Mathematical Modeling of Tuberculosis

An introduction

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Objectives of Session

- Consider the reasons for using modeling
- Describe how we model TB, including how we:
  - Conceptualize the pathogenesis of TB
  - Decide on and parameterize key model inputs
- Outline key modeling terminology and understand differences between types of models
- Outline approaches to sensitivity analysis in modeling

What is a model?

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

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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, simple, easy to control

Why Model Infectious Diseases?

As a research tool:

- To further our understanding of disease dynamics
- To generate information about disease parameters that are not well defined
- To understand the hypothetical impact of population level interventions
- To identify the most influential aspects of population level interventions

Ultimately- use this information as additional piece of evidence to guide policy (ideally with costing information)

Some 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

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 depends on…

1) How we conceptualize the disease/natural history

2) How we select model inputs to parameterize model

3) The type/structure of the model we use

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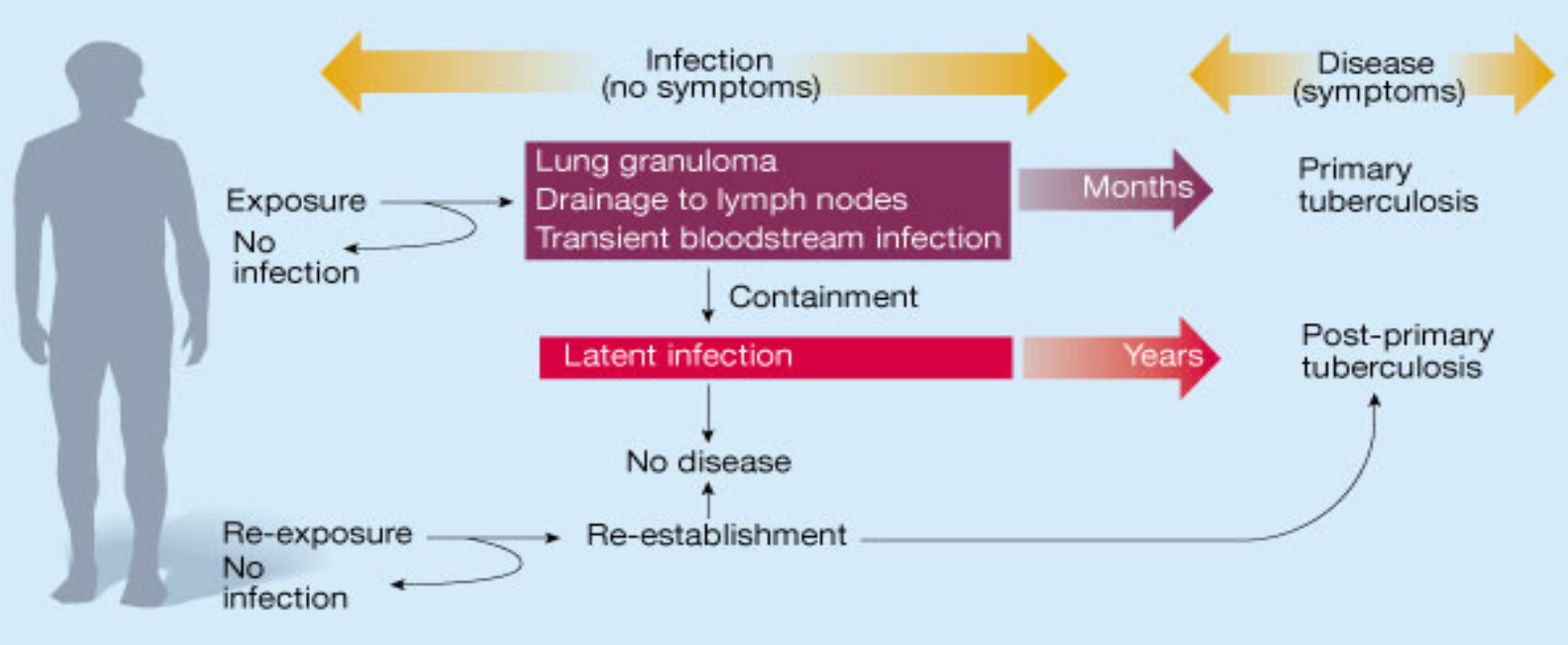
Complex natural history of TB



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

Important aspects of TB pathogenesis

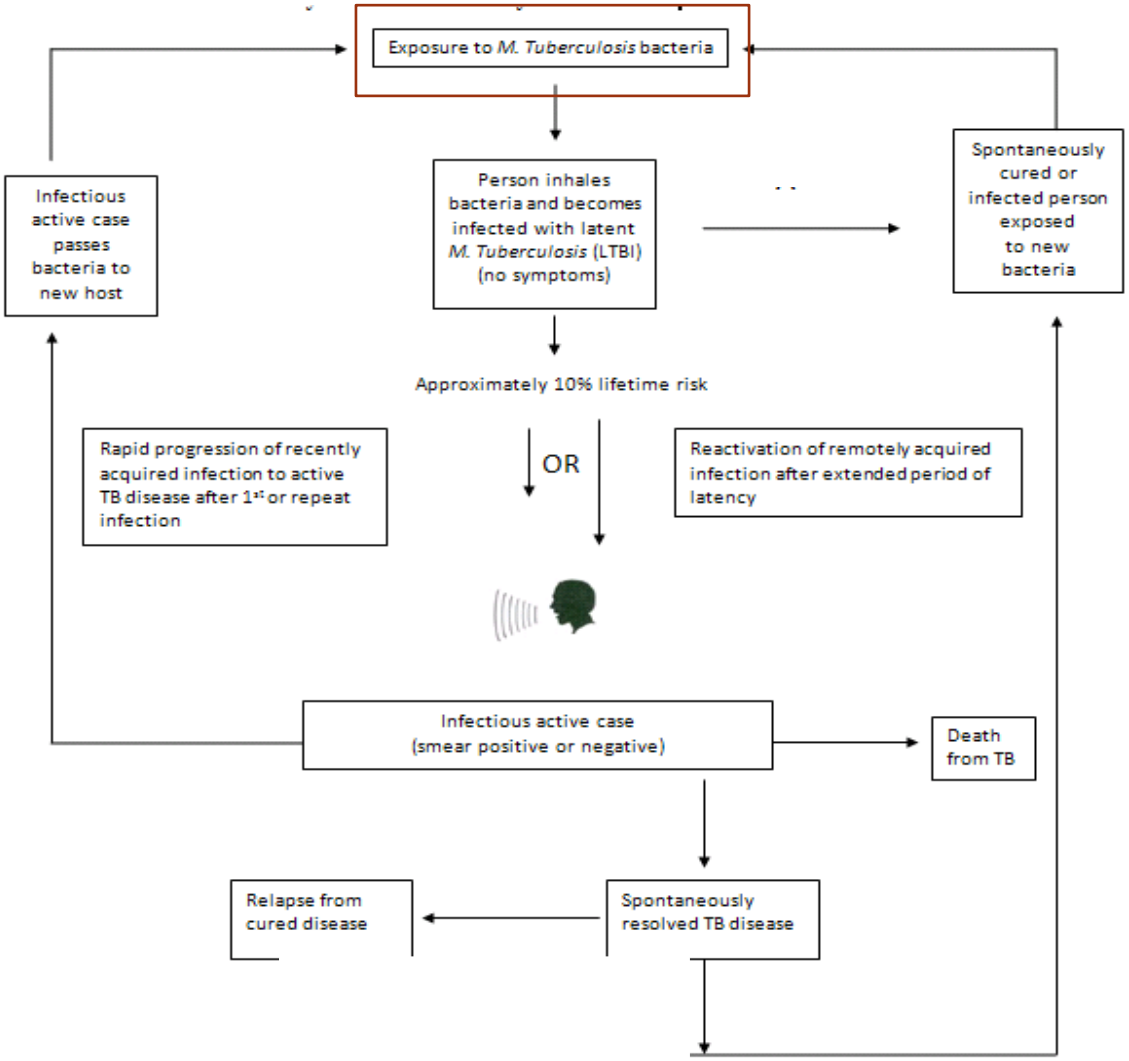
Complex figure but it highlights some of the key aspects of disease we need to think about including…

- 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 that an individual could encounter…

Generate a framework that a model could be based on…

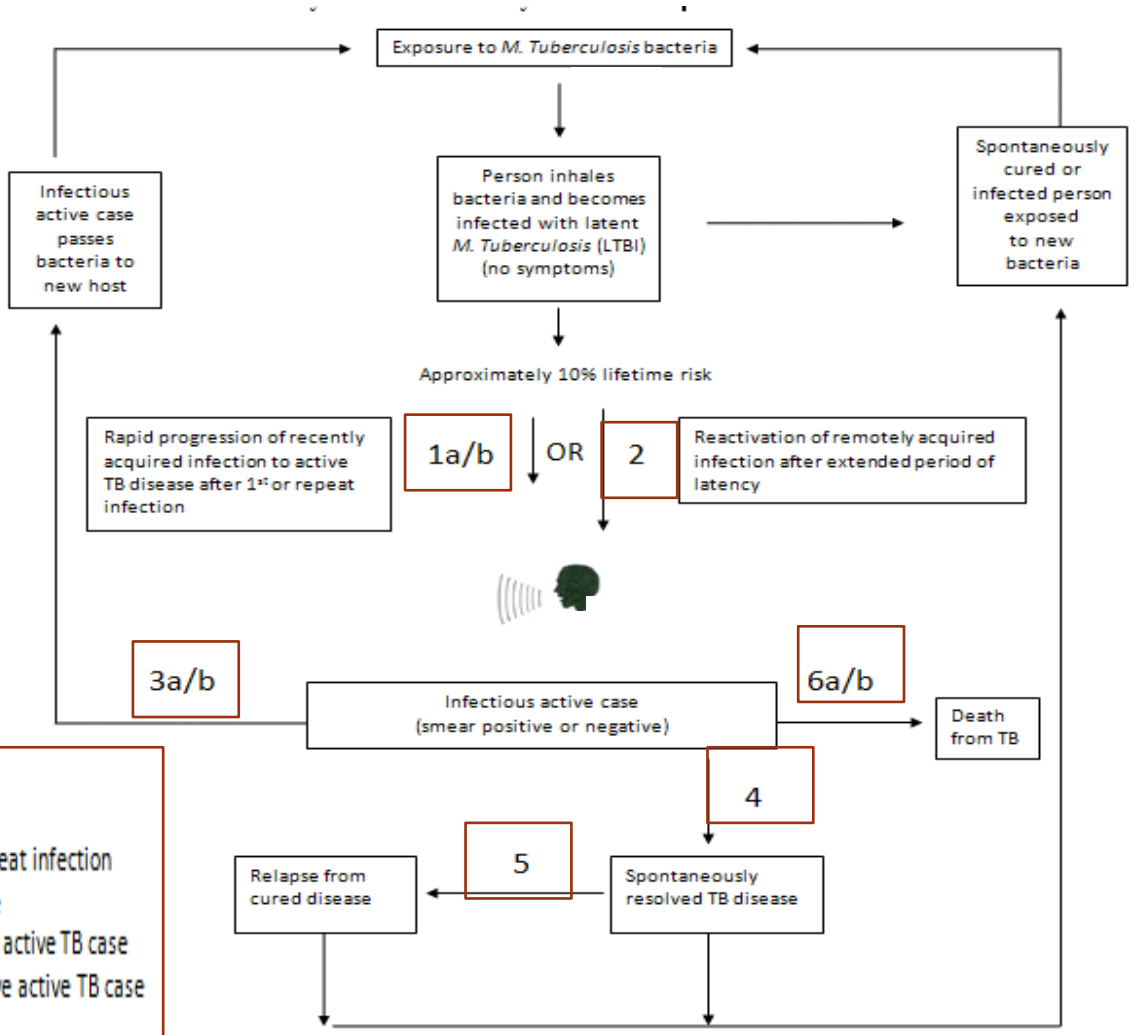


Adapted from Oxlade et al. Medical Decision Making, 2010

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 complex as more complex 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***

Model development depends on…

1) How we conceptualize the disease/natural history

2) How we select model inputs to parameterize model

3) The type/structure of the model we use

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

A word about selecting data (and how we conceptualize disease) ….

- Have been conducting a systematic review of IGRA cost-effectiveness studies
- Considered 16 published IGRAs
- Not trying to come up with summary estimates- instead trying to understand main determinants of results
- Preliminary findings shows WIDE variation in key assumptions and input values

Areas of significant variation:

- Initial prevalence of LTBI/ Active disease
- TB transmission and assumptions related to secondary cases
- Conceptualization of disease progression (ie. not considering a distinction between between rapid progression and reactivation)
- Reactivation/ disease progression rates
- Inclusion of adverse events
- Rates of adverse events
- Test characteristics (ie. sensitivity/ specificity & choice of cut-offs)
- Costing of: tests, LTBI treatment, active disease, adverse events
- Costing perspective

- Involvement of industry also seems to be an important determinant of findings (8/16 studies had industry involvement)

Model development depends on…

1) How we conceptualize the disease/natural history

2) How we select model inputs to parameterize model

3) The type/structure of the model we use

What type of model to choose?

- Depends on the specific question being asked
- 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 (or 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

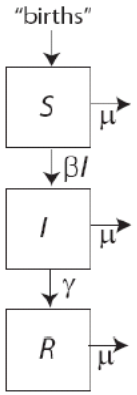
Most common modeling methods seen in TB literature

1) SIR (Susceptible- Infectious- Recovered) model

2) Decision Analysis

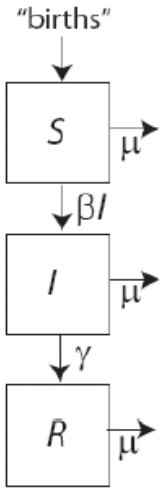
Method 1- SIR models

- 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 health and disease states

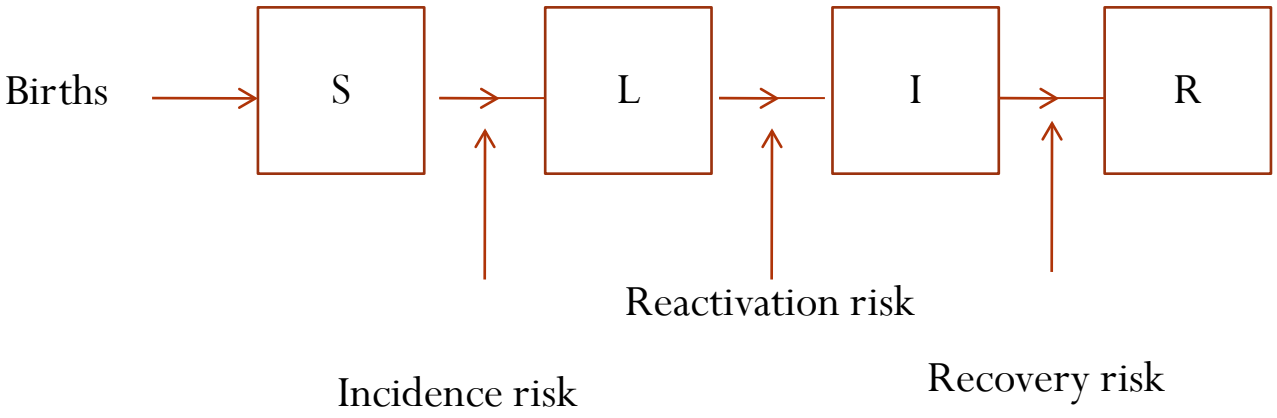
- For TB they are usually modified to include a "latent" state and termed "SLIR" models

- Software can keep track of population dynamics and how the population is distributed between states over time

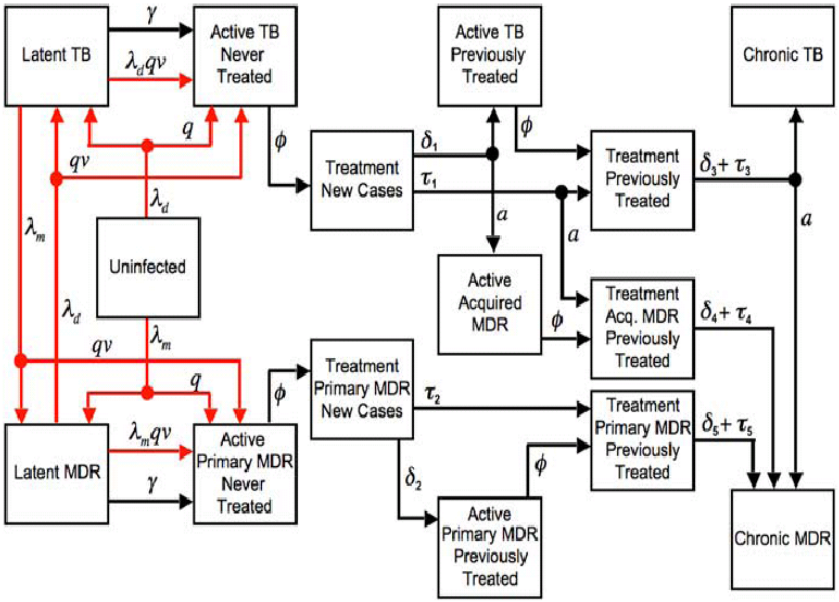
Most basic SLIR model:

Includes the following TB related states:

Susceptible (S), Latent (L), Infectious (I), Recovered (R)



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

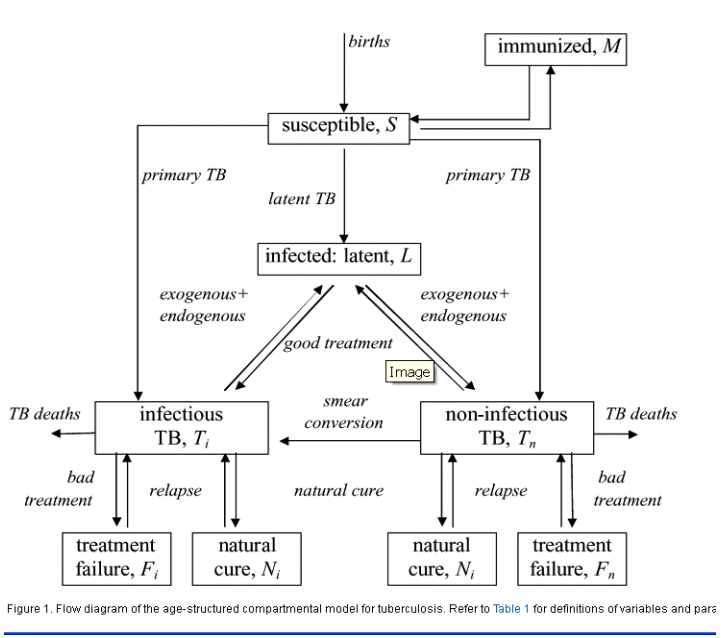
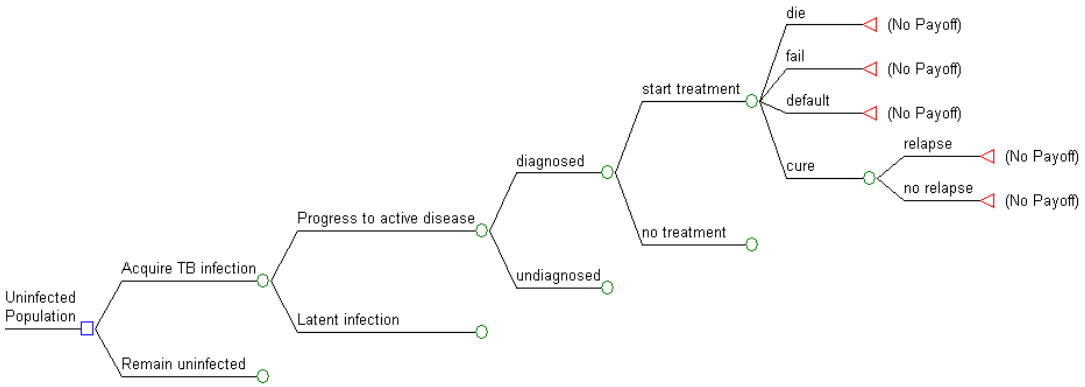


Figure 1. Flow diagram of the age-structured compartmental model for tuberculosis. Refer to Table 1 for definitions of variables and para

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

Method 2- Decision Analysis

- population based, deterministic, static models



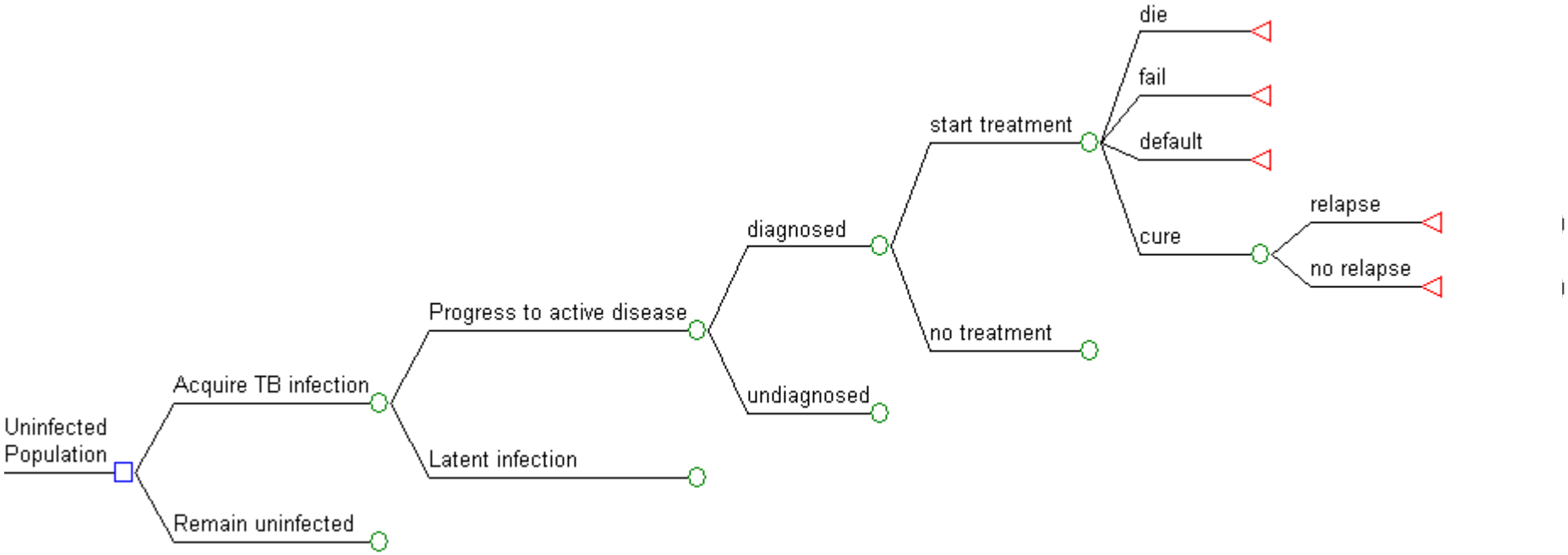
Decision analysis:

- 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

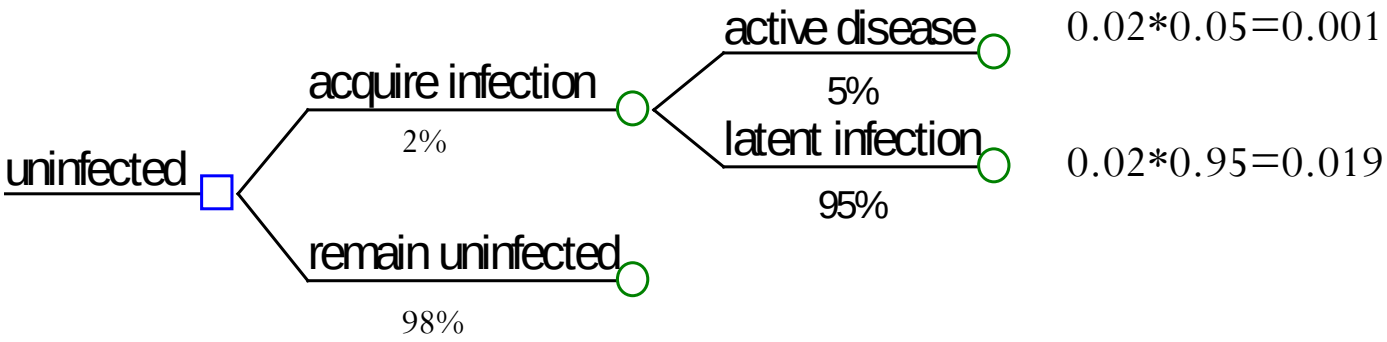
- Models can be easily modified for cost-effectiveness
- Tend to be popular with Economists for historical reasons
- Tend to be popular with many other people doing CEAs because of practical issues- easy to learn & user friendly

A sample TB decision tree



- User defined probabilities are entered at each decision point

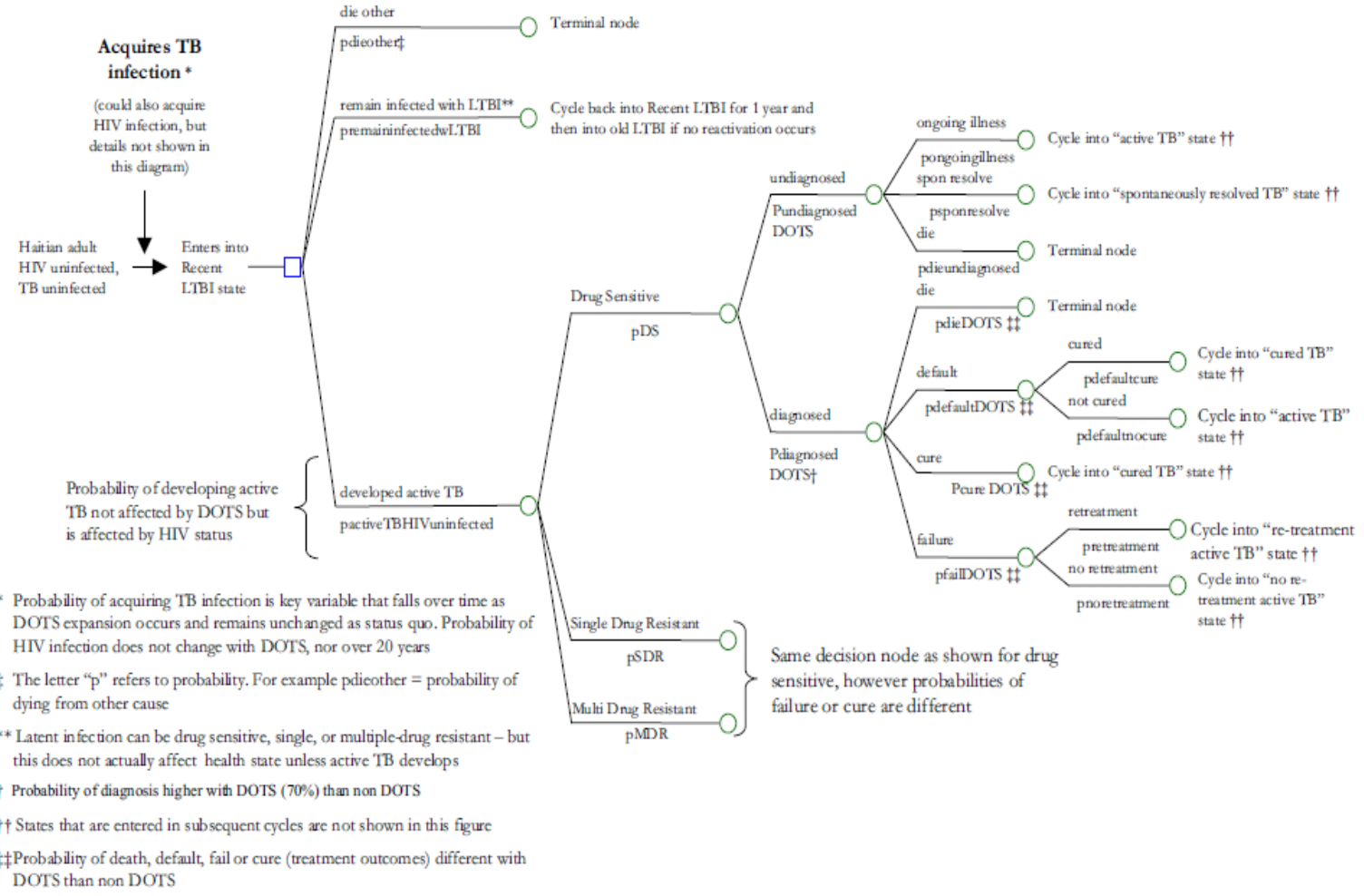
Decision analysis nodes with user defined probabilities



- Software can keep track of proportion of population in each end state (population progressing from left to right)) at the end of each "cycle" (more of that in a few slides)

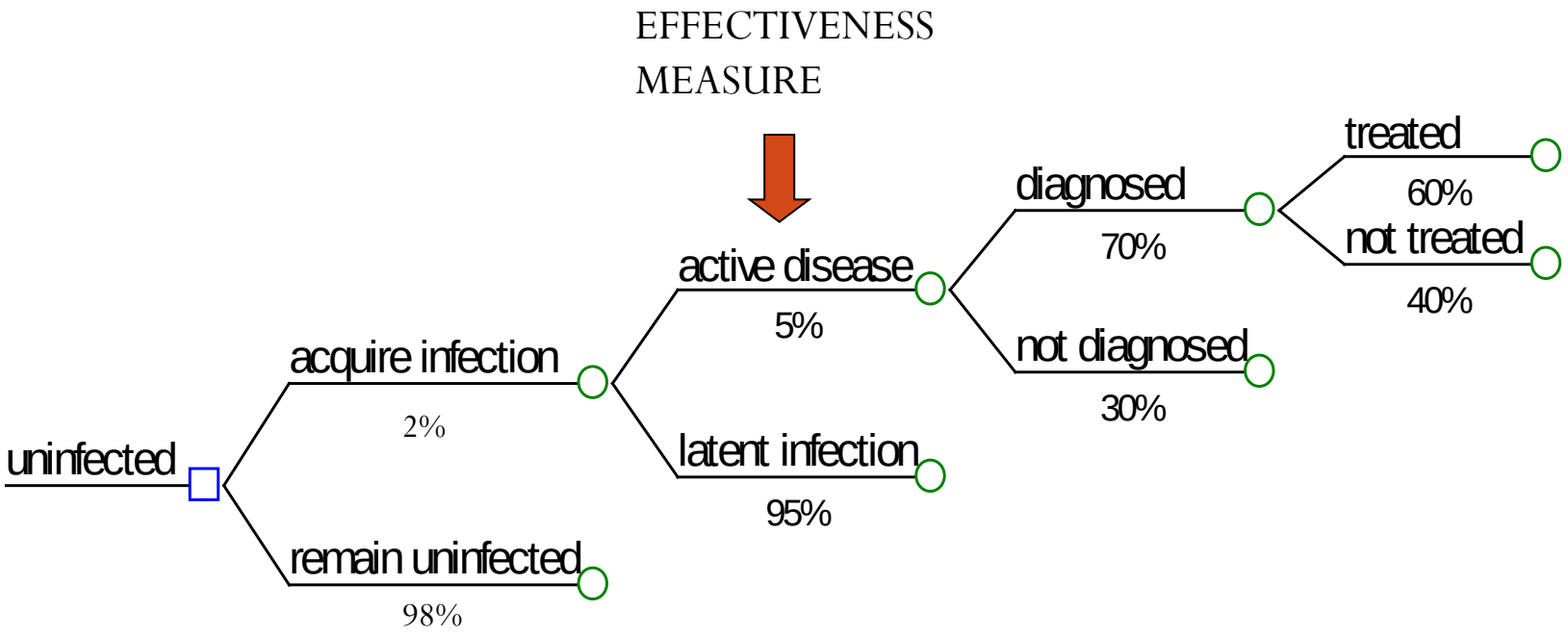
At end of first cycle :

- 0.1% of population will have active disease
- 1.9% of population will have latent infection
- 98% will remain uninfected



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

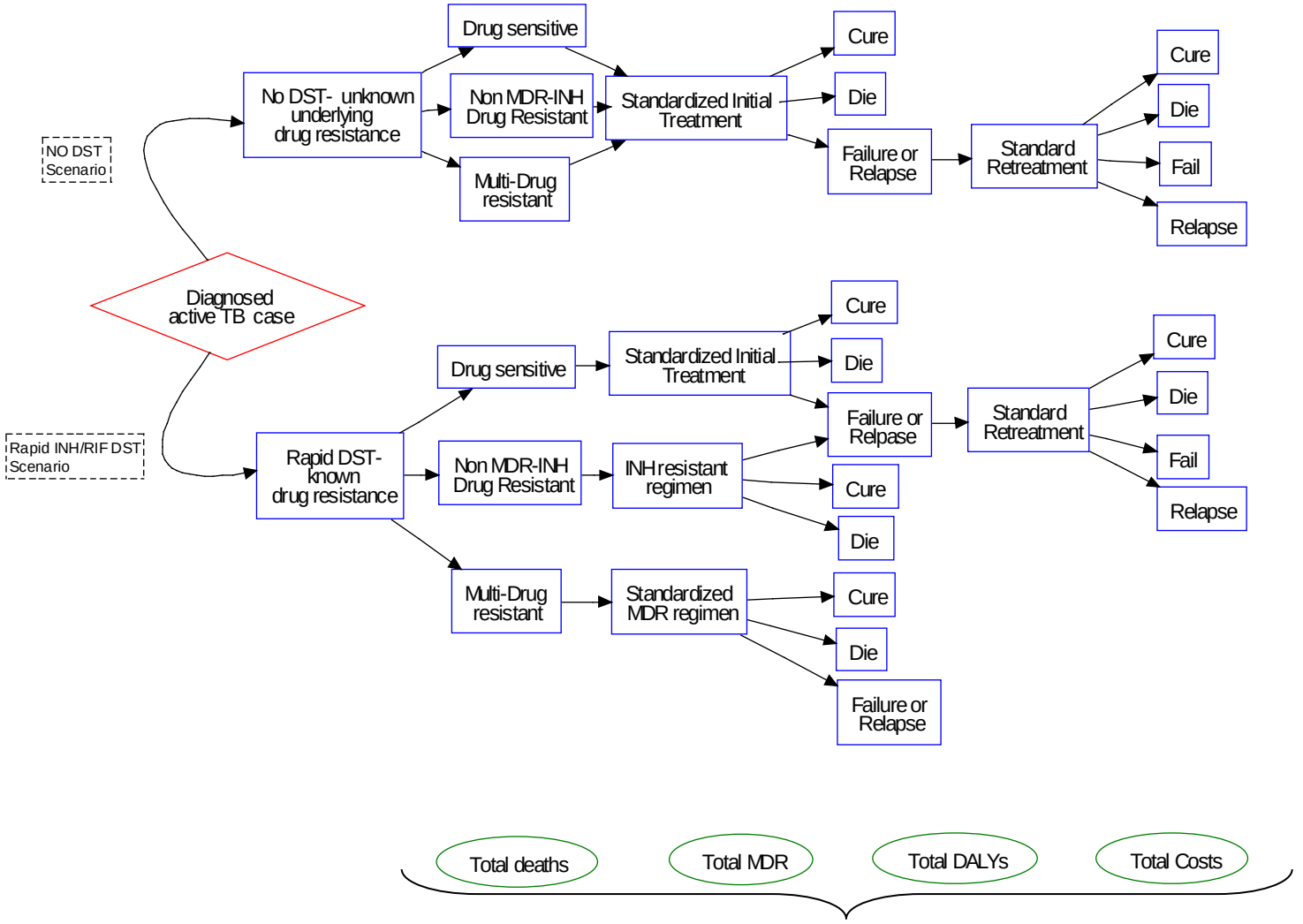
- Final model outcomes are calculated based on the probability of entering into a particular node and the price tag or effectiveness measure associated with that node

  - 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:



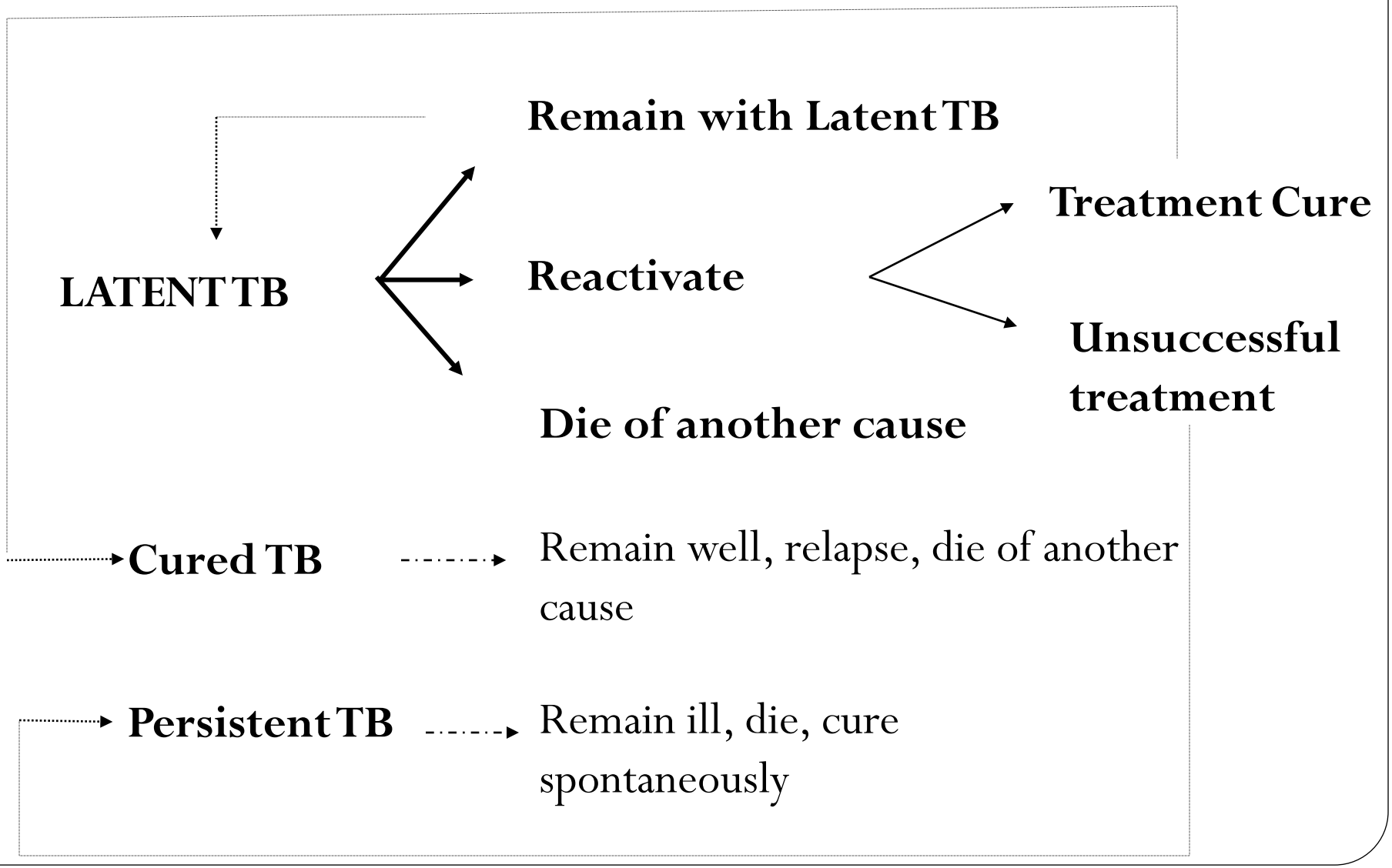
Oxlade et al, ERJ- In Press

SUM OF MODEL OUTPUT- Predicted for each scenario

A word about making projections over "time":

- Time component or "Cycling" is achieved using Markov modeling
- Useful when making predictions over multiple years
- Markov modeling allows for use of recurrent probabilities that change over time (or by cycle)
- Number of cycles is specified by the user
- Often see 20 "year/cycle" simulations in the TB literature- gives adequate time for outcomes to accrue

Markov model



Uncertainty in modeling

- Uncertainty in model predictions can arise from many sources including
  - Conceptualization of disease- too complex? too simple?
  - Inaccuracies/ uncertainty in input data
  - Use of inappropriate data/ inappropriate interpretation of data
  - (User error)
- Sensitivity analysis can be used to assess the impact of some of these uncertainties

Uncertainty and Sensitivity analysis in modeling

- Impact of the uncertainty from some of these sources can be quantitatively assessed through sensitivity analysis

- Involves specifying a potential range over which the parameter is thought to vary (range identified from the literature)

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]
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HIV uninfected	5%	2% – 15%	[24;66]
HIV infected – asymptomatic	33%	33% – 100%	Extrapolated
HIV infected – AIDS	100%	50% – 100%	[42;43;67–69]

Uncertainty and Sensitivity analysis in modeling

- Sensitivity analysis methods can either be deterministic (methods 1-4) or stochastic (method 5)

- Main types of sensitivity analysis used:
  1) One way sensitivity analysis
  2) Multi way sensitivity analysis
  3) Scenario analysis
  4) Threshold analysis
  5) Probabilistic sensitivity analysis

Types of Sensitivity analysis

- One way sensitivity analysis- estimates for each parameter are varied one at a time to investigate the impact on study results (not considered satisfactory because need to look at combined impact)

- Multi way sensitivity analysis- recognizes that more than one parameter is uncertain and that each could vary within its specified range. Better approach, but with many parameters there can be an infinite number of combinations to consider

From: Drummond et al, Methods for Economic Evaluations of health care programs- 3rd Edition

Types of Sensitivity analysis

- Scenario analysis- a series of scenarios are constructed representing a subset of the potential multi-way analysis (ie. best case or worst case scenarios)

- Threshold analysis- critical values of a parameter central to decision are identified- analyst determines threshold and then assess which combination (or what values) of parameters cause the threshold to be exceeded

- All of these approaches are deterministic (ie. don't include chance)

From: Drummond et al, Methods for Economic Evaluations of health care programs- 3rd Edition

Probabilistic sensitivity analysis (PSA):

- Often called Monte Carlo simulation
- Incorporates stochastic element into analysis
- PSA is important when you do not want an "average" result- provides a sense of uncertainty in predictions
- Requires defining ranges/distributions for parameters
- Can the run the model repeatedly (1000's of times) and each time it will select input parameter values from set distributions
- Can build up a distribution of outcomes and see range/uncertainty

From: Drummond et al, Methods for Economic Evaluations of health care programs- 3rd Edition

Limitations of Sensitivity Analysis (Drummond, 2005)

1) Variation of uncertain parameters one at a time ignores possible interaction between parameters
2) The analyst has discretion as to which variables and what alternative values are included in sensitivity analysis
3) Interpretation is arbitrary as there are not guidelines/standards as to what degree of variation in results is acceptable evidence that the analysis is robust

A word of warning….

Models are still models (of very complex processes) even if "sensitivity analysis" is performed

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

Models should be used as part of a body of evidence to make decisions

Summary of talk:

- Considered the reasons for using modeling
- Described how we model TB
- Outlined key modeling terminology/types of models
- Described SIR and Decision analysis models
- Outlined approaches to sensitivity analysis in modeling