Mathematical Modeling of Tuberculosis

An introduction

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Advanced TB Research Course: Montreal

July 18 2014

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.

Bull. Org. mond. Santé
Bull. Wld Hlth Org. } 1969, 41, 75-93

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 [1] & M. A. PIOT [2]

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

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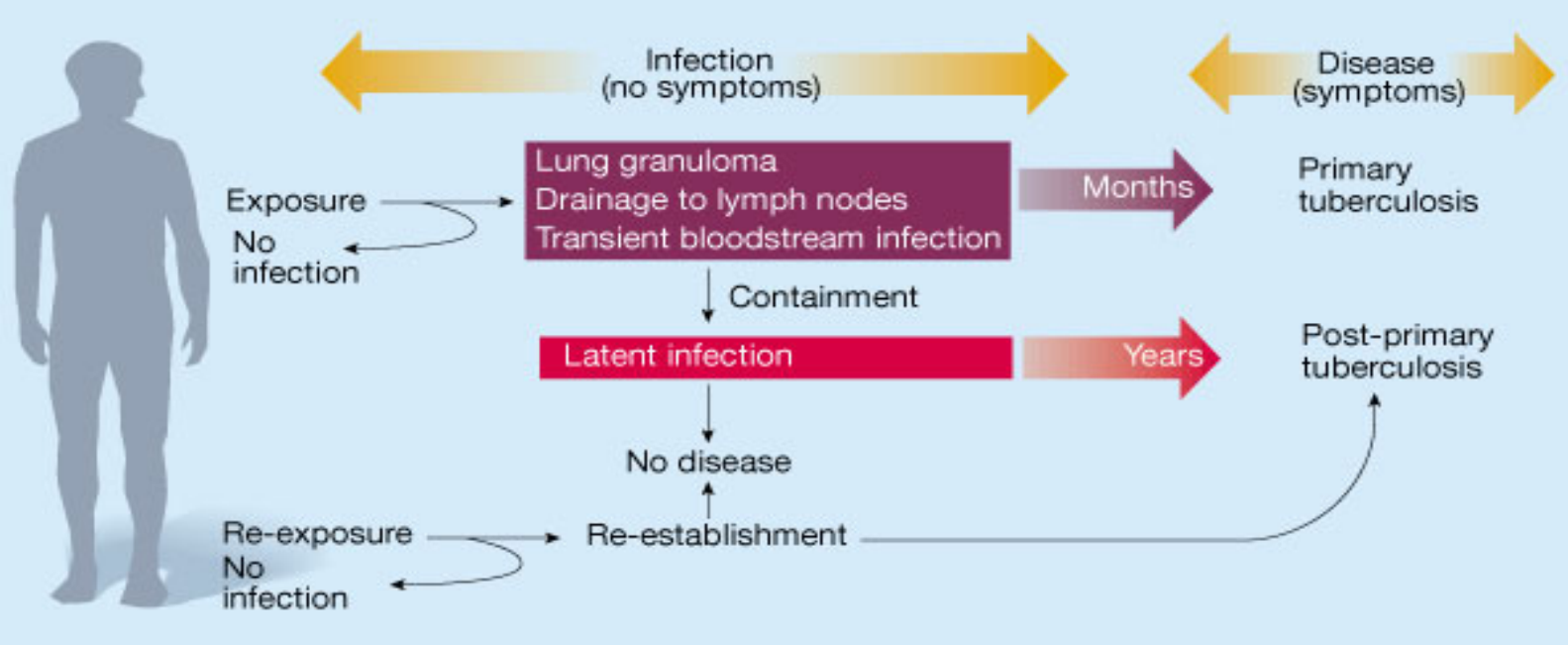
Complex natural history of TB



Bishai W. Lipid lunch for persistent pathogen. Nature 2000 August 17;406(6797):683-5.

Important aspects of TB pathogenesis

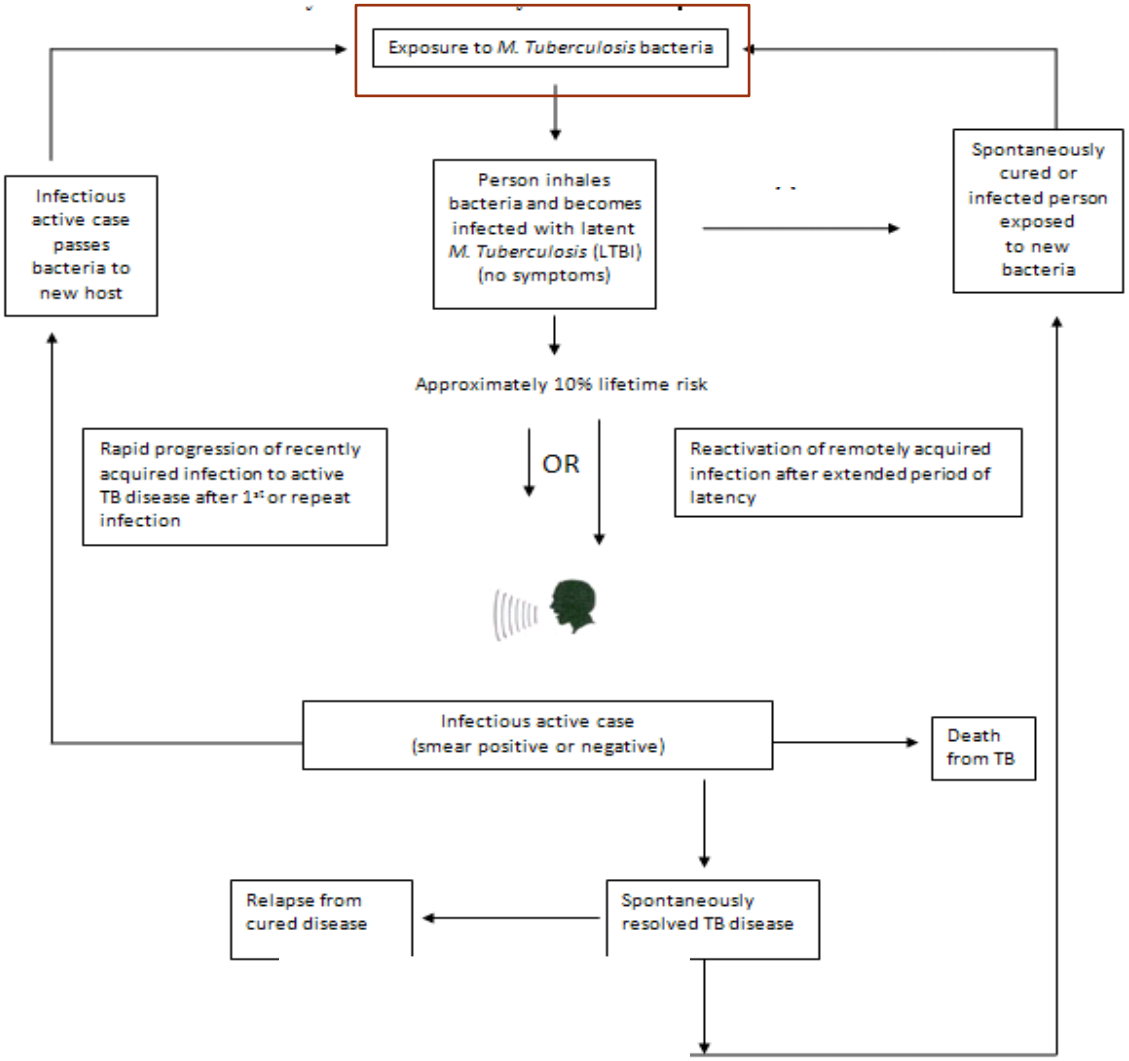
Figure highlights some of the key aspects of disease we need to think about including…

- 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…

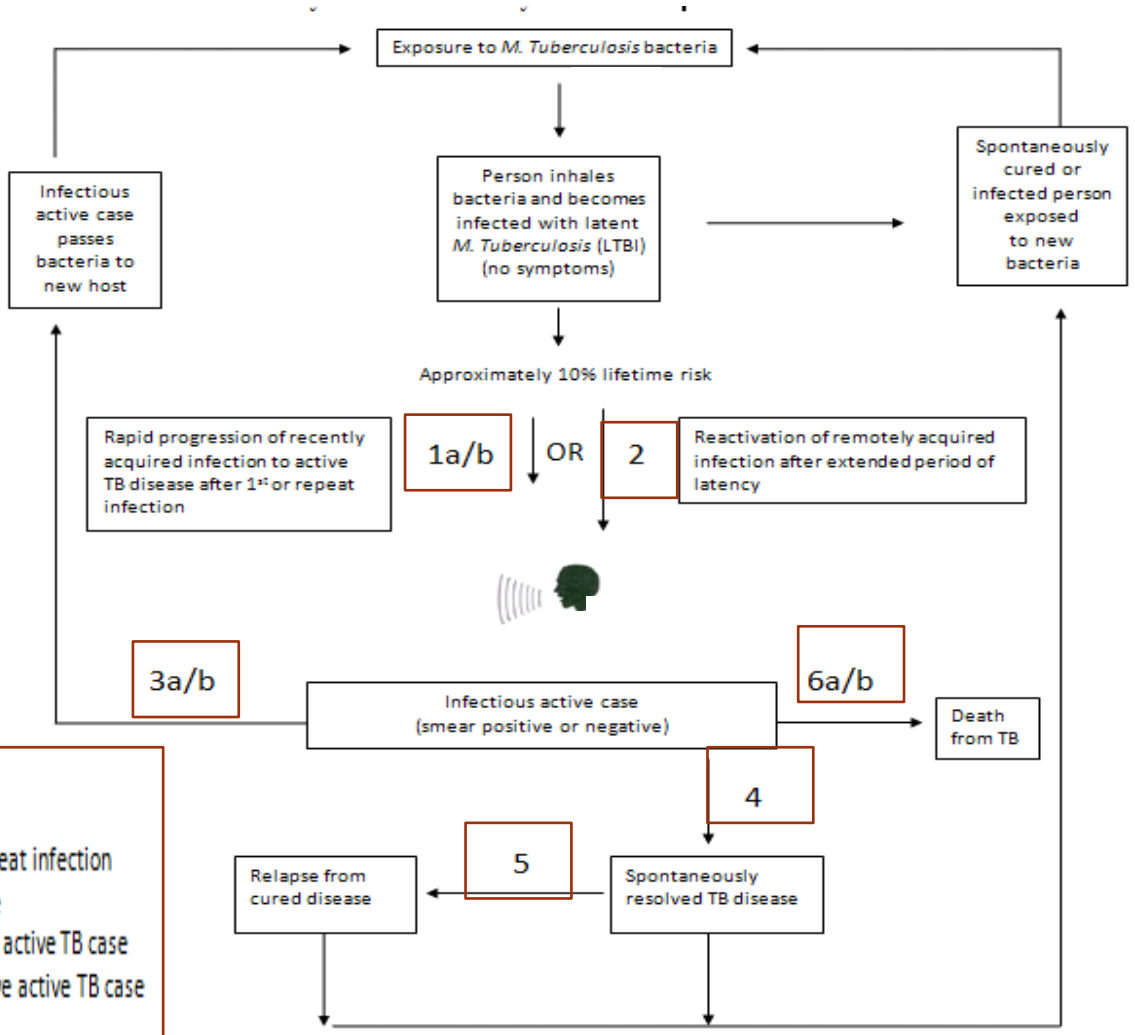


Adapted from Oxlade et al. Medical Decision Making, 2010

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:

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 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

PATHOGENETIC FACTOR	BASE	RANGE	REFERENCE
Reactivation from latent TB infection			
Present more than 2 years ("long-standing LTBI")*			
HIV uninfected	0.1%/year	0.1% – 0.2%/year	[28;29]
HIV infected – asymptomatic	3.4%/year	3.4% – 8.7%	[36;64;65]
HIV infected – AIDS	33%/year	33% – 67%	[36]
Within 2 years of new TB infection ("recent LTBI")			
HIV uninfected	5%	2% – 15%	[24;66]
HIV infected – asymptomatic	33%	33% – 100%	Extrapolated
HIV infected – AIDS	100%	50% – 100%	[42;43;67–69]
Within 2 years following re-infection			
HIV Uninfected	1%		[27;70]*
HIV infected	33% or 100%		Assumption
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)	[3;40;41]
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:

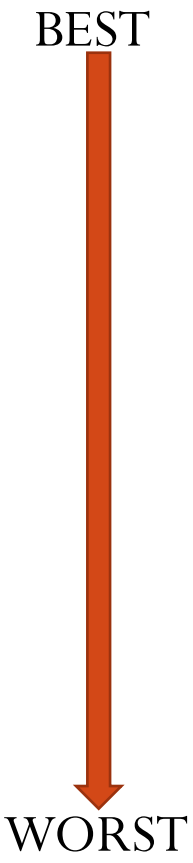
1) Conceptualize the disease/natural history

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



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

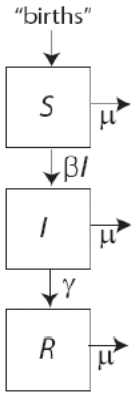
Most common modeling methods seen in TB literature

1) SIR (Susceptible- Infectious- Recovered) model

2) Decision Analysis

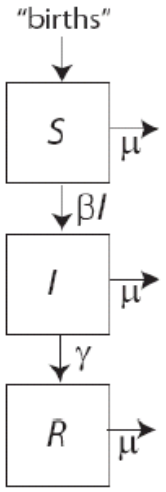
Method 1- SIR models

- 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

INT J TUBERC LUNG DIS 17(7):866–877

http://dx.doi.org/10.5588/ijtld.12.0573

Data needs for evidence-based decisions: a tuberculosis modeler's 'wish list'

D. W. Dowdy,*† C. Dye,‡ T. Cohen§¶

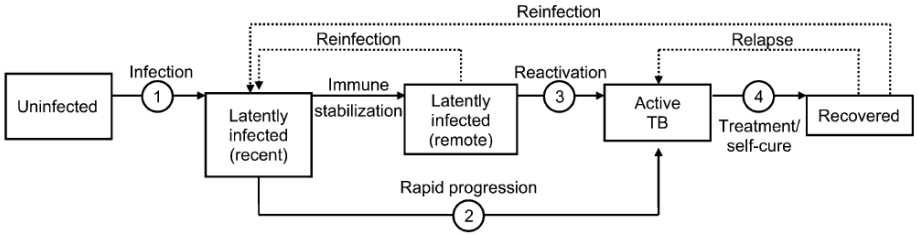


Figure 1 Simplified TB model: the basic structure that is common to many compartmental transmission models of TB. Health states are represented by boxes and transitions are indicated by arrows. We highlight assumptions necessary to estimate rates associated with four basic processes (in circles): infection,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

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:

dS/dt = (birth) – (infection)*S – (mortality)*S

2 Latently infected (recent), L1:

$dL1/dt$ = (infection)*[S + (1 – protection)*(L2 + R)] – (progression + stabilization + mortality)*L1

3 Latently infected (remote), L2:

$dL2/dt$ = (stabilization)*L1 – [reactivation + (1 – protection)*(infection) + mortality]*L2

4 Actively infected, A:

dA/dt = (progression)*L1 + (reactivation)*L2 + (relapse)*R – (treatment + self-cure + mortality + TB mortality)*A

5 Recovered, R:

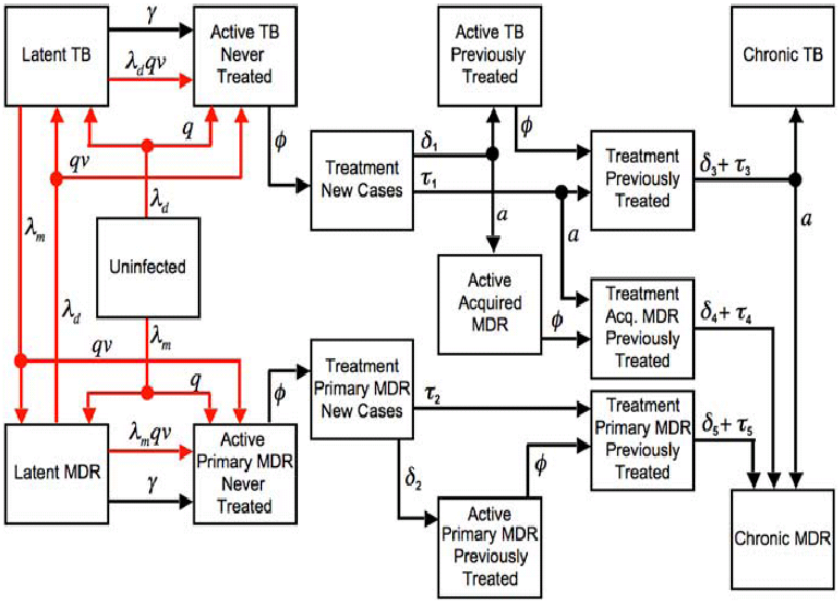
dR/dt = (treatment + self-cure)*A – [relapse + (1 – protection)*(infection) + mortality]*R

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
  - —The transmission rate is calibrated to give an annual steady-state TB incidence of 128/100 000/year, the global average.[1]
- mortality = 1/70 (life expectancy of 70 years)
- 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)[19]
- 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.

More Complex SLIR model:



Resch SC, Salomon JA, Murray M, Weinstein MC (2006) Cost-Effectiveness of Treating Multidrug-Resistant Tuberculosis. PLoS Med 3(7): e241

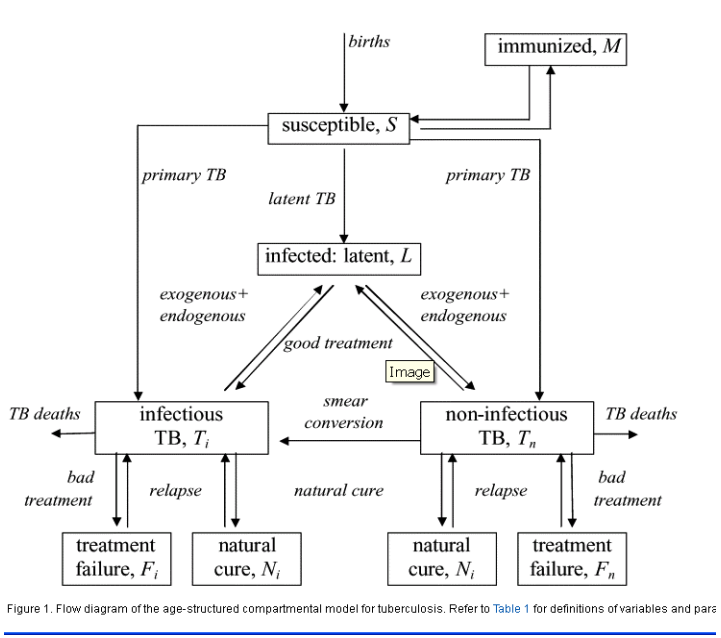


Figure 1. Flow diagram of the age-structured compartmental model for tuberculosis. Refer to Table 1 for definitions of variables and para

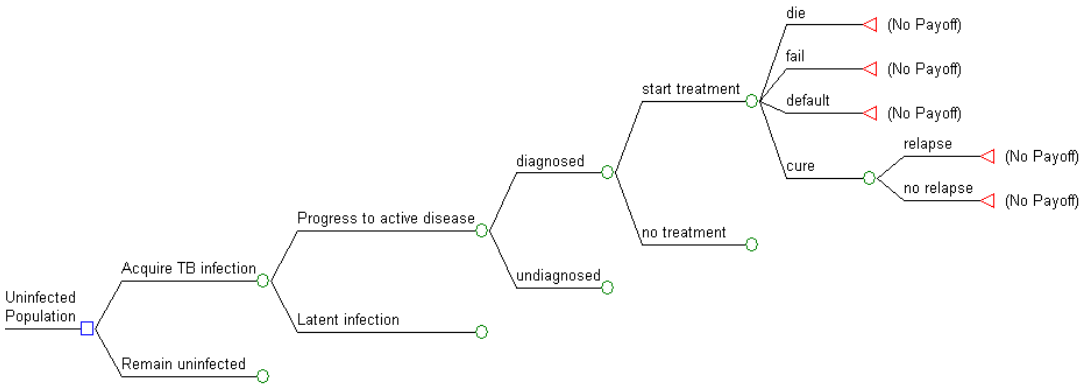
Dye et al. (1998). Lancet Dec 12;352(9144):1886-91.

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

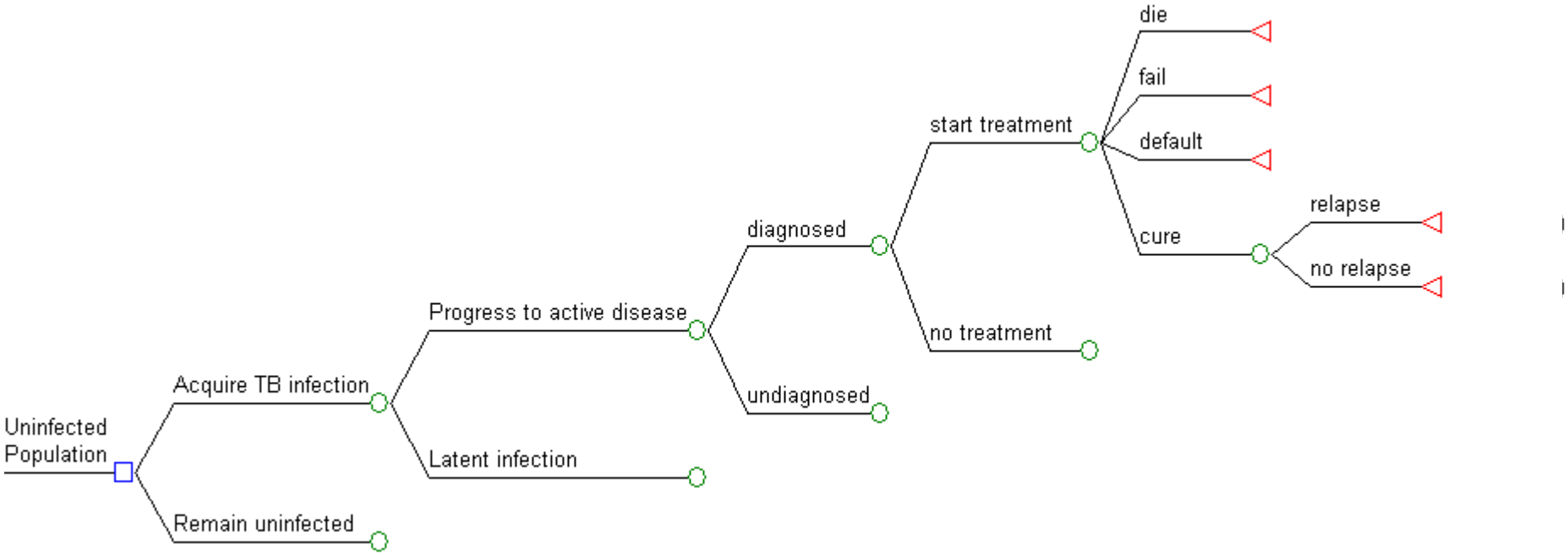
Decision Analysis-disadvantages

- What about transmission and population level impact of interventions?
  - Transmission is not inherently part of decision analysis model

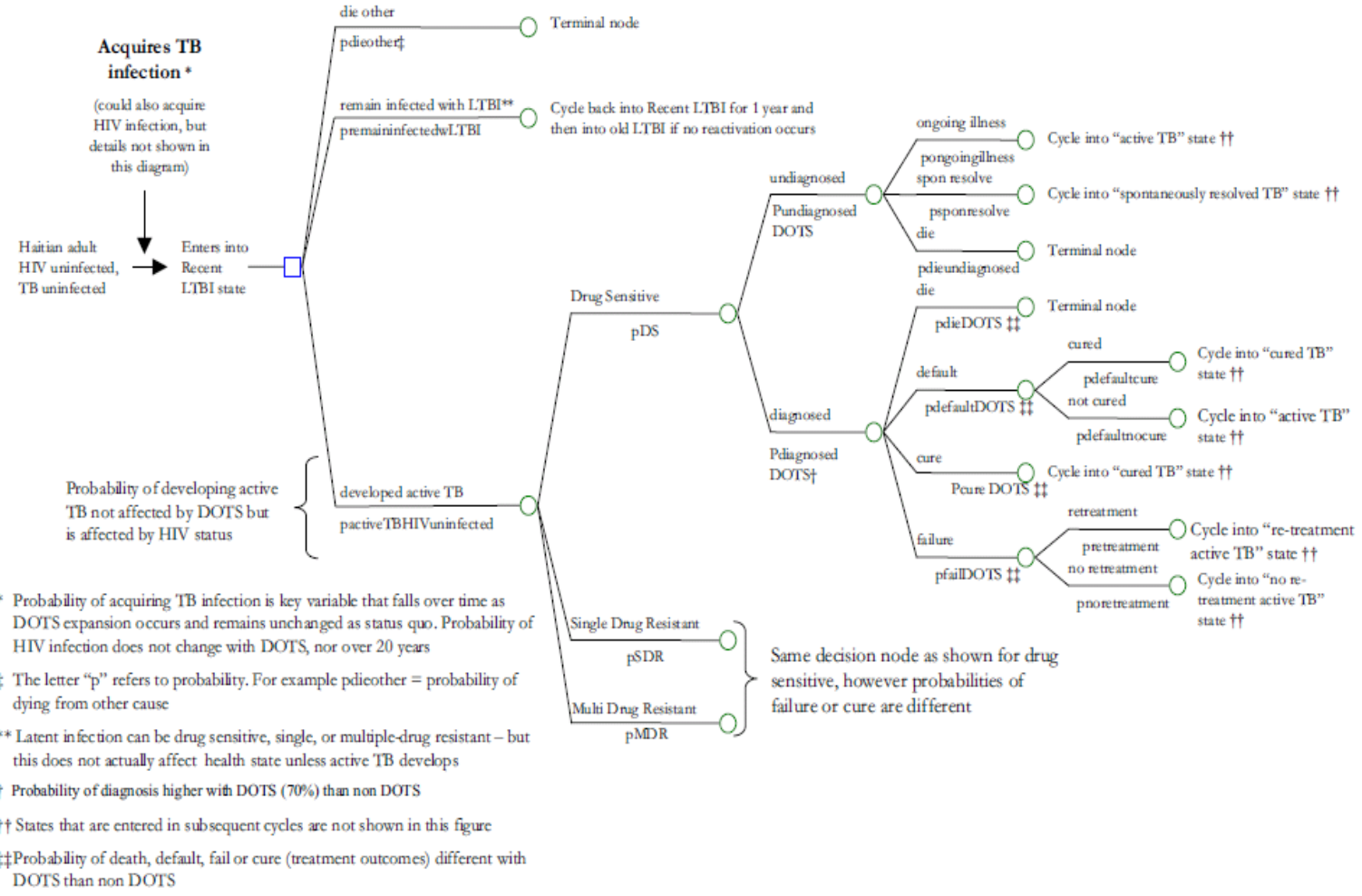
    Eg. The annual risk of infection is not sensitive to the changing number of infectious cases in the population

- Can be over come partially using Markov models and relying on assumptions about transmission

A sample TB decision tree

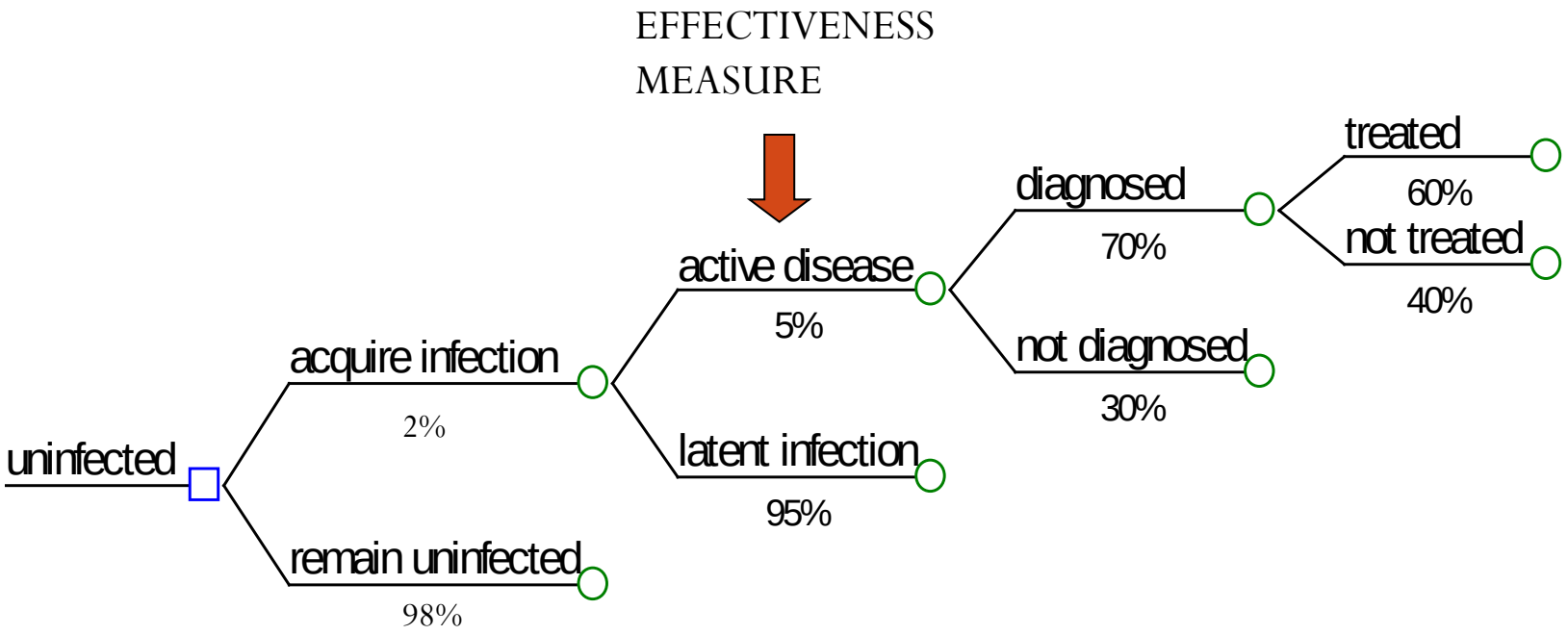


- User defined probabilities are entered at each decision point



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

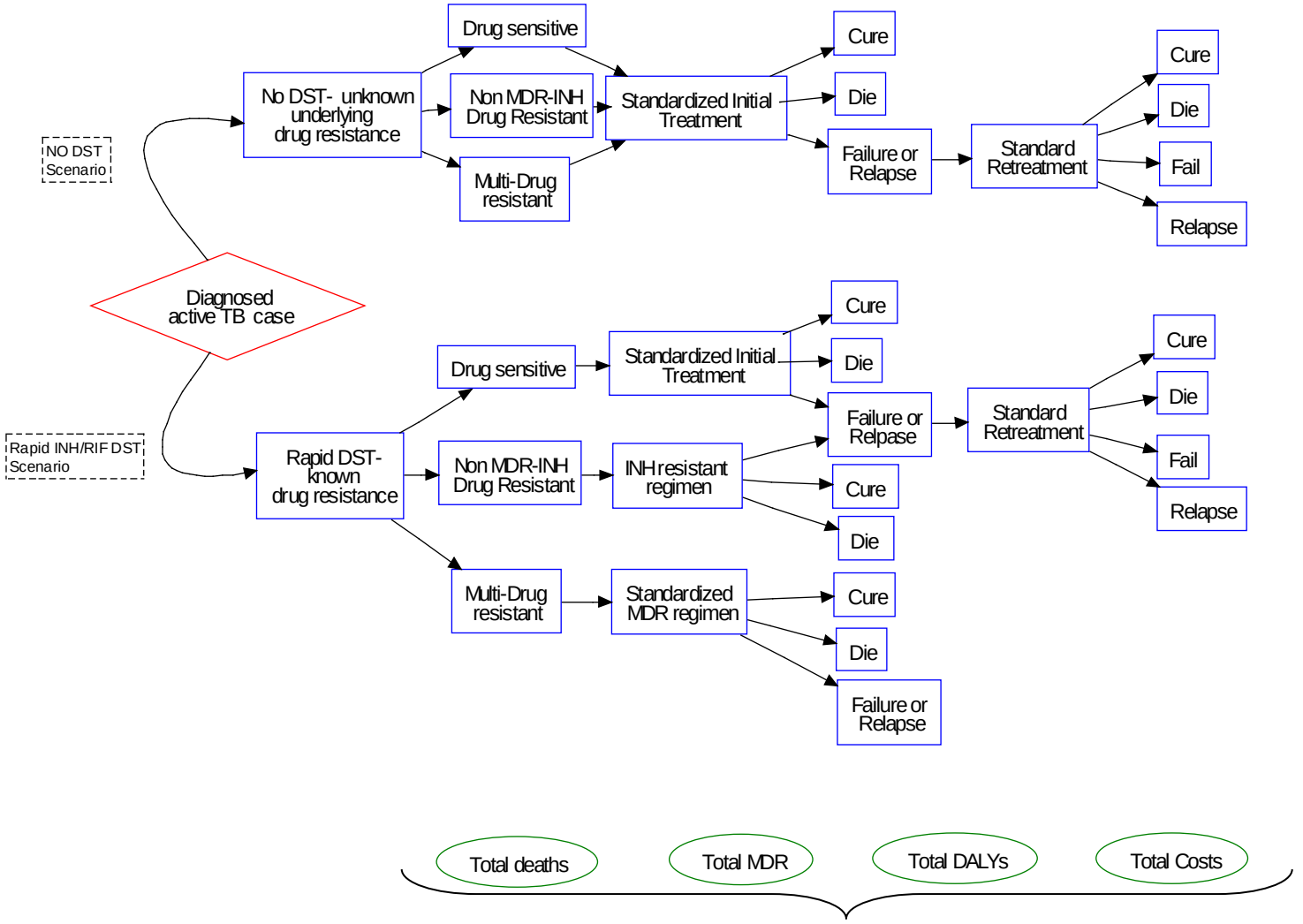
- Final model outcomes are calculated based on the probability of entering into a particular node and the price tag or effectiveness measure associated with that node

- 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:



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"