agenda to advance TB control in high HIV prevalence settings. In the present perspective, we summarise the key historical contributions of TB-HIV modelling following a systematic literature review and identify a future modelling research agenda that would help hasten the reduction of the TB-HIV epidemic.

METHODS

A detailed report of the meeting preparations, resources and documents available to the participants and discussion outcomes can be found on the TB MAC website (www.tb-mac.org/WorkAreas/WorkArea/1). In summary, to identify existing TB modelling and cost-effectiveness studies in high HIV prevalence settings (restricted for this review to sub-Saharan Africa or sub-populations with an adult HIV prevalence of over 5%), a systematic literature review was performed in September 2012. We searched PubMed, private libraries, existing reviews and mathematical modelling journals. Further details of the review methods and results are given in the Appendix, including details of the selection process in Figure A.* A formal assessment of model quality was considered to be beyond the scope of this review. Existing research priority agendas were also scanned for potential modelling questions (RMGJH and RGW) to stimulate discussions.[6–8]

The above documents were used as preparatory material for participants in a 2-day meeting in Johannesburg, South Africa, in September 2012 between key stakeholders. Participants, including empirical scientists, policy makers and mathematical modellers, to discuss modelling research questions in three main areas chosen to cover the breadth of TB care and control: 1) screening and treatment of active TB and latent tuberculous infection (LTBI), 2) TB

vaccines and immunology and 3) the economics of TB. Discussions during the meeting focused primarily on the potential opportunities for modelling efforts to hasten the reduction of the TB-HIV epidemic. On behalf of the meeting participants these lists of research questions were consolidated into key themes for TB care and control, which are described below.

KEY CONTRIBUTIONS OF TB MODELLING IN HIGH HIV PREVALENCE SETTINGS

The review identified 69 papers. A brief summary of these papers and a selection process flow chart can be found in the Appendix. Despite its public health relevance, modelling activity in TB was limited before 2005, after which six or more papers were published each year. Strikingly, nearly all TB-HIV models started from the perspective of the natural history of TB, adding a simple layer on HIV to the core structure on TB,[9] although there are notable exceptions to this trend.[10]

Natural history of TB in high HIV prevalence setting
In February 1992, Schulzer et al. published the first model to quantify the consequences of the emerging disastrous association between HIV and TB.[9] Later confirmed by others, these models predicted the steep rise in TB incidence that was to overwhelm many TB programmes in these, usually low-income, settings.[2,11–15]

Antiretroviral therapy and isoniazid preventive therapy
In 2003, Williams and Dye used modelling to show how the expansion of access to ART in high HIV prevalence settings would contribute little to controlling TB incidence in the population, unless ART was started early (e.g., at CD4 levels of 500/μl), with very high (85%) effective coverage.[10]

A large number (*n* = 17) of the modelling papers incorporated preventive therapy, usually isoniazid preventive therapy (IPT). However, the evaluation showed that assumptions on key parameters such as the level and duration of protection offered by IPT varied widely, complicating the interpretation of these generally positive results. Models assumed between a 34%[16] or 100%[17] reduction in the risk of TB during IPT, while the assumed duration of protection post-therapy varied between immediate loss of effect[18] to lifelong protection.[17]

Impact of additional interventions for TB-HIV
Mathematical models of TB-HIV have also been used to explore enhancements to DOTS-based programmes, including active case finding[19] and expanding access to culture-based diagnosis or drug susceptibility testing.[20] These models usually found that such enhancements could provide substantial benefits. In 2010, the World Health Organization

Table 1 The TB Modelling and Analysis Consortium

The TB Modelling and Analysis Consortium (TB MAC, www.tb-mac.org), formed in June 2012, aims 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. Its objectives are to:

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

To date TB MAC has held three meetings on high-priority issues: the first meeting was on the focus of this paper, TB control in high HIV prevalence settings, which was held in Johannesburg, South Africa, in September 2012; the second was on the impact and cost-effectiveness of current and future diagnostics for TB, which was held in Amsterdam, The Netherlands, in April 2013; and the third was on the rational introduction of new drugs and drug regimens, which was held in Beijing, China, in September 2013. TB MAC will hold four more meetings over 2014 and 2015. See www.tb-mac.org for full details, meeting reports and other resources useful for TB modellers including this TB-HIV literature review (www.tb-mac.org/resources)

TB = tuberculosis; HIV = human immunodeficiency virus.

endorsed a new TB diagnostic test, Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA), generating a need for models that explored costs benefits as well as operational aspects of integrating these novel devices into existing TB care and control infrastructure. While four papers in this review explored the individual benefits and costs,[21] none incorporated the population effect of improved diagnosis through a transmission component (note: one paper has since addressed this[22]).

Implementations of interventions for TB

Models can also inform policy questions on implementation of new interventions and tools. Often such models will include an operational modelling component that explicitly captures key parts of the health system.[23] While the importance of the operational modelling of combined TB-HIV interventions was recognised, little work has been done in this area, with only one paper addressing this issue, which evaluated the impact of a novel diagnostic tool.[23]

A RESEARCH AGENDA FOR MODELLING OF TB CONTROL IN HIGH HIV PREVALENCE SETTINGS

In the following sections, we identify five broad priority areas for TB modelling research for the support for TB care and control in high HIV prevalence settings, discuss the empirical evidence and suggest potential opportunities for future modelling efforts. Specific research questions in each area can be found in Table 2.

Priority area 1: diagnosis and mortality of TB-HIV

Among people living with HIV (PLHIV), TB is both more difficult to diagnose than in HIV-negative individuals and a major cause of death if untreated.[2] To reduce mortality, early diagnosis and the resulting access to lifesaving treatment for TB and often HIV, is key. It is therefore likely that intensified case-finding strategies (which aim to diagnose individuals at earlier stages of disease)[24] and improved diagnosis[20]

might have a disproportionate morbidity and mortality benefit among HIV-positive individuals with active TB disease. However, given the likely much shorter duration of overall TB disease and higher probability of smear-negative (i.e., presumably less infectious) disease,[2] the impact of such strategies on *M. tuberculosis* transmission and future TB disease incidence may be less pronounced.

Although the population-level benefits of intensified TB case finding and improved TB diagnosis among PLHIV have not been conclusively demonstrated,[24] models can use the best available data to help identify the approaches to diagnosis and case-finding that are likely to be most cost-effective if scaled up at the population level. For example, models that incorporate routes of care-seeking and diagnosis among individuals with HIV and TB can augment these findings by relating them to existing systems of care. Progress in this area is therefore clearly dependent on increasing the empirical evidence base related to the organisation of health systems for HIV and TB in resource-constrained settings (Priority area 3) as well as the progression (Priority area 2) and pathogenesis (Priority area 4) of TB-HIV.

Priority area 2: high risk of progression to active TB-HIV

HIV dramatically increases both the rate of TB infection progressing to disease (as measured by recurrent TB episodes with novel molecular fingerprints),[25] and the rate of progression from LTBI (as measured by a positive tuberculin skin test) to active TB disease.[26] Thus, the potential role of preventing progression (e.g., by using IPT or other preventive therapy regimens, ART or post-exposure vaccines) may be especially pronounced among this population. While IPT has been demonstrated to reduce the risk of active TB during treatment,[27] there is ongoing uncertainty about the duration of protection among PLHIV after therapy completion.[28] Recent modelling studies have suggested that the failure of isoniazid to sterilise is at least part of the explanation,[29] although

Table 2   Key TB-HIV modelling priority areas and sub-questions

1 Difficult diagnosis and high mortality of TB-HIV
  • What is the most (cost-) effective case finding strategy?
  • Can a simple algorithm be defined to guide optimal case-finding approaches for national programme staff and policy makers based on epidemiological data on ARI, case notification proportion and HIV prevalence?
  • What is the impact of reducing initial default and improving cure rates?
  • What is the (cost-) effectiveness of new point-of-care diagnostic tests and algorithms?
  • What might the contribution of novel therapeutic vaccines be?

2 High risk of disease progression to active TB-HIV
  • Can models help us understand the degree and duration of protection from (isoniazid) preventive therapy among PLHIV in different settings?
  • What might the contribution of novel post-exposure vaccines in various target groups be?

3 TB health systems in high HIV prevalence settings
  • How do operational processes influence the cost-effectiveness of TB control interventions in high HIV prevalence settings?
  • What is the efficiency of TB-HIV services, and how can we improve value for money?

4 Uncertainty in the natural progression of TB-HIV
  • Can models be used to quantify uncertainties in the natural history of *Mycobacterium tuberculosis* that are relevant for decision making, and make recommendations for how to prioritise data collection activities?
  • Would a highly simplified, user-friendly model for TB still be useful for policy makers?
  • Can we use models to define proxy measure of intervention impact?
  • Should we do a formal model comparison on the proportion of TB due to recent infection in relation to the estimated ARI?
  • What are the resource requirements to scale up TB control interventions in high HIV prevalence settings?

5 Combined interventions to control TB-HIV
  • Can a more complex model better estimate the impact of a range of combination TB prevention strategies?
  • What is the most cost-effective combination of existing TB control interventions in high HIV prevalence settings?
  • What might the contribution of novel pre/post-therapeutic vaccines be?

TB = tuberculosis; HIV = human immunodeficiency virus; ARI = annual risk of tuberculous infection; PLHIV = people living with HIV.

this may improve following immune recovery with ART co-therapy.[30]

The population-level effects of TB preventive interventions remain unclear. While models of the impact of preventive therapy among PLHIV should reflect this uncertainty, their guidance is needed to inform decisions regarding the scale-up of preventive therapy.

Advances in diagnostic tools to identify those individuals at highest likelihood for progression, coupled with better understanding of latency and partial immunity in TB-HIV (Priority area 4), can help to better inform the structure and parameterisation of these models. Earlier economic work on the potential cost-effectiveness and cost savings from preventive therapies will need to be revisited to incorporate updated understanding about the duration of effectiveness, individual level effects and costs of maintaining adherence to treatment.

Priority area 3: TB health systems in high HIV prevalence settings

TB requires intensive, often directly observed, therapy with a short course of inexpensive drugs, whereas HIV requires lifelong, mostly unsupervised treatment with expensive agents and regular therapeutic monitoring. However, in HIV-endemic regions, the patients taking these drugs are often the same, and synergistic efforts at linkage to TB and HIV care can improve systems of diagnosis and treatment at relatively low cost.[31]

Health systems in these settings must therefore adapt to this reality. Operational and economic models have great potential to inform decisions about how to structure health systems, in particular to inform the optimal level of service integration. Such models can identify ways to resolve both allocative inefficiencies (e.g., by combining resources in optimal ways to provide services for those who are co-infected) and technical inefficiencies (e.g., by combining services in optimal ways to improve outcomes). They can also assist in understanding the delays and costs that service users face, and how to reduce them.

Combined health system and economic models could also help identify the corresponding health systems investments needed to support the efficient operation of both TB and HIV services. To date, such health system models have been underutilised;[23] however, as resources for TB and HIV care become increasingly constrained, and new technologies continue to be scaled up, health systems models will become increasingly important in helping to maximise value for money.

Priority area 4: uncertainty in the natural history of TB-HIV

All epidemiological models of infectious diseases are limited by the current state of knowledge of the natural history of the pathogen. In the case of TB-HIV, we must consider not only two individual natural histories, but also the interaction of these two (potentially) chronic infectious diseases. The need for a more thorough understanding of the natural history of TB-HIV is clear.

The natural history of untreated HIV is well-known from cohort studies of HIV-infected individuals before the availability of ART, and some insight

exists into the natural history of TB from the pre-chemotherapy era (1950s). However, the availability of TB chemotherapy throughout the HIV era has meant that, for ethical and methodological reasons, studies to acquire this information in HIV-positive TB patients are not possible – including the infectious duration of untreated TB[32] (and its relationship to CD4 count and/or ART), TB mortality risk,[33] and the risk of re-infection and progression to disease relative to non-HIV-infected individuals (Priority area 2).

To accurately project the impact of interventions for TB in HIV-endemic regions, it is essential to better understand these elements of natural history. For example, the impact of early diagnosis cannot be accurately estimated without knowing the duration of infectiousness likely to be averted. Empirical studies that provide further insight into these areas are urgently needed; in the interim, models using existing data may be able to better define and communicate the bounds of our uncertainty.

Priority area 5: combined interventions to control TB-HIV

If we are ultimately to achieve aggressive targets for TB control in HIV-endemic regions, it is unlikely that we can rely on a single intervention.[34] Strategies for the control of complex epidemics such as HIV and TB will include multiple interventions for the foreseeable future. As such, we must deploy a combination of interventions that are intelligently targeted at different steps of the *M. tuberculosis* transmission cycle.

Given the growing number of potential interventions for the control of TB-HIV, including alternative screening and diagnostic approaches (Priority area 1), preventive strategies (Priority area 2) and alternative models for integrated care (Priority area 3), there is an opportunity for models to help identify which interventions will likely perform best when combined. For example, a combination of preventive treatment (targeting LTBI) and intensified case finding (i.e., targeting active disease) may be more effective than one of intensified case finding plus better passive diagnosis (i.e., both targeting active disease).[35] Economic considerations are also critical, as certain interventions may be more efficient to combine than others,[36] as both provider and patient costs are reduced through economies of scope.

To be able to provide such insight, new models with flexible structures capable of simulating the impact and cost-effectiveness of relevant combinations of interventions are urgently required. Such models could provide a platform for comparing alternative combinations of existing and novel interventions that go beyond current policy in terms of both impact and resource requirements, thus helping to chart the fastest, most cost-effective course

possible for the elimination of TB in settings of high HIV prevalence.

CONCLUSION

In this paper, we have identified five critical areas in which TB-HIV models can help advance TB control in high HIV prevalence settings. These include questions ranging from improved understanding of the natural history of TB-HIV to comparative impact and cost-effectiveness achievable from implementation and combination of TB-HIV control strategies. However, efficient and rapid progress towards the completion of this modelling agenda will require co-ordination between the modelling community and key stakeholders, including advocates, health policy makers, donors and national or regional finance officials. They will be faced with decisions that will increasingly reflect not simple, idealised comparisons of individual interventions, but rather a complex assessment of the optimal combination of available options in real-world settings. As such, effective models will incorporate operational components and inform the prioritisation, sequencing and expected consequences of combination approaches that involve both scaling up new techniques and improving existing systems.

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APPENDIX

Full search query for systematic literature review

We carried out a systematic literature review to identify existing tuberculosis (TB) modelling and cost-effectiveness studies in high human immunodeficiency virus (HIV) prevalence settings, with the aim of highlighting gaps in existing work against current research priorities and give an overview of the modelling methods used to date.

We searched the medical literature using a PubMed query which identified papers from an earlier narrative review in 2008.[1] The following search query was used in September 2012: (tuberculosis OR TB) AND ((mathem* AND (model OR models)) OR (mathem* modell*) OR (mathem* modeling) OR (modeling OR modelling) OR 'Population dynamics'[MeSH Terms] OR 'Population dynamics' OR 'System dynamics' OR 'Computer simulation' OR 'Computer simulation'[MeSH Terms]).

We searched mathematical modelling journals for any papers on TB (search for 'tuberculosis' OR 'TB') and scanned references from existing reviews for relevant papers. We also searched the personal libraries of TB MAC steering committee members (RGW, CD, AV, TC and DD) who kindly made their personal libraries available. To identify those relevant for high HIV prevalence settings, we included those papers that included any of the terms 'HIV', 'AIDS', 'human imm*' or 'Africa' in their title, keywords or abstract.

Papers were eligible for full-text review if they were written in English and described a mathematical model of TB. For the purposes of this review, in defining 'mathematical model', we followed Garnett et al.[2] and included decision analytic, cohort, transmission, operational or within-host models, but excluded purely statistical models and studies using models to estimate only resource requirements. Papers were also excluded if they did not model or use data from populations with high HIV prevalence (restricted to sub-Saharan Africa or subpopulations with an adult HIV prevalence of over 5%). Details of the selection process are given in the Figure.[3]

Paper selection was done by RMGJH; data extraction was done by RMGJH with support from RGW.
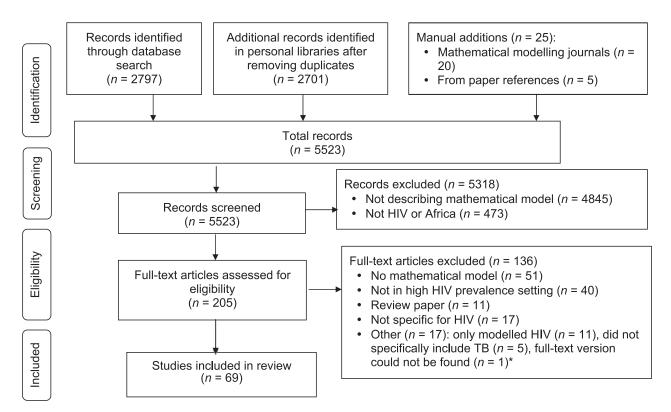

Figure A   Systematic review flow chart for selection of papers. HIV = human immunodeficiency virus; TB = tuberculosis.[3] Note: File with references can be downloaded at http://www.tb-mac.org/resources.

Table A Summary of studies identified in the systematic review

Reference	Year	First author	Primary research question	Main modelling method used	Area of contribution*
[4]	1992	Bermejo	What is the impact of HIV on TB incidence in developing countries?	Other (static algebraic)	1
[5]	1992	Schulzer	What will be the impact of the HIV epidemic on future TB rates in sub-Saharan Africa?	†	1
[6]	1993	Heymann	What is the impact of preventive and curative regimens on TB in Africa?	†	2
[7]	1993	Massad	How do HIV and TB interact in homogeneously mixing populations?	†	1
[8]	1994	Dolin	What is the global TB incidence and mortality between 1990 and 2000?	Other	1
[9]	1994	Schulzer	How does a generalised HIV epidemic accelerate the rise of TB incidence?	†	1
[10]	1995	Masobe	What are the costs and benefits of providing IPT to a HIV-positive population?	‡	2
[11]	1997	Foster	What are the costs and benefits of providing IPT to HIV-positive individuals in Zambia?	§	2
[12]	1998	Dye	What is the impact of DOTS on global TB control?	†	3
[13]	1999	Bell	What is the cost-effectiveness of IPT in sub-Saharan Africa?	‡	2
[14]	1999	Kirschner	What are the within-host interaction dynamics of *M. tuberculosis* and HIV?	¶	1
[15]	2001	Porco	What is the amplification impact of the HIV epidemic on TB outbreaks?	†	1
[16]	2001	Wilton	What is the cost-effectiveness of DOTS vs. non-DOTS treatment to reduce the spread of MDR-TB?	§	3
[17]	2002	Murray	What are the social, demographic and clinical determinants of cluster distribution?	‡	1
[18]	2002	Raimundo	What is the accelerating impact of HIV infection on TB incidence in a closed population?	†	1
[19]	2003	Corbett	What is the relationship between HIV prevalence and TB incidence and mortality in a population?	Other (static algebraic)	1
[20]	2003	Currie	What are the relative benefits of treating active TB vs. TB and HIV prevention in high HIV prevalence countries?	†	2
[21]	2003	Williams	What is the potential population-level impact of ART on TB incidence?	‡	2
[22]	2004	Guwatudde	What is the potential impact of IPT on TB in sub-Saharan Africa?	†	2
[23]	2005	Baltussen	What are the costs and health benefits of TB control in Africa and South East Asia?	§	3
[24]	2005	Currie	What are the costs and benefits of seven TB control strategies in high HIV prevalence countries?	§	3
[25]	2005	Naresh	What are the dynamics of HIV and TB co-infection in a variable size population?	†	1
[26]	2006	Bachmann	What is impact of IPT vs. ART on progression to TB disease in HIV-positive individuals?	§	2
[27]	2006	Cohen	What is the potential contribution of IPT to the emergence of drug-resistant TB?	†	2
[28]	2006	Dowdy	What is the impact of enhanced diagnostics on TB in a high HIV prevalence setting?	†	3
[29]	2006	Hughes	How well can an individual-based model predict a TB epidemic in a high HIV prevalence country?	†	1
[30]	2006	Jacquet	What are the costs and benefits of expanding DOTS in Haiti?	§	3
[31]	2006	Magombedze	How do cytotoxic lymphocytes and the immune system determine whether an infection progresses to TB disease?	¶	1
[32]	2006	Shrestha	What are the costs and benefits of TST screening before initiating IPT in HIV-positive individuals in Uganda?	§	2
[33]	2007	Basu	What was the potential of control measures to reduce nosocomial transmission of XDR-TB in Tugela Ferry?	†	3
[34]	2007	Shrestha	What are the costs and benefits of an IPT programme in HIV-positive individuals in Uganda?	§	2
[1]	2008	Bacaer	What is the impact of control measures on TB disease in South African Township?	†	2
[35]	2008	Basu	How could cross-strain immunity affect the spread of DR-TB?	†	1
[36]	2008	Dowdy	What is the impact of expanded culture and drug susceptibility testing on TB mortality and incidence?	†	3
[37]	2008	Dowdy	What are the potential costs and benefits of a point-of-care TB diagnostic test in South Africa, Brazil and Kenya?	§	3
[38]	2008	Escombe	What is the relative infectiousness of MDR-TB in HIV-positive individuals?	†	1
[39]	2008	Magombedze	What are the immune mechanisms involved in *M. tuberculosis* HIV co-infections?	¶	1
[40]	2008	Millen	What are the main factors that contribute to the overall delay in diagnosis of TB?	§	1

Table (continued)

Reference	Year	First author	Primary research question	Main modelling method used	Area of contribution*
41	2008	Sanchez	What is the impact of reduced treatment duration and enhanced case detection and cure on TB incidence and mortality in populations with generalised HIV epidemics?	†	3
42	2008	Sharomi	What are the synergistic interactions between HIV and *M. tuberculosis* in a population?	†	1
43	2008	Wilkins	What are the population pharmacokinetics of rifampicin in pulmonary TB patients in South Africa?	¶	1
44	2009	Basu	How can epidemics of XDR-TB be averted in South Africa?	†	3
45	2009	Basu	What factors impact on the evolution of *M. tuberculosis* strain virulence?	†	1
46	2009	Basu	What are the benefits and risks of various IPT strategies in HIV clinics?	†	2
47	2009	Bhunu	What are the mathematical properties of an *M. tuberculosis*-HIV co-infection model that includes ART?	†	2
48	2009	Dowdy	Can short-term 5–10% annual declines in TB incidence be sustained by high case detection alone?	†	3
49	2009	Laxminarayan	Do the economic benefits of the Global Plan to Stop TB (2006–2015) exceed the costs?	§	3
50	2009	Naresh	What is the effect of TB on the spread of HIV infection in a logistically growing population?	†	1
51	2009	Roeger	What are the mathematical properties of a combined TB-HIV population model?	†	1
52	2009	Sanchez	What factors can explain the rise in TB incidence in Kenya, given the declining HIV trends?	†	1
53	2010	Bonnet	What is the cost-effectiveness of direct vs. bleach sedimentation smear microscopy?	§	3
54	2010	Williams	What is the potential population-level impact of ART on TB incidence in nine African countries?	†	2
55	2010	Wood	What are the driving factors behind the high ARI in children in a South African community?	†	1
56	2011	Basu	What interventions can interrupt *M. tuberculosis* transmission in institutional settings?	†	3
57	2011	Dodd	What factors influence the performance and cost-effectiveness of TB active case finding?	†	3
58	2011	Lin	How can an operational model support a rational choice of TB diagnostic strategy?	†	4
59	2011	Mellor	Does incorporating household structure in a discrete event simulation model of TB and HIV allow a comparison of contact tracing and active case finding in high-risk groups?	‡	3
60	2011	Mills	How do contact patterns affect the population-wide impact of IPT?	†	2
61	2011	Pretorius	What are the statistical properties of TB episodes in a small South African community?	†	1
62	2011	Samandari	What is the cost-effectiveness of adding a CXR to a symptom-only screen before IPT?	§	2
63	2011	Srivastava	What is the impact of pharmacokinetic variability on MDR-TB emergence in *M. tuberculosis* strains?	¶	1
64	2011	Tseng	What is the cost-effectiveness of a BCG replacement vaccine in Zambia?	§	3
65	2011	Uys	What is the impact of background transmission rates on the relationship between the case detection rate and the resulting decline in ARI?	†	1
66	2011	Vassall	What is the impact of introducing Xpert on the cost-effectiveness of TB care?	§	3
67	2012	Abimbola	What is the cost-effectiveness of Xpert or culture-based screening for TB in patients initiating ART?	§	3
68	2012	Andrews	What is the cost-effectiveness of smear, Xpert or culture-based screening for TB in patients initiating ART?	§	3
69	2012	Maheswaran	What is the cost-effectiveness of intensified case finding and IPT in HIV-positive individuals in sub-Saharan Africa?	§	2
70	2012	Manabe	What is the cost-effectiveness of 4HR vs. 6HE# for the continuation phase in anti-tuberculosis treatment in Uganda?	§	3
71	2012	Sergeev	What is the impact of HIV on the dynamics of DR-TB?	†	1

* Describes the main area where the TB modelling paper contributed to: 1 = natural history of TB in high HIV prevalence setting; 2 = ART and IPT; 3 = impact of additional interventions for TB-HIV; 4 = implementations of TB interventions.
† Compartmental population-based model with a dynamic transmission component, i.e., the risk of infection at a given time is dependent on the prevalent number of infectious TB cases at that time.
‡ A population model without the dynamic transmission component.
§ Cost-effectiveness model using a decision tree (including Markov models) method.
¶ Usually a compartmental model that captures within-host processes of *M. tuberculosis* infection and TB disease.
# H = isoniazid; R = rifampicin; E = ethambutol. Numbers before the letters indicate the duration in months of the phase of treatment.
HIV = human immunodeficiency virus; TB = tuberculosis; IPT = isoniazid preventive therapy; MDR-TB = multidrug-resistant TB; ART = antiretroviral therapy; TST = tuberculin skin test; XDR-TB = extensively drug-resistant TB; DR-TB = drug-resistant TB; ARI = annual risk of infection; CXR = chest X-ray; BCG = bacille Calmette-Guérin; Xpert = Xpert® MTB/RIF.

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RESUME

Les approches existantes de la lutte contre la tuberculose (TB) n'ont eu qu'un succès relatif dans les zones à prévalence élevée de virus de l'immunodéficience humaine (VIH). Dans un contexte de ressources de plus en plus limitées, un modèle mathématique peut augmenter la compréhension et soutenir les politiques de mise en œuvre de stratégies plus susceptibles d'offrir des bénéfices en termes d'économie et de santé publique. Dans cet article, nous présentons un aperçu des contributions passées et récentes de la modélisation de la TB dans ce domaine clé et suggérons une façon de répondre plus efficacement à l'épidémie de TB-VIH grâce à un programme de recherche de modélisation en se basant sur des discussions d'experts lors d'une réunion convoquée par le Consortium de modélisation et d'analyse de la TB. Le programme de recherche a identifié des domaines hautement prioritaires pour les futures activités de modélisation, notamment : 1) les difficultés de diagnostic et la mortalité élevée de la TB-VIH ; 2) le risque élevé de progression de la maladie ; 3) le système de prise en charge de la TB dans les zones à haute prévalence du VIH ; 4) l'incertitude de la progression naturelle de la TB-HIV ; et 5) les interventions combinées pour la TB-VIH. Une progression efficace et rapide vers l'achèvement de ce programme de modélisation nécessitera une coordination entre la communauté de modélisation et les partenaires principaux, responsables de plaidoyer, décideurs politiques, donateurs et responsables financiers nationaux ou régionaux. Un dialogue continu s'assurera que les nouveaux résultats sont réellement diffusés et que les nouvelles questions relatives aux politiques sont prises en compte rapidement.

RESUMEN

Los enfoques actuales de lucha contra la tuberculosis (TB) solo han alcanzado una eficacia parcial en las zonas con alta prevalencia de la infección por el virus de la inmunodeficiencia humana (VIH). En el contexto de una restricción progresiva de los recursos, los modelos matemáticos pueden mejorar la comprensión y dar mayor respaldo a las políticas encaminadas a la ejecución de las estrategias con mayor probabilidad de aportar beneficios de salud pública y ventajas económicas. En el presente artículo se examinan las contribuciones pasadas y recientes de la modelización en esta importante aspecto y se propone una forma de avanzar, mediante un programa de investigación en modelización, que respalde una respuesta más eficaz a la epidemia de TB-VIH, a partir de los intercambios de los expertos durante una reunión convocada por el Consorcio de Modelización y Análisis en TB. El programa de investigación encontró esferas de alta prioridad para las futuras iniciativas de modelización, como son: 1) el diagnóstico difícil y la alta mortalidad de la coinfección por el TB-VIH; 2) el alto riesgo de progresión hacia la enfermedad tuberculosa; 3) los sistemas de atención de la TB en los entornos con alta prevalencia del VIH; 4) la incertidumbre sobre la evolución natural de la TB-VIH; y 5) las intervenciones conjuntas en materia de TB-VIH. El progreso eficaz y rápido hacia la culminación de este programa de modelización exigirá una coordinación entre la comunidad de la modelización y los principales interesados directos, entre ellos los promotores, los responsables de elaborar las políticas sanitarias, los donantes y los funcionarios encargados de las cuestiones financieras a escala nacional y regional. Un diálogo sostenido logrará la difusión eficaz de los resultados recientes y el planteamiento oportuno de nuevos aspectos relacionados con las políticas.