A Simple Introduction to Tuberculosis Modelling

Union World Conference on Lung Health

Mexico

www.tb-mac.org

Learning objectives

1. Introduce you to the basic structures, assumptions, principles, and concepts of Tuberculosis modelling

2. Introduce key aspects of *Mtb* natural history and impact & cost-effectiveness of TB care & control programmes

3. Provide hands-on experience of using a TB models, and the insights into the transmission dynamics and control that they can provide

4. Provide training in how to critically appraise modelling papers

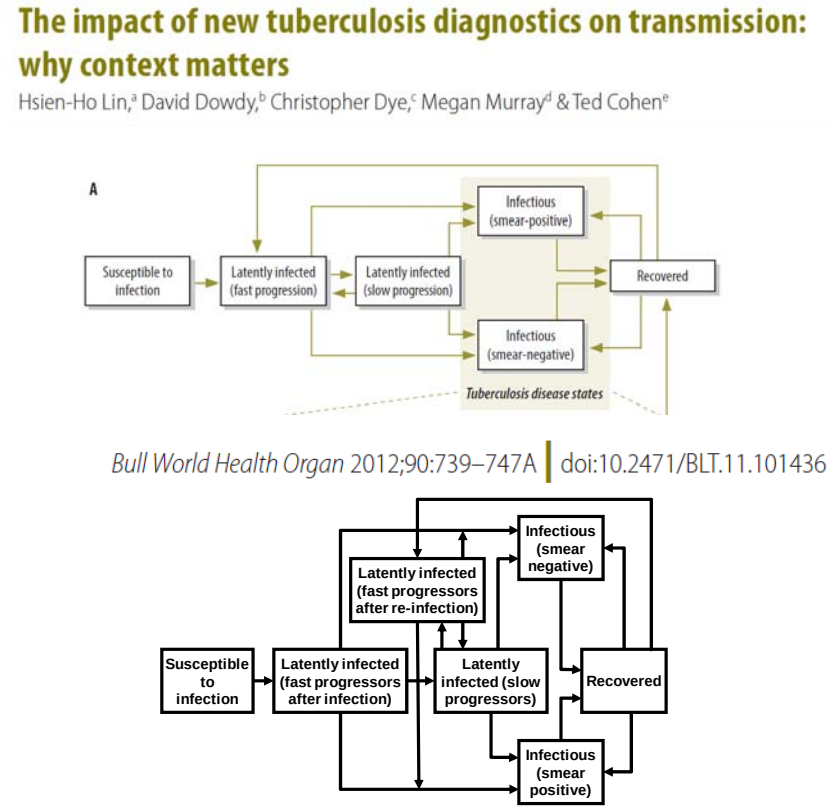
5. Highlight the modelling resources available from the TB Modelling and Analysis Consortium (TB MAC)

Overview of the day

- 8:00 – 8:10 **Introduction to the day** (Richard)
- 8:10 – 8:50 (40m) Lecture 1: **An introduction to Tuberculosis modelling** (Richard)
- 8:50 – 10:35 (1h45m) Practical 1: **Setting up a model of *Mtb*** (Emilia & Tom) (take coffee anytime if needed)
- 10:35– 11:30 (55m) Paper Discussion: **How to critically review a modelling paper** (Philip and Finn)
- 11:30 – 12:25 (55m) Lecture 2: **Tuberculosis modelling – Interventions and cost effectiveness** (Rein and Fiammetta)
- 12:25 – 13:50 (1h25m) Practical 2: **Modelling the impact and cost effectiveness of TB Interventions** (Emilia, Tom & Fiammetta) (take coffee anytime if needed)
- 13:50 – 14:00 **Summary of the day and TB MAC** (Richard)

Example model used throughout day (*Lin et al*, 2012)

- There is a large TB modelling literature
- To help with learning, we will often refer to the same model
- As all models, this model has its strengths and weaknesses



Adapted from Lin, WHO Bull, 2011

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Who are we?

A Simple Introduction to Tuberculosis Modelling

Richard White

LSHTM/ TB MAC

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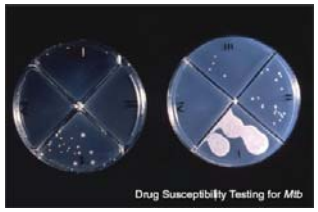
Lecture 1: A Simple Introduction to Tuberculosis Modelling

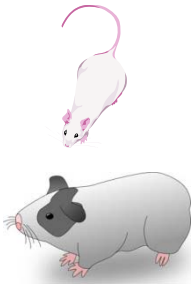
- Session learning objectives
  1. Understand what a TB model is, and why we might bother setting one up
  2. Understand the steps to setting up a TB model

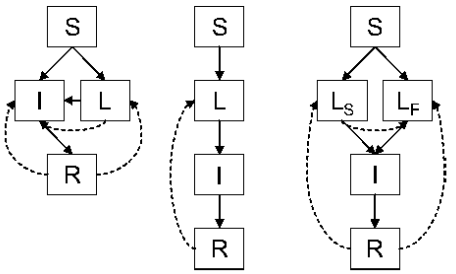
What is a (TB) model?

- A model is any approximation or simplification of reality
  - A picture
  - In vitro
  - Animal
  - Statistical
  - Mathematical

- *'Models are always wrong, but some are useful'* George Box







Colijn, 2006

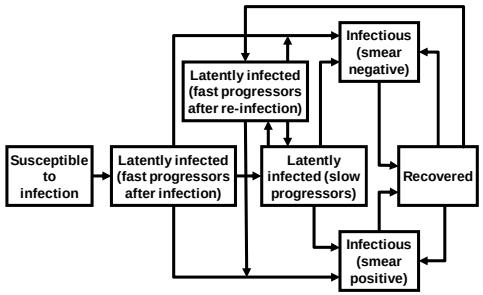
$$\frac{dS(t)}{dt} = -\beta \frac{I}{N}(t)S(t)$$

$$\frac{dL(t)}{dt} = \ldots$$

$$\frac{dI(t)}{dt} = \ldots$$

Why bother setting up a TB model?

- Many reasons
  - Understand natural history or epidemiology
  - Control strategies / RCTs
    - Estimate impact
    - Key determinants
    - Power calculations
  - Identify what research/ data collection would be most useful
  - 'Campfire' around which to think about a problem
- *Lin et al* used a model to estimate the impact of new TB diagnostics



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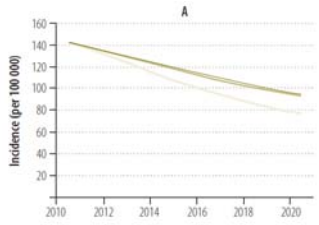

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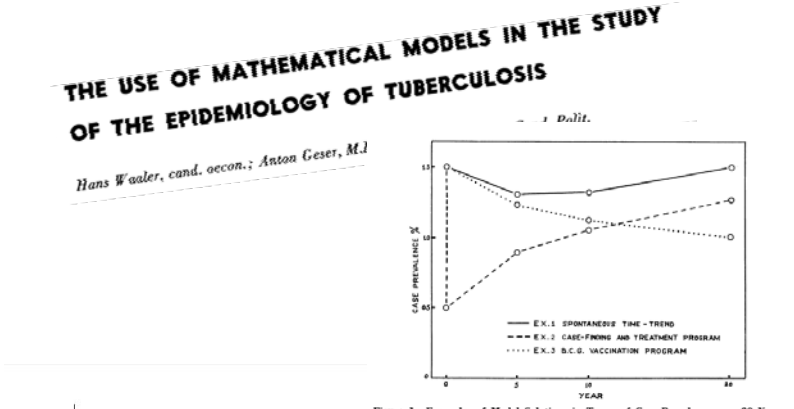
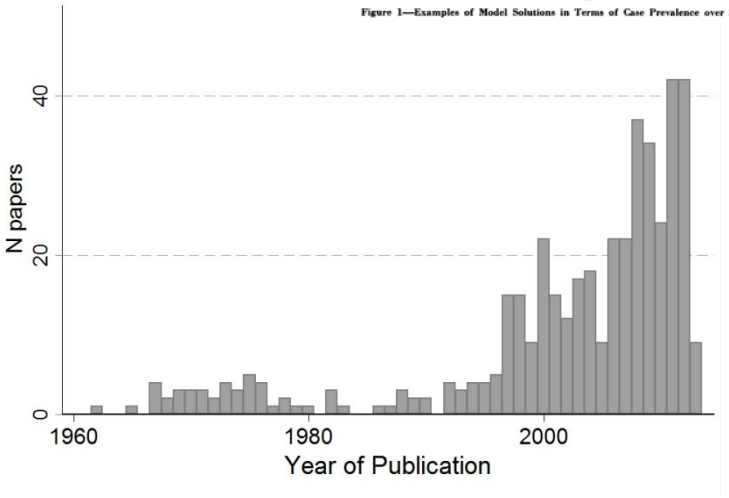
There is lots of TB modelling out there

- First published mathematical model applied to TB was by Hans Waaler in 1962
- Since then over 400 papers published
  - See http://tb-mac.org/Resources for all modelling papers


THE USE OF MATHEMATICAL MODELS IN THE STUDY OF THE EPIDEMIOLOGY OF TUBERCULOSIS

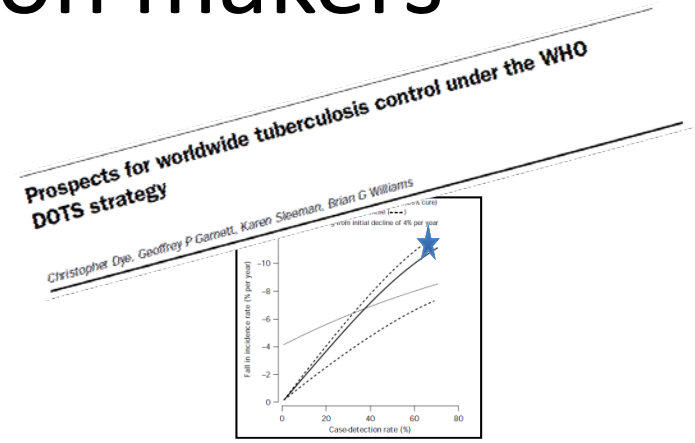
Hans Waaler, cand. oecon.; Anton Geser, M.D.

Figure 1—Examples of Model Solutions in Terms of Case Prevalence over 20 Years



Modelling is (increasingly) used by policy/decision makers

- Key TB example: Dye, 1998
  - Global impact of DOTS
  - Key outcome
    - TB disease incidence & TB mortality
  - Findings
    - Where TB stable and HIV absent, 70% case detection and 85% cure would ↓
      - incidence by 11%/y
      - mortality by 12%/y
    - Smaller impact in populations in which incidence already in decline because ↓ % disease due to reinfection
    - BUT predicted impact not observed ...
- Research funding decision making
  - Modelling required component of recent NIH HIV combination-prevention RCT proposals ('PopART'…)
  - BMGF changed policy of vaccine research funding citing modelling evidence
- Govt Policy
  - UK Joint Committee on Vaccination and Immunisation
  - Modelling used in first ever TB and HIV investment case in South Africa => screening & conditional grant
  - ↑ in USA



"… We can reverse this trend. Mathematical models show that scaling up combination prevention to realistic levels in high-prevalence countries would drive down the worldwide rate of new infections by at least 40-60%…."

US Secretary of State, Nov 8, 2011

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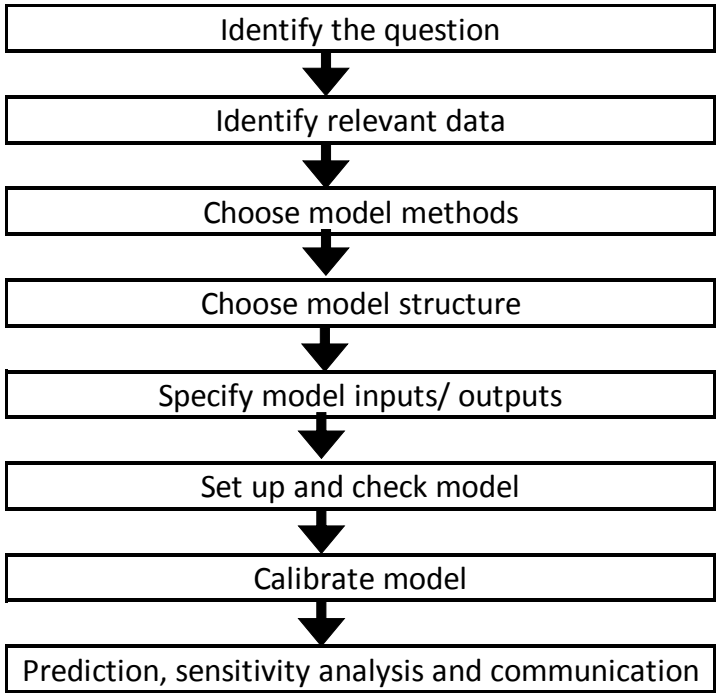
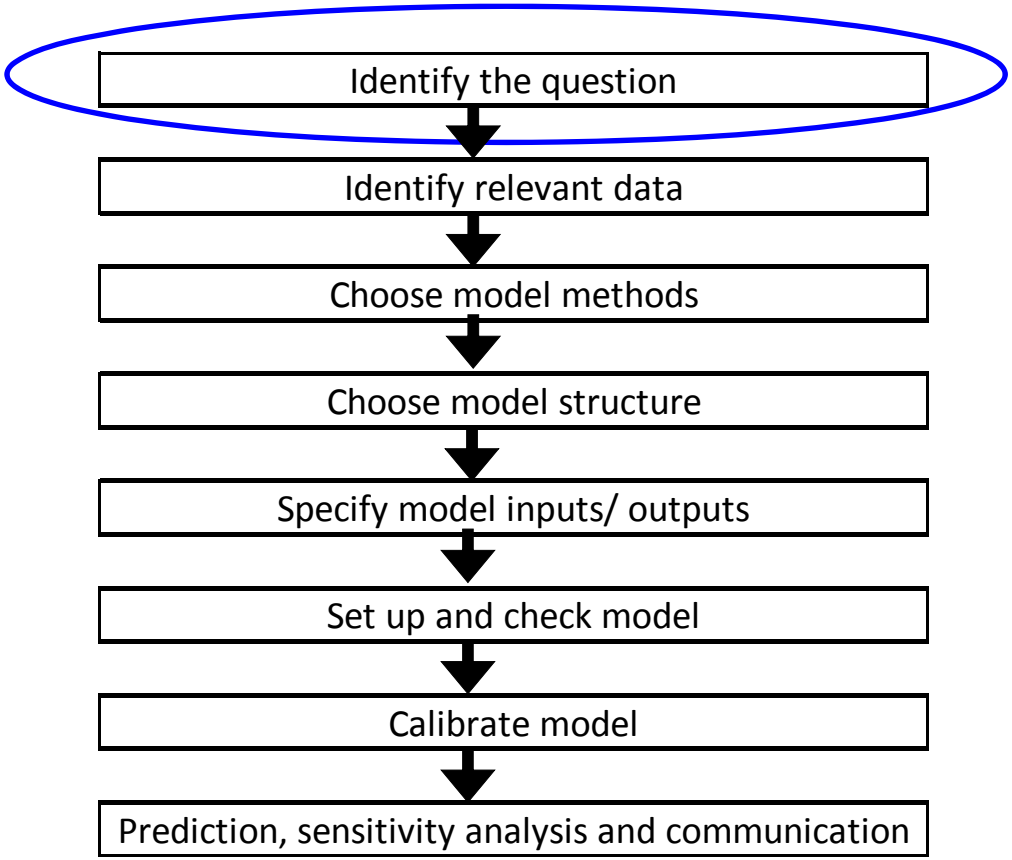
Steps to set up a model

- Ok, so we have an issue on which we think a model may help stop us making a daft decision
  - How do we go about it?
- Only main steps shown
- Looks straightforward but iterative in reality



After Vynnycky & White, 2010

Steps to set up a model

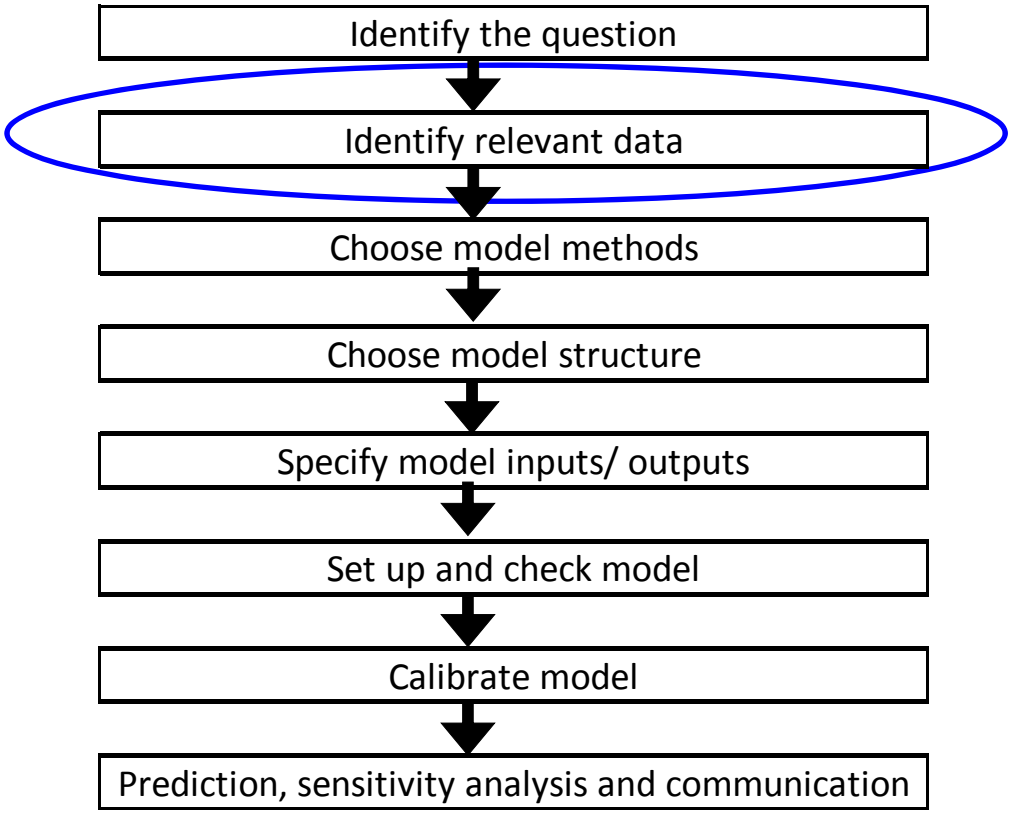


Identify the question

- First two steps apply to any scientific question
- What exactly do we want to know?
- Check other approaches (eg statistical analysis) can't answer
- Use to set model structure and ensure results relevant

- *Lin et al*
  - To estimate the impact of new tuberculosis diagnostics on tuberculosis transmission, given the complex contextual factors that can lead to patient loss before diagnosis or treatment

Steps to set up a model



Identify relevant data

- Collate existing knowledge
  - Research papers, grey literature, lab reports, existing modelling exercises...
  - Organise quantitatively by
    - Transmission
    - Epidemiology
    - Natural history
    - Control options
  - Discuss review with experts

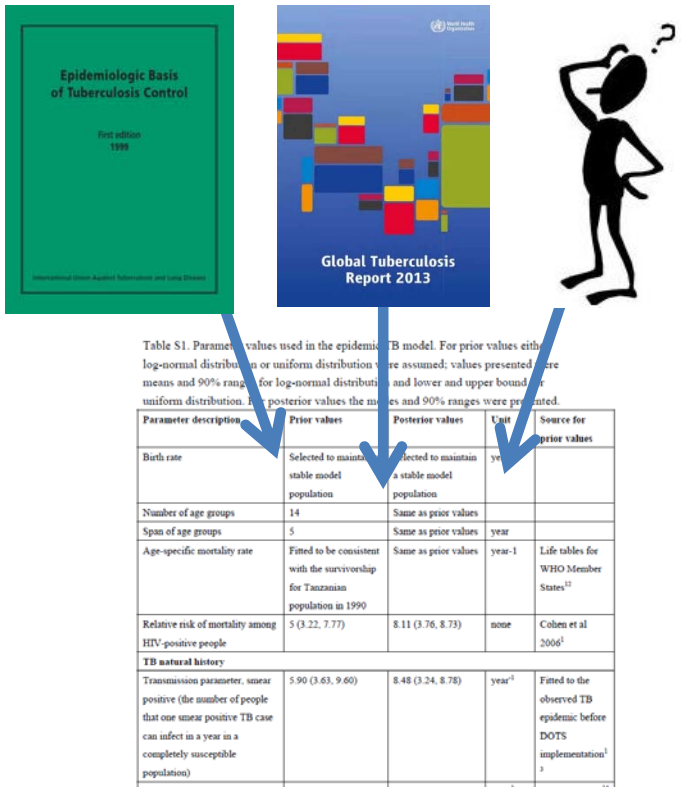
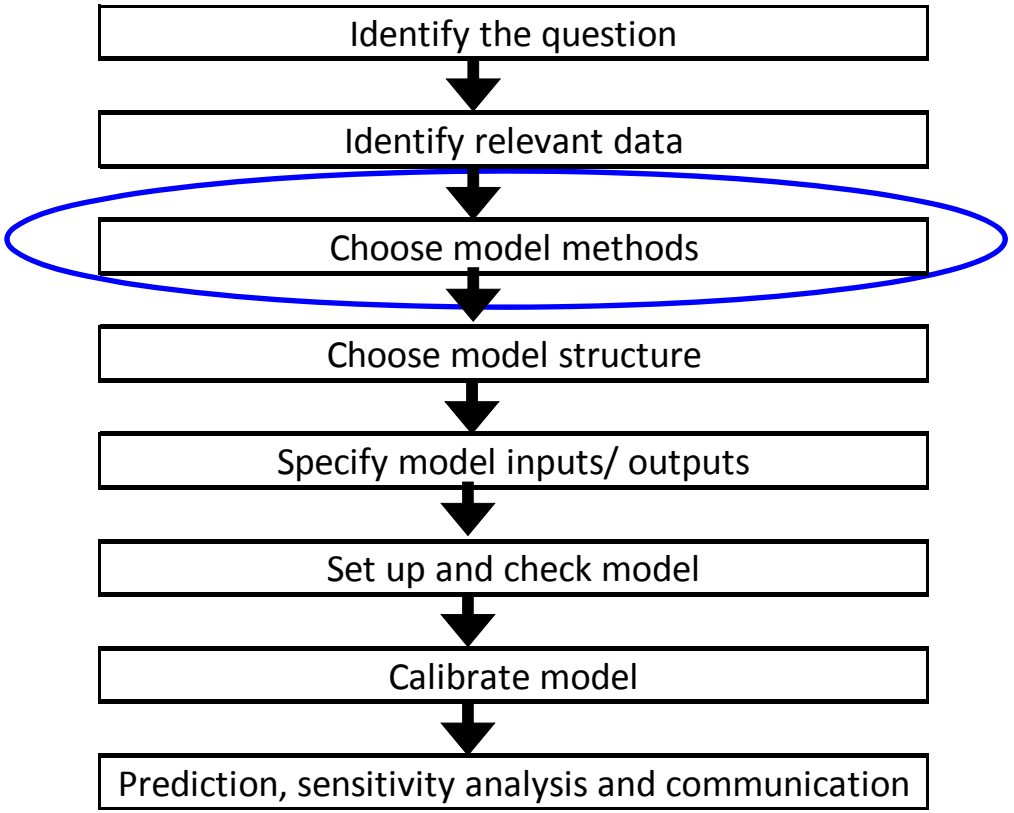


Table S1. Parame values used in the epidemi TB model. For prior values eith log-normal distribu n or uniform distribution re assumed; values presented re means and 90% rang for log-normal distribut and lower and upper bound r uniform distribution. r posterior values the m es and 90% ranges were pr nted.

Parameter description	Prior values	Posterior values	Unit	Source for prior values
Birth rate	Selected to maintain stable model population	lected to maintain a stable model population	ye	
Number of age groups	14	Same as prior values		
Span of age groups	5	Same as prior values	year	
Age-specific mortality rate	Fitted to be consistent with the survivorship for Tanzanian population in 1990	Same as prior values	year-1	Life tables for WHO Member States[32]
Relative risk of mortality among HIV-positive people	5 (3.22, 7.77)	8.11 (3.76, 8.73)	none	Cohen et al 2006[1]
TB natural history				
Transmission parameter, smear positive (the number of people that one smear positive TB case can infect in a year in a completely susceptible population)	5.90 (3.63, 9.60)	8.48 (3.24, 8.78)	year[-1]	Fitted to the observed TB epidemic before DOTS implementation[1 3]

Rieder, H. L. (1999). Epidemiologic basis of tuberculosis control
WHO TB Report 2013 ; Lin, WHO Bull, 2011

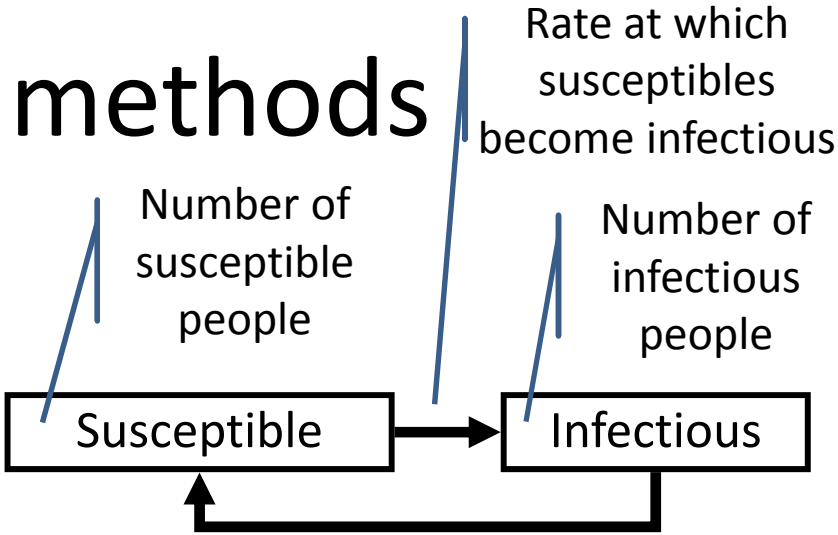
Steps to set up a model

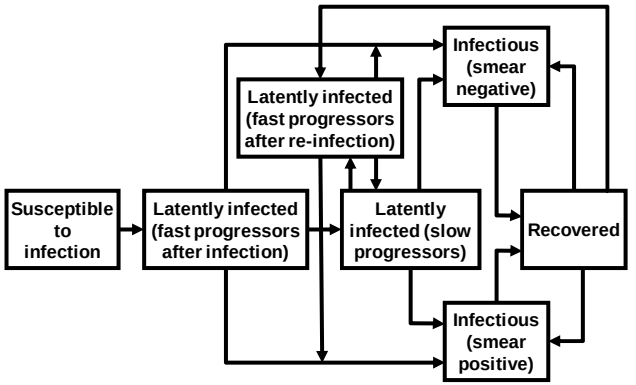


Chose model methods

- Method depends on needs
  - Do you need to see how quickly changes will occur over time? (dynamic vs. static)
  - Do you want to model at the level of groups or individuals? (compartmental vs. individual based)
  - Do you need to see effects of chance? (stochastic vs. deterministic)
  - Do you need to explicitly see the effect on transmission (transmission vs. cohort)

- Most infectious disease models are *dynamic, compartmental, deterministic, transmission* models
  - As *Lin et al*, and practical
  - Tend to focus on this approach for rest of day





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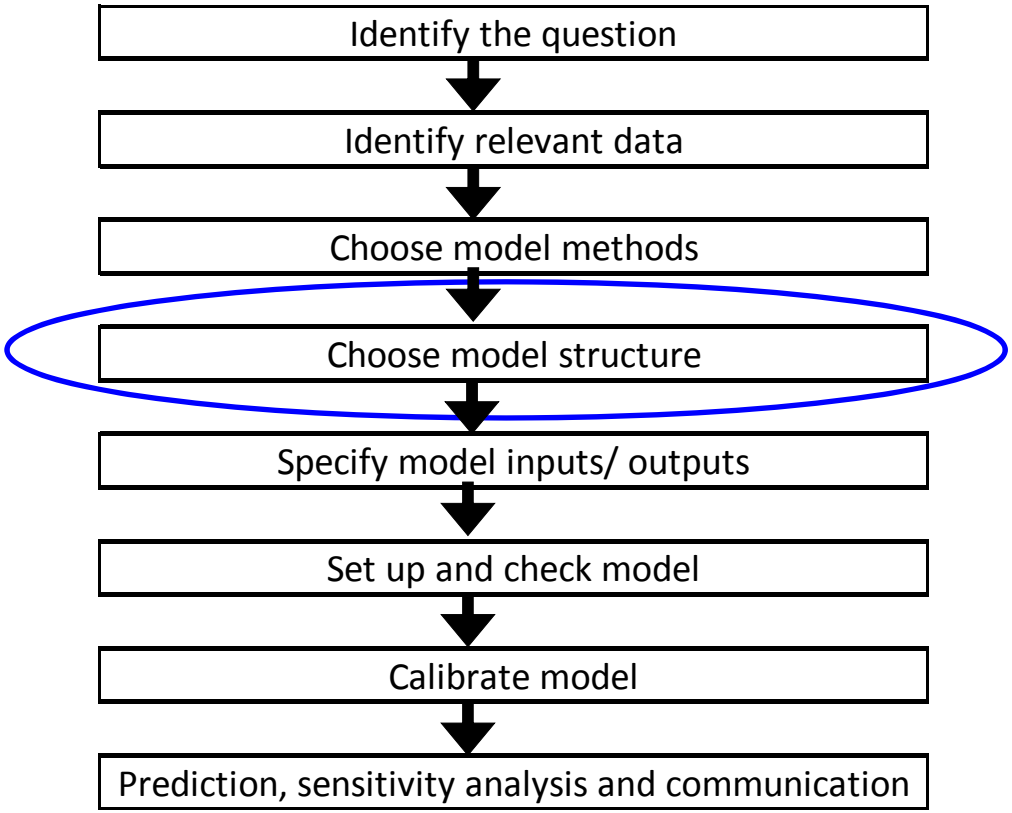
Steps to set up a model



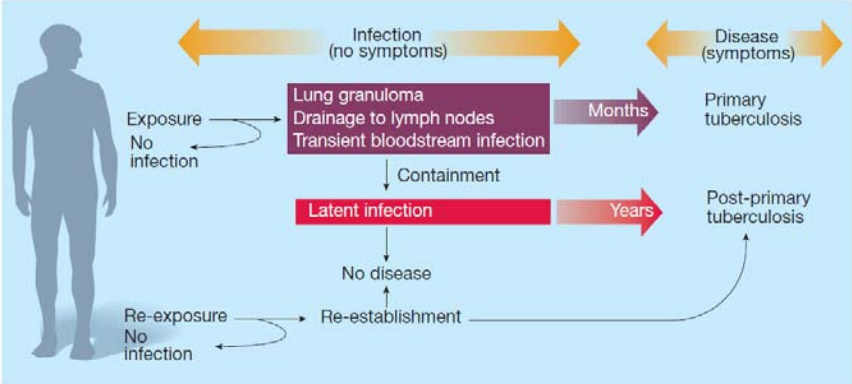
Chose model structure

- Structure for TB models tricky
- *Mtb* natural history is complex and poorly understood (as difficult to diagnose)
- Key features
  - Distinction between infection and disease
    - most infections don't result in disease
    - disease may result after a long delay
    - but more likely after a short one
    - age-dependent
  - **Reinfection**
    - individuals may be infected again
    - but some protection from disease
  - heterogeneity in infectiousness
  - Interactions with HIV, diabetes ...

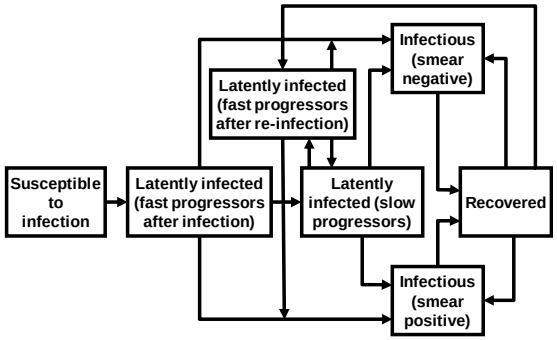
- Model structure will also depend on
  - population groups you want to have results on
  - time period over which you want to model

- While bearing in mind that *'models should be as simple as possible and no simpler'* ~Einstein

- All models simplify, but most TB models tend to incorporate the top key features above



Bishai, Nature, 2000



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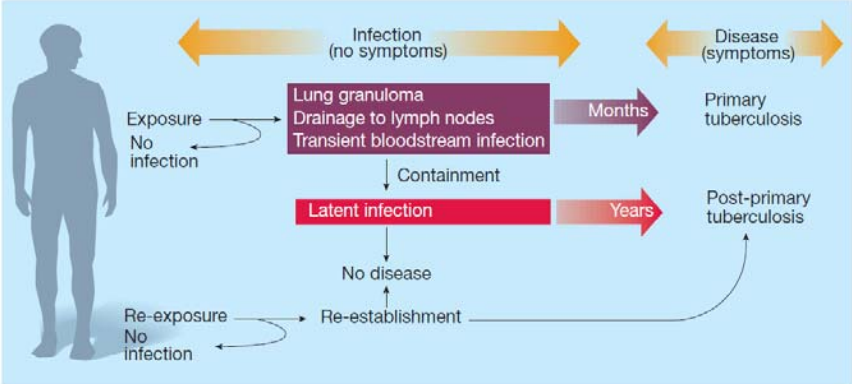
Chose model structure

- Take key features of TB and see how modellers implement them



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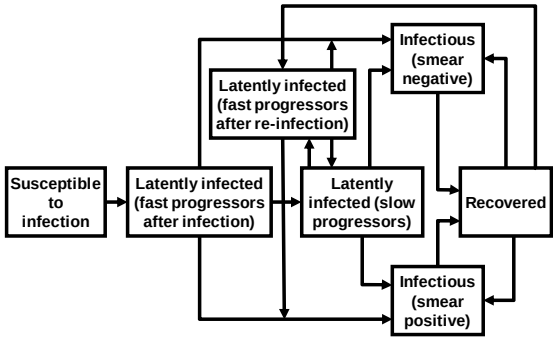
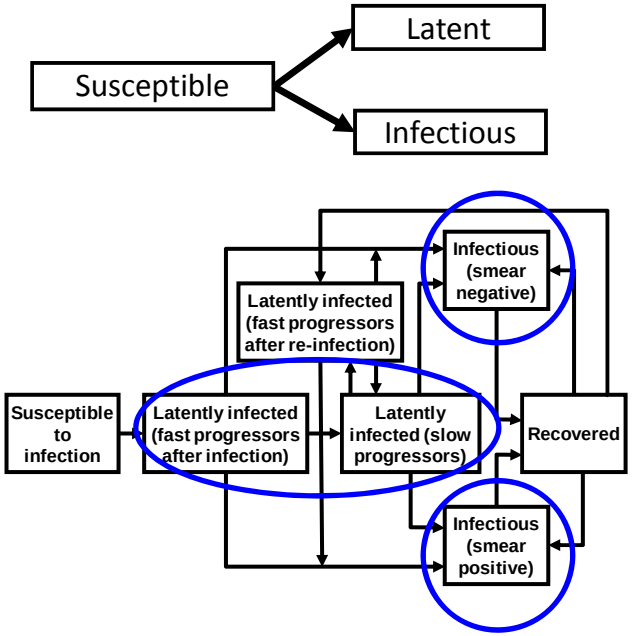


Adapted from Lin, WHO Bull, 2011

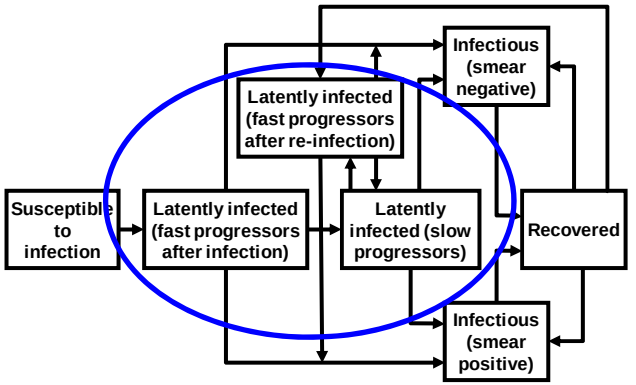
Distinction between infection and disease

- Infection and disease states modelled separately
- Infection incidence modelled as either
  - leading to latent or diseased directly
  - all disease reached via moving thru ‘latent’ state(s) (as *Lin et al*)



Declining risk of disease by time since infection

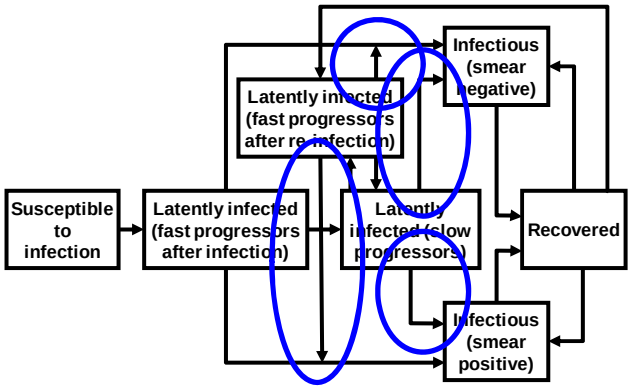
- Model at least two states of latency
  - Recently (re)infected
  - Infected a longer time ago
  - *Lin et al* modelled three
- Model higher rates of progression to disease among recently (re)infected (*'fast progressors'*) than those infected a longer time ago *('slow progressors')*



Reinfection

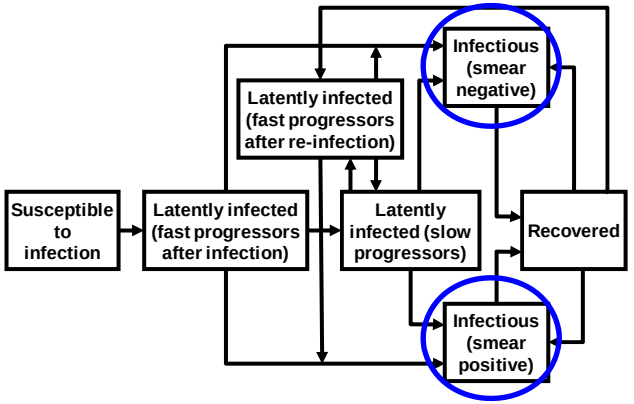
- Reinfection is often modelled just by changing the arrows (the rates) from latent to disease boxes
- These arrows now represent
  - progression after reactivation of latent disease, **and**
  - reinfection and rapid progression

- Protection due to current infection against disease after reinfection - typically modelled as a lower risk of progressing to disease, than for initial infection



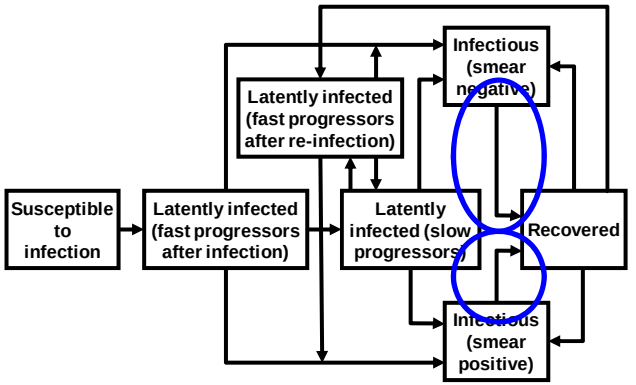
Variable infectiousness

- Variable infectiousness is traditionally represented by a smear positive and a smear negative box



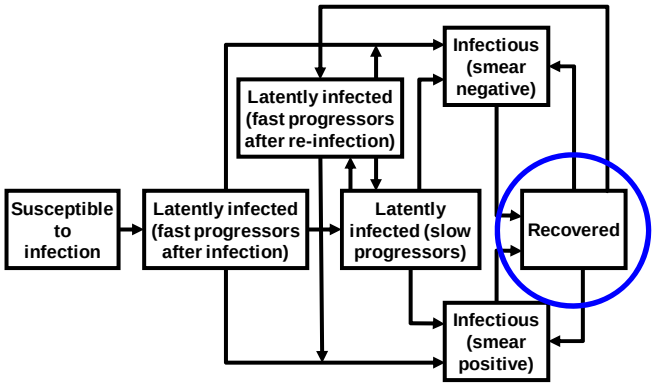
Detection and treatment

- Detection and treatment is most simply modelled as rate of detection, treatment and recovery
- As with all of these simplifications, this ignores much real-life complexity
  - see later today



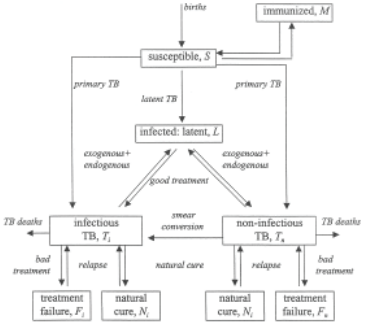
Recovered

- What happens after ‘successful’ treatment depends on what the modeller thinks ‘successful’ treatment does
- *Lin et al* assume ‘Recovereds’
  - are at risk of reactivation (relapse), ie are not totally cured
  - Have some protection against disease after reinfection, ie different from ‘susceptibles’

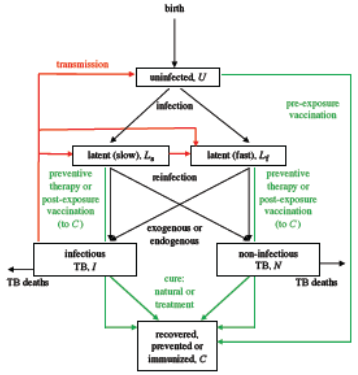


Many other structures

- Many other structures
  - Assuming different natural history
  - Incorporating other things that the modeller
    - thinks are important
    - wants to explore
    - Eg, MDR, HIV ...

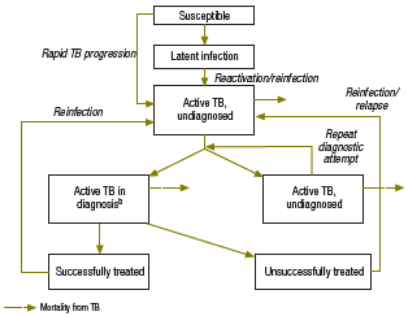


(a) [Dye et al.; 1998]



(b) [Dye and Williams; 2008]

(c) [Dye and Williams; 2000]



(d) [Dowdy and Chaisson; 2009]

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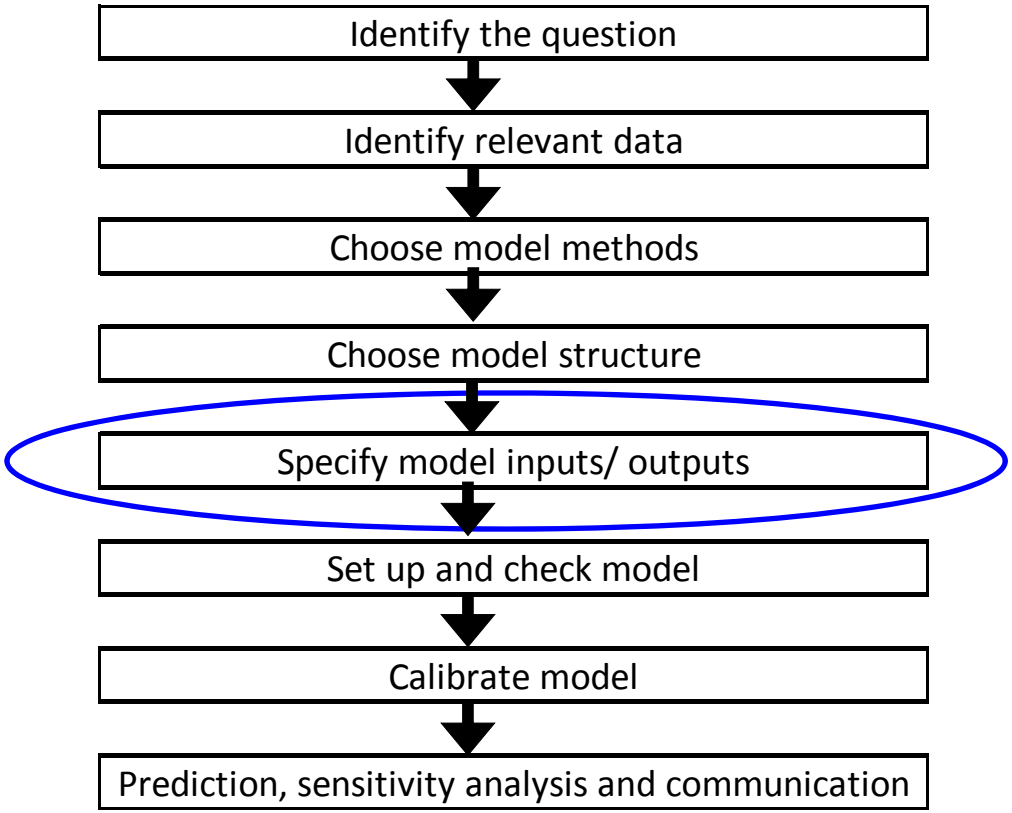
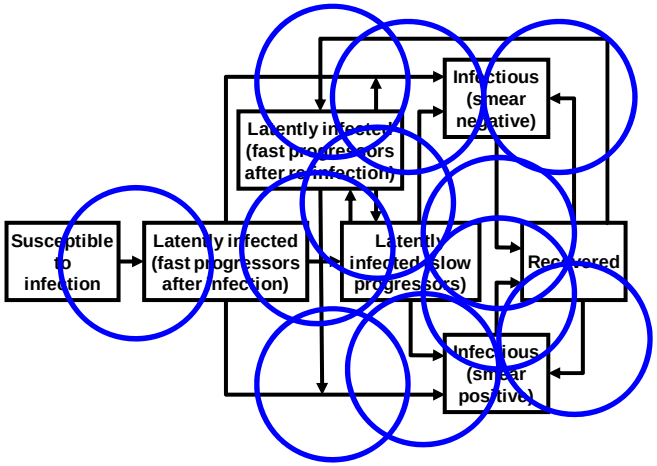
Steps to set up a model



Specify model inputs/ outputs

- Need to come up with ranges for model input and outputs, eg
  - Effective contact rate (ecr)
    - one that is sufficient to lead to transmission if it occurs between an uninfected and an infectious person
  - Rate of TB disease self cure
  - TB disease mortality rate
  - Detection and treatment rate
  - TB disease incidence

- Main problem is usually lack of data, estimate using
  - Primary data collection
  - Data analysis (statistical modelling)
  - Other modelling exercises
  - Expert opinion (?)



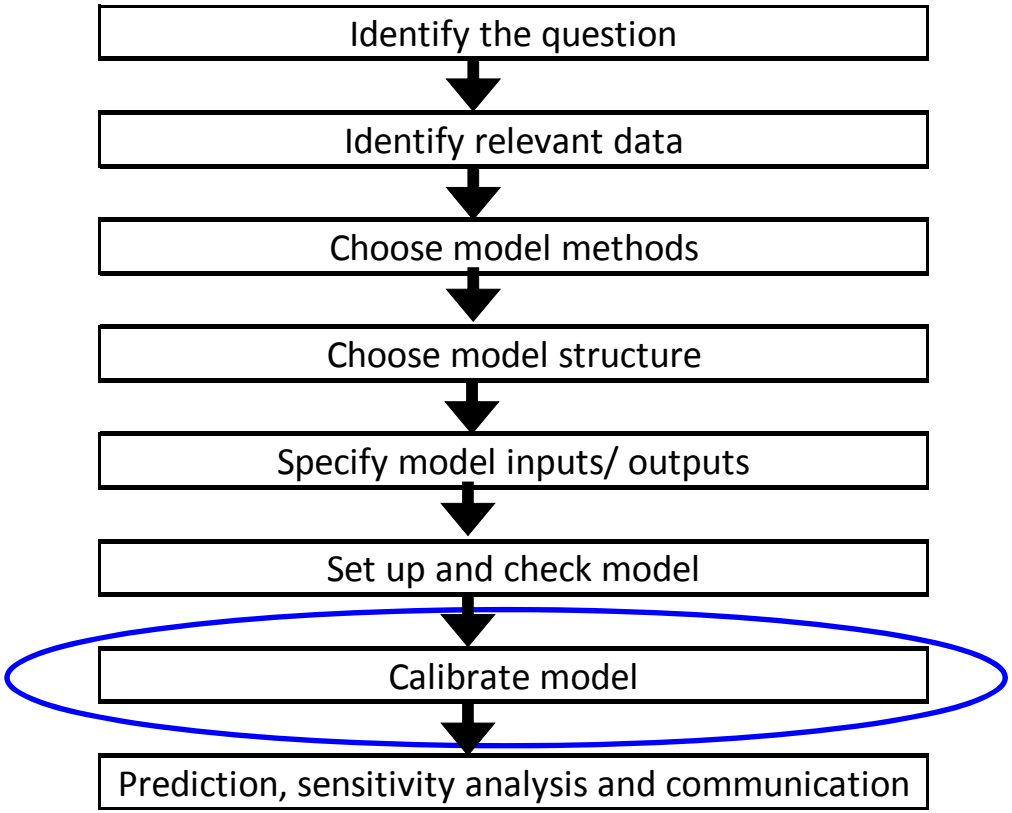
Set up and check model

- Once model structure designed and input parameters specified,
- Model equations can be set up using spreadsheet or computer program
- Predict (eg) the number of cases, deaths over time...

- Much bug checking, error correction, lack of sleep...

http://simpsons.wikia.com/wiki/Jeffrey_Albertson

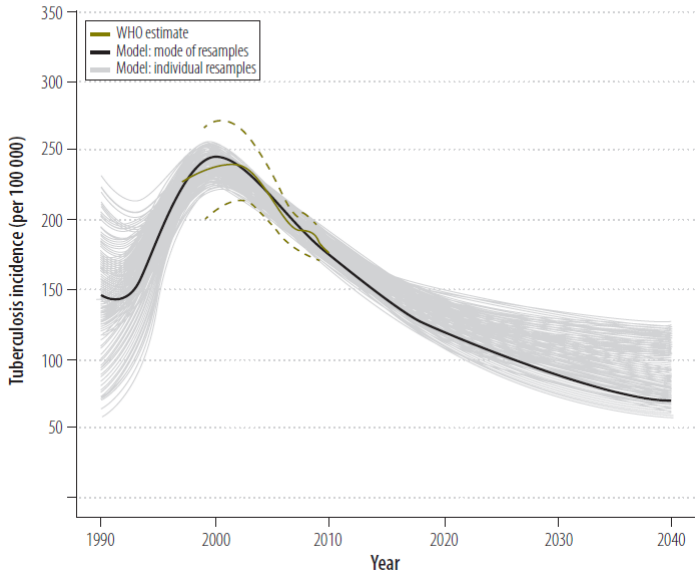
Steps to set up a model



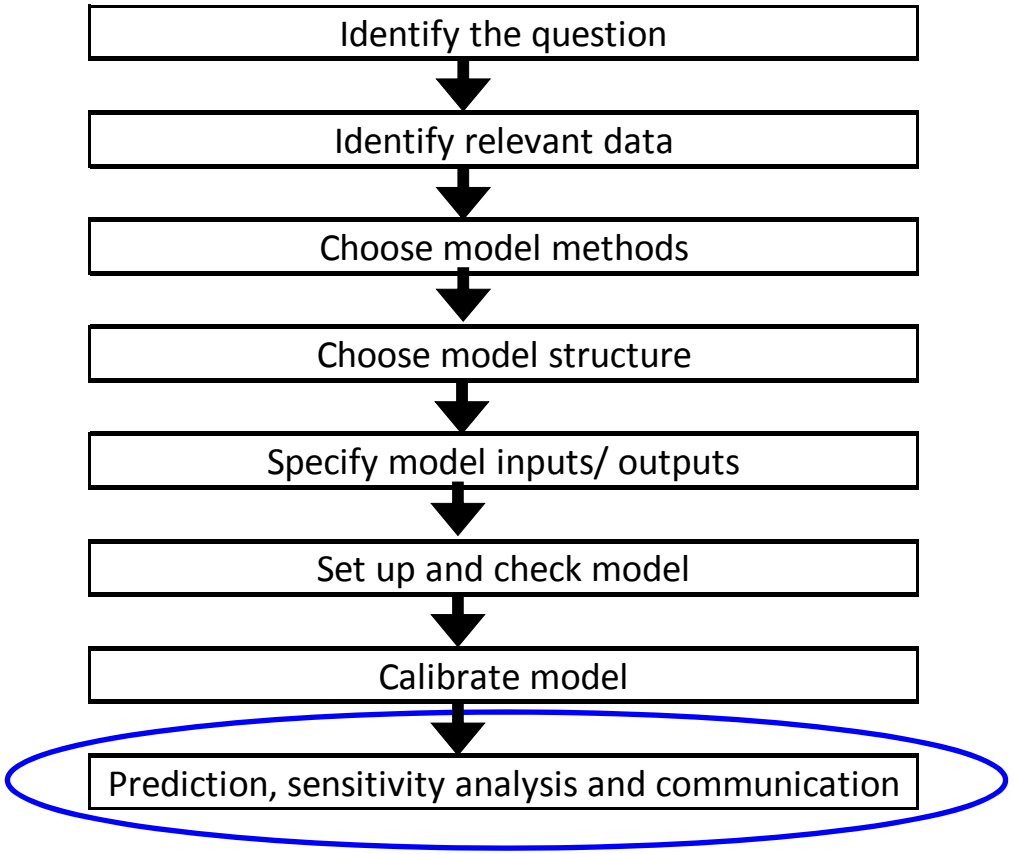
Calibrate model

- Model outputs are commonly calibrated to important characteristics relevant to the research question, eg
  - population size, disease burden, ...
- *Lin et al*, calibrated to TB disease incidence trend

Fig. 2. **Incidence of tuberculosis (all forms) in the United Republic of Tanzania based on WHO estimates and projected incidence based on the calibrated epidemic model**



Steps to set up a model



Prediction, sensitivity analysis and communication

- Once model has been bug checked and has been calibrated to available data
- Use model to make **predictions**
- *Lin et al* predicted the impact of 3 diagnostic strategies on TB incidence, prevalence and mortality trends, and *Mtb* infection incidence

- Will be much uncertainty in these predictions
- Modellers job to carry out **sensitivity/ uncertainty analysis** and to communicate this uncertainty clearly
- *Lin et al* explore sensitivity to operational factors or health systems 'context'

- **Communication** considerations critical
  - Publish work with technical appendix (peer review and reproducibility)
  - Policy briefings for decision makers?
  - Release tool for use?

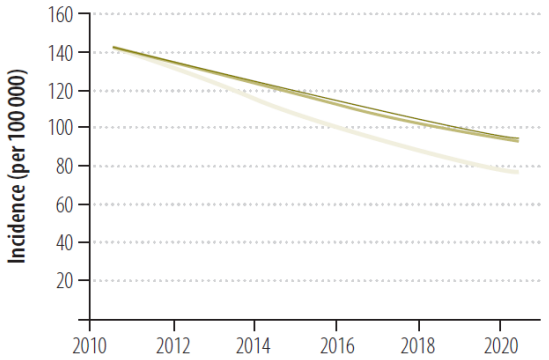
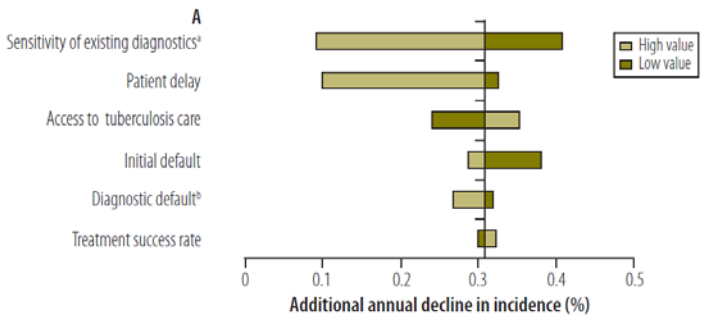


Fig. 4. **Sensitivity analysis on the influence of operational factors on the impact of a sensitivity diagnostic tool on annual decline in pulmonary tuberculosis incidence**



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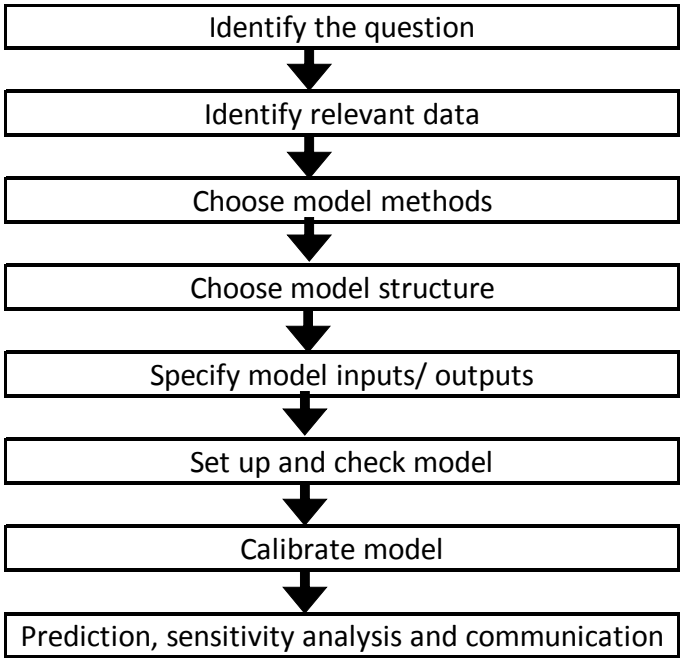
Summary of the session

I hope you now ...

1. ... understand what a TB model is, and when you might bother setting one up
2. .. understand the steps to setting up a TB model

Now let's get our hands on our first TB model ...



A Simple Introduction to Tuberculosis Modelling

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[All other sessions here]

A Simple Introduction to Tuberculosis Modelling

Summary of Day

and TB MAC

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Summary of the day

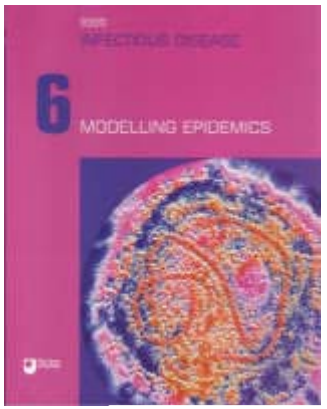
- Summary

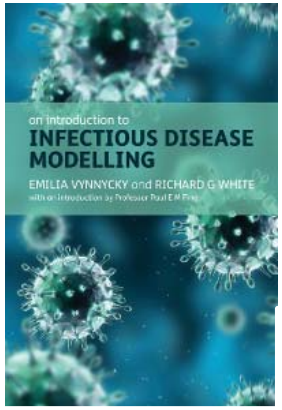
1. Introduce participants to the basic structures, assumptions, principles, and concepts of Tuberculosis modelling
2. Introduce key aspects of Mtb natural history and the impact and cost-effectiveness of TB care & control programmes
3. Provide hands-on experience of using a TB models and the insights into the transmission dynamics and control that they can provide
4. Provide training in how to critically appraise modelling papers.
5. Highlight the modelling resources available from the TB Modelling and Analysis Consortium (TB MAC).

- *Now get on and adapt the models for your own use...*

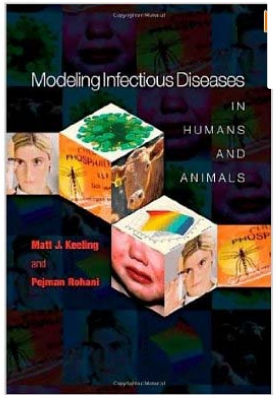
Further reading

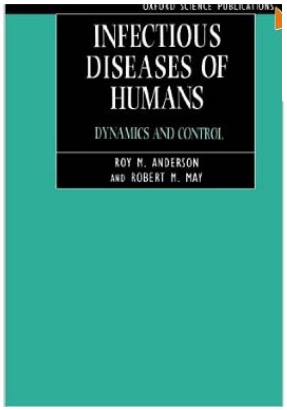
- Gentler introductions
  - Modelling epidemics. Farrington. Open University Press. 2008
  - An introduction to infectious disease modelling. E Vynnycky and RG White. Oxford University Press, 2010.
    - For further details and computer exercises: www.anintroductiontoinfectiousdiseasemodelling.com
    - Also available as a ebook





- More mathematical
  - Modeling infectious diseases in animals and humans. M Keeling and P Rohani. Princeton University Press, 2007
  - Infectious diseases in humans. RM Anderson and RM May. Dynamics and control. Oxford University Press, 1991





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Further courses

- An introduction to infectious disease modelling and its applications
  - LSHTM, 2 wk summer course (https://goo.gl/LhwN99)
- Advanced TB Diagnostic Research
  - McGill, 2 wk summer course, includes diagnostic modelling (https://goo.gl/FgdZZN)
- Mathematical Models for infectious Disease Dynamics
  - Cambridge, UK, Feb, uses R, 2 wks (https://goo.gl/NQGAvW)
- Individual-based Modeling in Epidemiology
  - 5d, Nov, Antwerp (https://goo.gl/XhijRy)
- Statistics and Modeling in Infectious Diseases
  - Washington, July, 3wk (https://goo.gl/265AcK)
- Epidemiology and control of infectious disease
  - Imperial, London, Summer course (https://goo.gl/MVFDjJ)
- Summer boot camp of infectious disease modeling
  - Hokkaido University, Japan (https://goo.gl/EtFhDj)
- Modeling and Analysis of Infectious Diseases
  - Summer, 2 wk, NCTS, Taiwan (https://goo.gl/Q6j6f7)

Many other courses...

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MONASH University

World Health Organization

aighd

HARVARD UNIVERSITY

INSTITUTE FOR DISEASE MODELING
INTELLECTUAL VENTURES

The Global Fund

BILL & MELINDA GATES foundation

Yale University

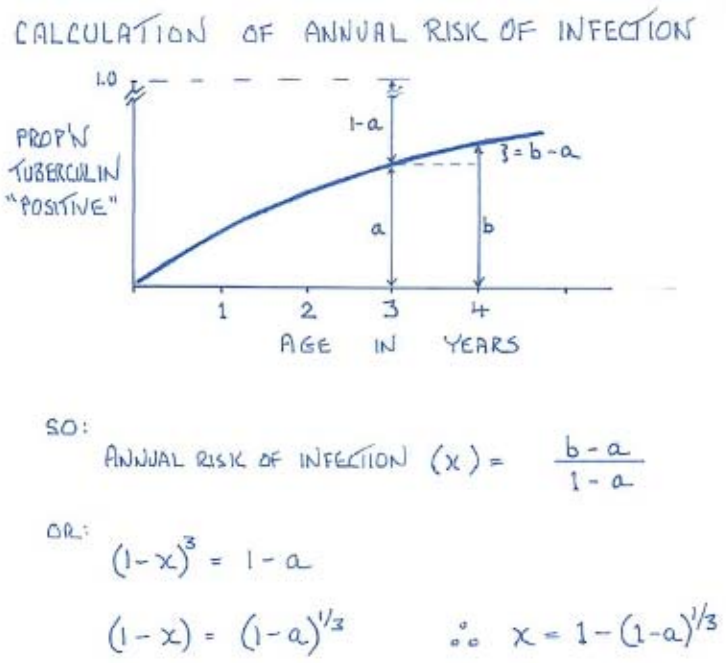
JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

USAID FROM THE AMERICAN PEOPLE

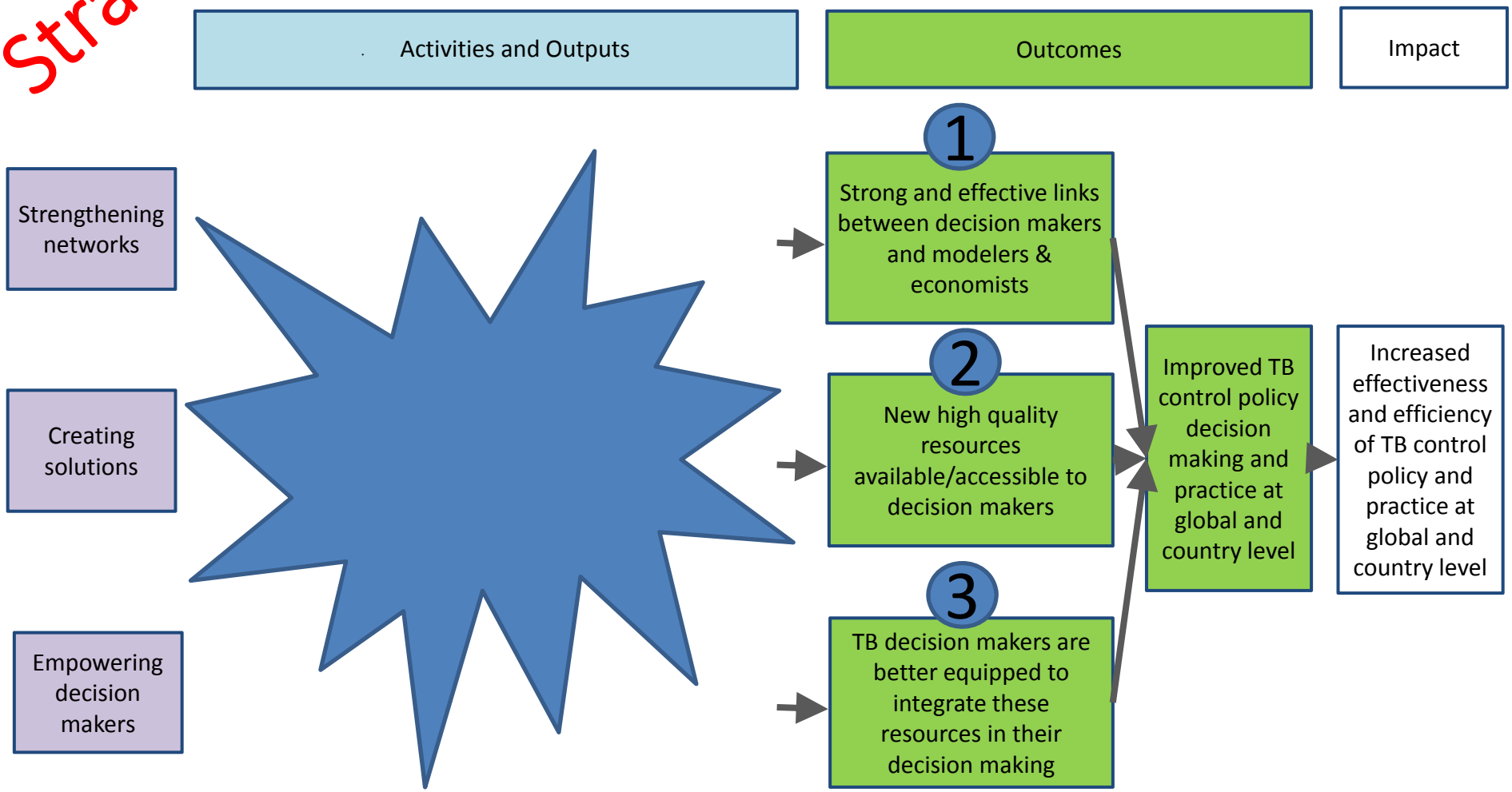
UCL

TB MAC background

- Complex natural history, range of interventions, variation in settings => global and country decision makers face great uncertainty
- Modelling can be used to compare strategies and quantify uncertainty
- But
  - Lack of co-ordination
  - Limited data, models and modellers
  - Decision makers & modellers uninformed



Strategy


Activities and Outputs
Outcomes
Impact
Strengthening networks
Creating solutions
Empowering decision makers
1
Strong and effective links between decision makers and modelers & economists
2
New high quality resources available/accessible to decision makers
3
TB decision makers are better equipped to integrate these resources in their decision making
Improved TB control policy decision making and practice at global and country level
Increased effectiveness and efficiency of TB control policy and practice at global and country level

TB MAC who's who

Open to anyone using mathematical models or other quantitative methods to answer TB control questions



Committee

Current

- Katherine Floyd - WHO
- Anna Vassall - LSHTM
- Ted Cohen - Yale
- David Dowdy – JHU
- Michael Kimerling – KNCV
- Philip Welkhoff - IDM
- David Wilson – Gates
- Nick Menzies – Harvard
- James Trauer – Monash







Future

- Frank Cobelens - AIGHD
- Hsien-Ho Lin –Taiwan University
- Jason Madan –Warwick

Core Advisory Panel

- Ibrahim Abubakar – UCL
- Sevim Ahmedov – USAID
- Liz Corbett - LSHTM
- Philippe Glaziou - WHO
- Johannes Hunger – Global Fund





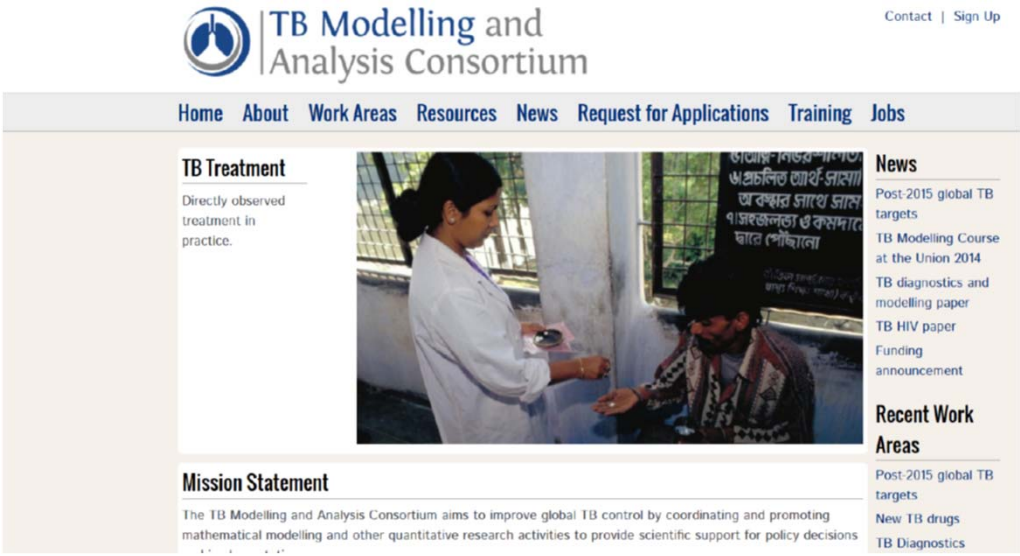
Secretariat

- Christina Albertsen
- Finn McQuaid
- Rein Houben
- Richard White




TB MAC Resources

- Up to date information, meeting reports, jobs, and funding news
- Systematic reviews databases
  - All mathematical and economic TB modelling
  - TB-HIV
  - Diagnostics
- Join up to mailing list (email tb-mac@lshtm.ac.uk)



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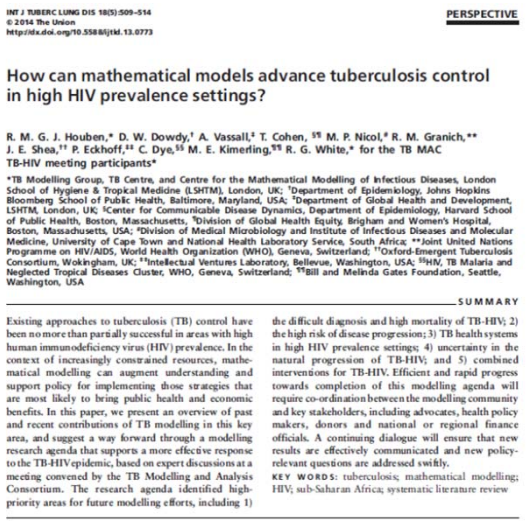
TB MAC Activities

- Previous work areas
  - TB/HIV, Diagnostics, Drugs
  - Post-2015 WHO Targets – 3 meetings
  - Socio-economic determinants
  - Case finding

- Funding for modelling work
  - Case finding – open until 31 October 2017!
  - http://tb-mac.org/RFAs/RFA/10

- TB Modelling Course at Union Conferences (Today!)



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PERSPECTIVE

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

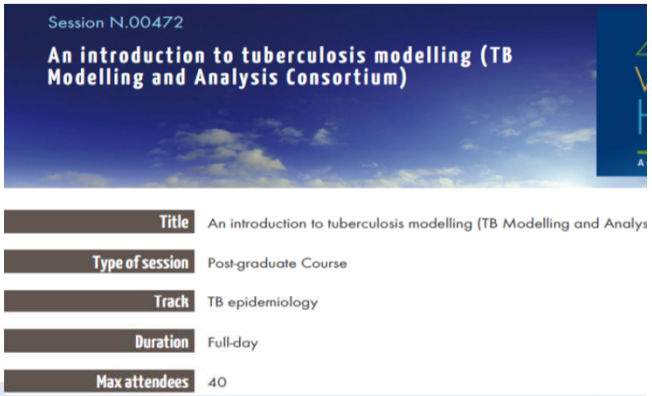
R. M. G. J. Houben,* D. W. Dowdy,† A. Vassall,‡ T. Cohen, §¶ M. P. Nicol,# R. M. Granich,** J. E. Shea,†† P. Eckhoff,‡‡ C. Dye,§§ M. E. Kimerling,¶¶ R. G. White,* for the TB MAC TB-HIV meeting participants*

*TB Modelling Group, TB Centre, and Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine (LSHTM), London, UK; †Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; ‡Department of Global Health and Development, LSHTM, London, UK; §Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, ¶Division of Global Health Equity, Brigham and Women's Hospital, Boston, Massachusetts, USA; #Division of Medical Microbiology and Institute of Infectious Diseases and Molecular Medicine, University of Cape Town and National Health Laboratory Service, South Africa; **Joint United Nations Programme on HIV/AIDS, World Health Organization (WHO), Geneva, Switzerland; ††Oxford-Emergent Tuberculosis Consortium, Wokingham, UK; ‡‡Intellectual Ventures Laboratory, Bellevue, Washington, USA; §§HIV, TB Malaria and Neglected Tropical Diseases Cluster, WHO, Geneva, Switzerland; ¶¶Bill and Melinda Gates Foundation, Seattle, Washington, USA

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



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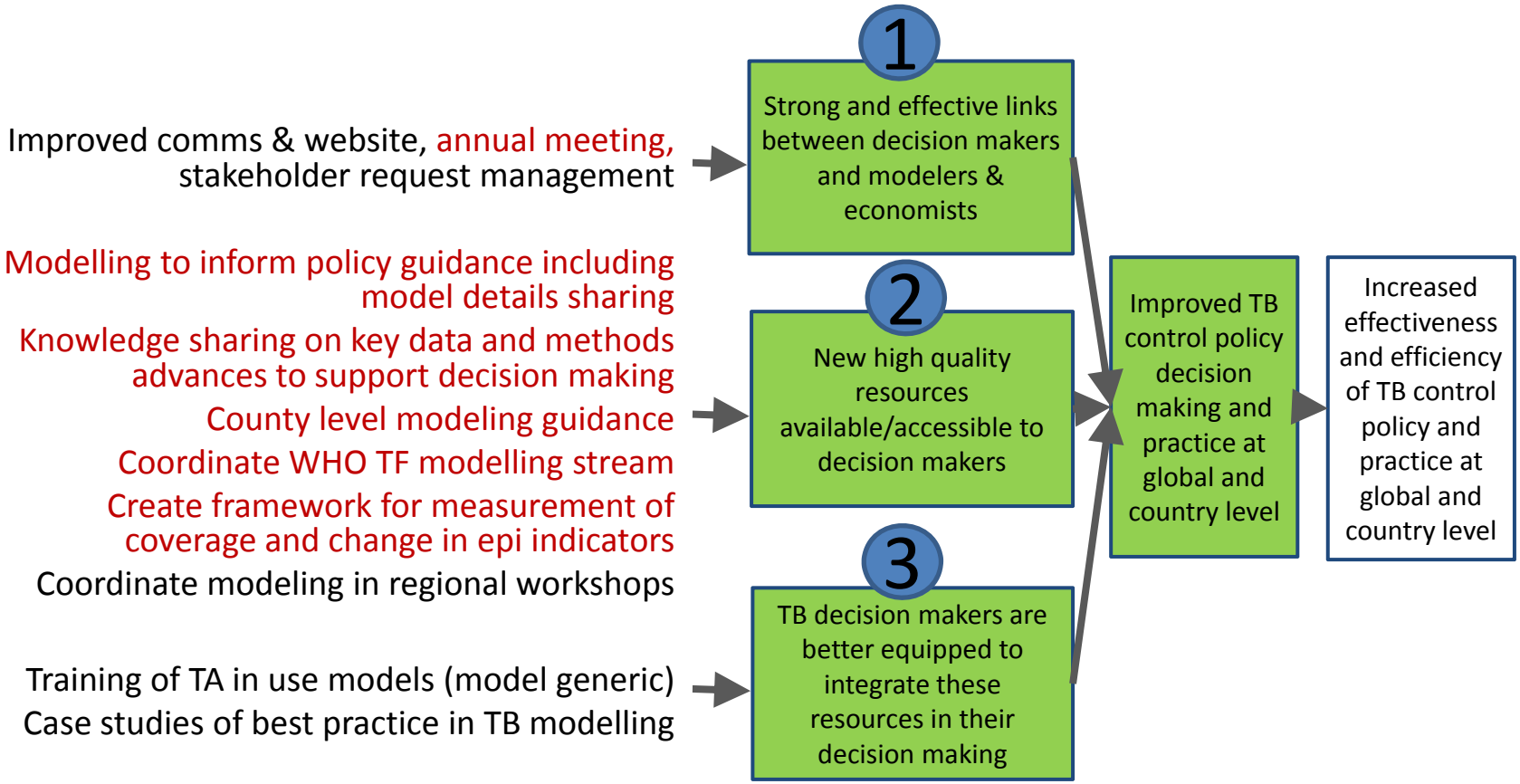
TB MAC key activities 2017-20



Any questions about TB MAC, or ways to take your modelling interests forward?

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