A **Simple** Introduction to Tuberculosis Modelling

Union World Conference on Lung Health
Mexico

[www.tb-mac.org](http://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
Who are we?
A Simple Introduction to Tuberculosis Modelling

Richard White
LSHTM/ TB MAC
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

\[ \frac{dS(t)}{dt} = -\beta \frac{I(t)}{N} S(t) \]
\[ \frac{dL(t)}{dt} = \ldots \]
\[ \frac{dI(t)}{dt} = \ldots \]
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

Adapted from Lin, WHO Bull, 2011
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
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

www.tb-mac.org
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

Identify the question
Identify relevant data
Choose model methods
Choose model structure
Specify model inputs/outputs
Set up and check model
Calibrate model
Prediction, sensitivity analysis and communication

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Steps to set up a model

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Identify the question

• First two steps apply to any scientific question
• What exactly do we want to know?
• Check other approaches (e.g., 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
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[Diagram showing the steps]

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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

Rieder, H. L. (1999). Epidemiologic basis of tuberculosis control
Steps to set up a model

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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

Adapted from Lin, WHO Bull, 2011
Steps to set up a model

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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

*Adapted from Lin, WHO Bull, 2011*

*Bishai, Nature, 2000*
Chose model structure

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

Bishai, Nature, 2000

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’’)

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[TB Modelling and Analysis Consortium](www.tb-mac.org)
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]
Steps to set up a model

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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

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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
Steps to set up a model

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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?
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...

- Identify the question
- Identify relevant data
- Choose model methods
- Choose model structure
- Specify model inputs/outputs
- Set up and check model
- Calibrate model
- Prediction, sensitivity analysis and communication

[Diagram showing the steps of setting up a TB model]
A Simple Introduction to Tuberculosis Modelling
[All other sessions here]
A Simple Introduction to Tuberculosis Modelling

Summary of Day
and TB MAC

www.tb-mac.org
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
    • For further details and computer exercises: www.anintroductiontoinfectiousdisease modelling.com
    • Also available as a ebook

• More mathematical
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
• Individual-based Modeling in Epidemiology
  – 5d, Nov, Antwerp (https://goo.gl/XhijRy)
• Statistics and Modeling in Infectious Diseases
• Epidemiology and control of infectious disease
  – Imperial, London, Summer course (https://goo.gl/MVFDiJ)
• 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...
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
TB decision makers are better equipped to integrate these resources in their decision making.
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)
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!)
TB MAC key activities 2017-20

1. Improved comms & website, annual meeting, stakeholder request management
   - Strong and effective links between decision makers and modelers & economists

2. Modelling to inform policy guidance including model details sharing
   - Knowledge sharing on key data and methods advances to support decision making
     County level modeling guidance
     Coordinate WHO TF modelling stream
     Create framework for measurement of coverage and change in epi indicators
     Coordinate modeling in regional workshops
   - New high quality resources available/accessible to decision makers

3. Training of TA in use models (model generic)
   - Case studies of best practice in TB modelling
   - TB decision makers are better equipped to integrate these resources in their decision making

Increased effectiveness and efficiency of TB control policy and practice at global and country level
Any questions about TB MAC, or ways to take your modelling interests forward?
A Simple Introduction to Tuberculosis Modelling

Summary of Day and TB MAC