Objectives of Session

- Discuss why we use models
- Understand what we can and can not do with models
- Describe how we model TB
- Outline key modeling terminology and understand differences between types of models
What is a model?

Models are symbolic representations of real life, evidently simplified drastically so as to be logically or mathematically tractable.

The Use of an Epidemiological Model for Estimating the Effectiveness of Tuberculosis Control Measures

Sensitivity of the Effectiveness of Tuberculosis Control Measures to the Coverage of the Population

H. T. Waaler & M. A. Piot

Representative, simplification, easy to control
Why Model Infectious Diseases?

1) To understand the hypothetical impact of population level interventions

More Specifically:

- To move from individual level epidemiologic data to making projections across entire populations
Why Model Infectious Diseases?

• 2) To identify the most influential aspects of population level interventions

Also…

• 3) To further our understanding of disease dynamics
• 4) To identify and generate information about disease parameters that are not well defined

• Can be helpful to guide future data gathering efforts
Ultimately....to (help) make decisions

• To give decision makers additional information upon which to base decisions

• To help decision makers make decision TODAY (or at least this year!)

  • For example, how do we imagine a new tool will perform in the short term/long term in a new setting?

  • How much it will cost to roll out a new tool a particular setting and population?
Advantages of Modeling

• Is flexible- can consider hypothetical situations or specific populations
• Can consider situations/populations that could not be evaluated through a trial
• Can be used to generalize/extrapolate trial findings (over time or across populations)
• Can be useful for hypothesis generating
• Can take advantage of “average” data (ie. meta analysis data)
• Low cost (relative to other research methods)
What models are NOT good for...

- Predicting the future - they are NOT “Crystal balls”
- Providing precise absolute estimates of cost and impact
- Generating accurate estimates that are derived from poor data
- Understanding problems that are very complex
- Capturing heterogeneity that we are not aware of (or don’t understand)
What models are good for...

- Comparing the relative impact and cost of two different well-defined interventions
- Understanding problems in a logical and transparent fashion
- Identifying weakness in our conceptualization of problem
- Making our assumptions explicit
Why Model TB?

- Complex and poorly understood natural history
- Many unanswered questions about the impact of interventions
- Difficulties in conducting interventional research (lag between infection and disease)- requires long trials
- Susceptible populations need to be studied
- Practical, logistical and ethical challenges in conducting interventions in low/middle income countries
- Trials can be expensive, especially if long
How do we model TB?
Model development:

1) Conceptualize the disease/natural history

2) Select data/model inputs to parameterize model

3) Select type/structure of the model
Model development:

1) Conceptualize the disease/natural history

2) Select model inputs to parameterize model

3) Select type/structure of the model
Complex natural history of TB

Important aspects of TB pathogenesis

Figure highlights some of the key aspects of disease we need to think about including…

- Initial infection
- Possible re-infection
- Rapid progression from primary infection to disease
- Reactivation from longstanding latent infection
- Spontaneous Cure
- Relapse from spontaneous cure
- Death from TB
How does this translate into a model?

- Start by conceptualizing different disease states (compartments) that an individual could encounter…
Generate a framework that a model could be based on...

Adapted from Oxlade et al. Medical Decision Making, 2010
How does this translate into a model?

- Next, consider the risk of moving from one disease state to another (pathogenetic transitions)…
Incorporate key transitions into framework.

**Key Model Inputs:**

1. Probability of progressing to active TB disease after new 1st/repeat infection
2. Probability of reactivation from latent infection to active TB disease
3. Number of infections generated from a smear positive/negative active TB case
4. Probability of spontaneous resolution of a smear positive or negative active TB case
5. Probability of relapse from spontaneously cured active TB case
6. Case fatality rate for smear positive/negative active TB disease
Some Key Pathogenetic transitions/Model Inputs

1a/b. Probability of progressing to active TB disease after new 1st /repeat infection

2. Probability of reactivation from latent infection to active TB disease

3a/b. Number of infections generated from a smear positive/negative active TB case

4. Probability of spontaneous resolution of a smear positive or negative active TB case

5. Probability of relapse from spontaneously cured active TB case

6a/b. Case fatality rate for untreated smear positive/negative active TB disease
Quickly become more and more complex as different aspects of TB epidemiology are considered.

Table 2: Probabilities of outcomes with different TB and HIV health states

<table>
<thead>
<tr>
<th>PATHOGENETIC FACTOR</th>
<th>BASE</th>
<th>RANGE</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactivation from latent TB infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present more than 2 years (&quot;long-standing LTBI&quot;)*</td>
<td>0.1%/year</td>
<td>0.1% – 0.2%/year</td>
<td>[28:92]</td>
</tr>
<tr>
<td>HIV uninfected</td>
<td>3.4%/year</td>
<td>3.4% – 8.7%</td>
<td>[36:65]</td>
</tr>
<tr>
<td>HIV infected – asymptomatic</td>
<td>33%/year</td>
<td>33% – 67%</td>
<td>[36]</td>
</tr>
<tr>
<td>HIV infected – AIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 2 years of new TB infection (&quot;recent LTBI&quot;)</td>
<td>5%</td>
<td>2% – 15%</td>
<td>[24:66]</td>
</tr>
<tr>
<td>HIV uninfected</td>
<td>33%</td>
<td>33% – 100%</td>
<td>Extrapolated</td>
</tr>
<tr>
<td>HIV infected – asymptomatic</td>
<td>100%</td>
<td>50% – 100%</td>
<td>[42:67-69]</td>
</tr>
<tr>
<td>HIV infected – AIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 2 years following re-infection</td>
<td>1%</td>
<td></td>
<td>[27:70]*</td>
</tr>
<tr>
<td>HIV Uninfected</td>
<td>33% or 100%</td>
<td>Assumption</td>
<td></td>
</tr>
<tr>
<td>HIV infected</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Outcomes of untreated smear positive TB

Mortality – 1 year, 2 years | 33%, 50% | From [71] |
Spontaneous remission | 25% | [72] |
Relapse after spontaneous remission | 2.5%/year | 1.3% – 2.5%/year | [72:73] |

Outcomes of treated smear positive TB

Relapse after cure (total over next 2 years) | 3.0% | 1.5% – 5% | [74:78] |
Cure rate if default (SDR or drug sensitive) ** | 62.4% | | [31-34] |
Effect of drug sensitivity or treatment outcomes | | | |
Relative risk of failure if single drug resistant | 2.0 | | [79] |
Relative risk of failure if multi-drug resistant | 10.5 | | [79] |
Relative risk of death if single drug resistant | 1.0 | | [79] |
Relative risk of death if multi-drug resistant | 4.5 | | [79] |
If MDR – Probability of cure with treatment | 48% | 48%-73% | [22:80] |
- Probability of death with treatment | 12% | 12%-26% | [22:80] |

HIV Infected and TB

Average duration of HIV infection – Total | 9.8 years | 7.3–9.8 | [35-81] |
- Time spent in HIV asymptomatic state | 9.0 years | | [35] |
Annual risk of progression of asymptomatic HIV to AIDS | 7% | 7%-9% | [35-81] |
Annual risk of death from HIV: HIV asymptomatic state | 4.6% | | [35] |
Annual risk of death from HIV: AIDS | 22% | | [35] |
Effect of prior active TB on relative risk of death from HIV | 2.2 | (2.2 – 4.0) | [34:01] |
Effect of HIV infection on relative risk of death during TB treatment (drug sensitive or single drug resistance) | 2.25 | | [37-39:82] |
Relapse after successful TB treatment (cured) | 3.1% | 3.1% – 6.4% | [83-85] |

* Assume that rate of reactivation more than two years after TB infection is the same whether it is after a first infection, or after re-infection.
** Transfer out considered equivalent to default [30]. Overall cure rate if default based on timing of default (from [31]), and cure rates from trials of

Jacquet et al, Impact of DOTS expansion on tuberculosis related outcomes and costs in Haiti, BMC Public Health 2006, 6:209
How much heterogeneity and other detail to include?

- Depends on research question!
- In reality it also depends on many more things:
  - how much data we have?
  - how much good data we have?
  - how much we know about our patient population?
  - how much we know about the “context” (ie. Health system, epidemiologic parameters)?
  - how important the “context” is?
  - how generalizable we want the projections to be?

At the end of the day we find balance - we have to keep model simple and transparent
Model development:

1) Conceptualize the disease/natural history

2) Select data/model inputs to parameterize model

3) Select type/structure of the model
Data sources used to parameterize models

- Published literature
  - Meta analyses
  - RCT’s
  - Cohort studies
  - Other published data

- Model generated through calibration

- Global reports (ie. WHO)
- Unpublished literature
- Expert Opinion
- Assumption
- Unexplained

BEST

WORST
Model development:

1) Conceptualize the disease/natural history

2) Select model inputs to parameterize model

3) Select type/structure of the model
What type of model to choose?

Depends on:

• Specific question being asked (i.e. is transmission important?)
• Data that are available to parameterize the model
• Familiarity of the analyst with different modeling techniques
• Complexity needed and time requirements for model development
• Ease and speed of simulation

Adapted from: Vynnycky and White, An introduction to Infectious Disease Modeling, OUP, 2010
Basic types of models:

- Confusing and inconsistent use of terminology

Key concepts in understanding types of models:

- Population based vs. Individual based models
- Deterministic vs. Stochastic models
- Dynamic vs. Static models
- Transmission model
Population based vs. individual based models

Population based:

- Keep track of populations of individuals
- Divide population into mutually exclusive groups
- Homogeneity within groups
- Can sub-divide into more groups

- Characteristics of populations are averaged together- model simulates changes in averaged characteristics of the whole population
Population based vs. individual based models

**Individual Based:**

- Models keep track of individuals in the population
- Each individual has an ID- characteristics of each individual are tracked through time
- Allow better exploration of heterogeneous agents, social/spatial interactions, complex relationships
Deterministic vs. stochastic models

Deterministic models:

- All parameters are fixed - no random element
- Model predictions remain the same with every trial run under the same conditions
- Describe what happens “on average” in a population.
- Seen more frequently in the literature, due to its simpler methods
Deterministic vs. stochastic models

Stochastic models:

- Incorporate chance into the model
- Results will vary with every model trial
- Important when considering small populations where chance might play a role
Dynamic vs. static models

Differ only in way that the risk of infection (ARI) is modeled

- Dynamic models: risk of infection will always depend on the number of infectious individuals in the population at a given point in time

- Static models: the annual risk of infection is not sensitive to the changing number of infectious cases in the population
Inclusion of TB transmission

TB transmission model = Dynamic model - implicitly takes transmission into account

- Static models - do not include a transmission component

- May attempt to take transmission into account by making assumptions about:
  - Number of contacts per index case
  - Probability of secondary case occurring from contact

- The annual risk of infection is not sensitive to the changing number of infectious cases in the population
Most common modeling methods seen in TB literature

1) SIR (Susceptible- Infectious- Recovered) model

2) Decision Analysis
Method 1- SIR models

- population based, deterministic, dynamic (thus transmission) models
SIR (Susceptible- Infectious – Recovered) models:

- Simplify natural history in order to divide the population into the most basic states of health and disease.

- Use difference/differential equations to determine the rate of transfer between compartments.

- For TB they are usually modified to include a “latent” state and called “SLIR” models.

- Software can keep track of population dynamics and how the population is distributed between states over time.
Data needs for evidence-based decisions: a tuberculosis modeler’s ‘wish list’

D. W. Dowdy, C. Dye, T. Cohen

Table 1  Simplified model of TB transmission

We used differential equations to develop a simplified model of TB transmission, as shown in Figure 1. The differential equations used were:

1. Susceptible, S:
   \[ \frac{dS}{dt} = (\text{birth}) - (\text{infection}) * S - (\text{mortality}) * S \]

2. Latently infected (recent), L1:
   \[ \frac{dL1}{dt} = (\text{infection}) *[S + (1 - \text{protection}) *(L2 + R)] - (\text{progression} + \text{stabilization} + \text{mortality}) * L1 \]

3. Latently infected (remote), L2:
   \[ \frac{dL2}{dt} = (\text{stabilization}) * L1 - [\text{reactivation} + (1 - \text{protection}) *(\text{infection}) + \text{mortality}] * L2 \]

4. Actively infected, A:
   \[ \frac{dA}{dt} = (\text{progression}) * L1 + (\text{reactivation}) * L2 + (\text{relapse}) * R - (\text{treatment} + \text{self-cure} + \text{mortality} + \text{TB mortality}) * A \]

5. Recovered, R:
   \[ \frac{dR}{dt} = (\text{treatment} + \text{self-cure}) * A - (\text{relapse} + (1 - \text{protection}) * (\text{infection}) + \text{mortality}) * R \]

For these equations, each capital letter represents the number of people in the compartment (per 100,000), and \( dX/dt \) denotes the change in compartment size \( X \) per unit time. We used the following quantities:

- birth = sum of all mortality (to maintain a stable population)
- infection = (transmission rate) * A
- protection = 0.50 (50% efficacy against reinfection if latently infected or recovered)\(^{18,19} \)
- progression = 0.03 per year (primary progression after recent infection)\(^{19} \)
- stabilization = 0.2 per year (recent infection period of 5 years)\(^{18} \)
- reactivation = 0.0005 per year (reactivation after remote infection)\(^{20} \)
- relapse = rate of relapse after recovery, calibrated such that 11% of incident TB is retreatment\(^{1} \) (final value = 0.0034/year)
- treatment = rate of successful diagnosis and treatment, calibrated to give steady-state TB prevalence of 178 per 100,000, the global average\(^{1} \)
- self-cure = 0.167 per year (spontaneous recovery without treatment, 50% case fatality)\(^{21} \)
- TB mortality = 0.167 per year (mortality rate of untreated TB)\(^{21} \)

**TB** = tuberculosis.

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**Figure 1**  Simplified TB model: the basic structure that is common to many compartmental transmission models of TB. Health states are represented by boxes and transitions are indicated by arrows. We highlight assumptions necessary to estimate rates associated with four basic processes (in circles): infection, rapid progression, reactivation, and treatment/recovery. Mortality (not shown) also occurs from each box. TB = tuberculosis.
More Complex SLIR model:


Figure 1. Flow diagram of the age-structured compartmental model for tuberculosis. Refer to Table 1 for definitions of variables and parameters.
SLIR models - limitations

- Simple models are preferred (harder to assess more complex trajectories eg. diagnostic pathways)

- Software tends to have limited integrated sensitivity analysis

- Lacks integrated cost effectiveness capability
Method 2- Decision Analysis

- population based, deterministic, static models
Decision analysis:

- More than just a modeling method - A systematic approach to decision making under conditions of uncertainty

- Disaggregating a complex problem into smaller problems and elements which can easily be understood

- Requires defining events in terms of their logical and temporal sequence
Decision Analysis - advantages

- Easy to learn & user friendly
- Can capture more complex pathways
- Integrated costing capability and can be easily modified for cost-effectiveness
- Extensive and sophisticated sensitivity analysis
What about transmission and population level impact of interventions?

Transmission is not inherently part of decision analysis model

Eg. The annual risk of infection is not sensitive to the changing number of infectious cases in the population

Can be overcome partially using Markov models and relying on assumptions about transmission
A sample TB decision tree

- User defined probabilities are entered at each decision point
Jacquet et al, Impact of DOTS expansion on tuberculosis related outcomes and costs in Haiti, *BMC Public Health* 2006, 6:209
Decision analysis nodes with measures of effectiveness (or costs) added

- Effectiveness measures and cost estimates can be entered at every relevant node.
- Model can keep track of different effectiveness measures - depends on question being asked.
Decision analysis

- Final model outcomes are calculated based on the probability of entering into a particular node and the price tag or effectiveness measure associated with that node.
  - Individuals move through the decision trees for a specified amount of time.
  - Costs and rewards accrue over the simulation.
  - At end of simulation get a tally of specified outcomes (eg. TB related costs per person, number of TB cases, number of TB deaths, etc for each intervention considered (outcomes).
Comparing Scenarios:

1. **Diagnosed active TB case**

   - **No DST - unknown underlying drug resistance**
     - Drug sensitive → Cure
     - Non MDR-INH Drug Resistant → Multi-Drug resistant → Failure or Relapse → Standardized Retreatment → Die
     - Standardized Initial Treatment → Die
   - **Rapid DST - known drug resistance**
     - Drug sensitive → Cure
     - Non MDR-INH Drug Resistant → INH resistant regimen → Cure
     - Multi-Drug resistant → Standardized MDR regimen → Cure
     - Standardized Initial Treatment → Failure or Relapse → Standard Retreatment → Cure

2. **Total Costs**
   - **Total DALYs**
   - **Total MDR**
   - **Total deaths**
   - **Total Costs**

   **SUM OF MODEL OUTPUT- Predicted for each scenario**

Oxlade et al, ERJ 2011
Summary: Models are good for...

- Estimating outcomes that are otherwise hard to measure
- Making relative comparisons
- Making assumptions explicit
- Help to generate a deeper understanding of problems/questions
- Can be used to guide data collection efforts
Summary: Models are not so good for...

- Predicting the future
- Giving precise estimates
- Working magic with bad/limited data
- Can only work to level of complexity that we understand/have data to support
Summary...

- Different approaches to disease conceptualization exist
- Many different sources of data exist
- Different types of models are available

Choice depends on:
- The research question
- The data that we have to work with
- The assumptions that we are willing to make
- How quickly we need the results
- The expertise of the modelling “team”