Using Mathematical Models for Health Economic Analyses

Ruanne V. Barnabas, MBChB, D.Phil
Associate Professor, Global Health, Allergy & Infectious Disease
University of Washington
Outline

- Introduction to modeling
- Infectious disease modeling
- How models can be used to estimate health outcomes
  - Example: Potential impact of ART for prevention
  - What study data can you use to parameterize models
- When to use which model
- Primer on Decision
An introduction to Mathematical Models

- Framework for understanding and communicating infectious disease
- Explicit assumptions help delineate which parameters are based on evidence
- Quantitative or qualitative results are compared with observed or experimental data
- Validated models can be used to estimate the potential impact of interventions (e.g. ART for prevention)

Models in health economic analyses

- Used to structure the economic question and compare all relevant alternatives
- Extrapolate beyond observed data
- Link intermediate and final endpoints
- Generalize results to other settings/patient groups
- Synthesize evidence to simulate comparisons where RCTs don’t exist
- Indicate the need for further research

HERC short course, Oxford, 2012
Synthesizing knowledge

Not all models are mathematical!
Why can’t we use classical epidemiology to answer questions about infectious disease dynamics?

Why use a (potentially complicated) model?

• Infectious diseases are different because they are caused by transmission of a pathogen

• Prevalence of infection is the key risk factor for incidence.

• Prevalence reflects incidence at earlier time-point—leads to circularity and non-linear dynamics of infectious disease epidemics

• Classic regression of risk factors on disease risk do not incorporate prevalence.
  • \( \ln(\text{disease}) = b_0 + b_1\text{AGE} + b_2\text{SEX} \ldots + b_3\text{Income} \)
Population Attributable Fraction (PAR)

- PAR is a useful epidemiologic measure.
- It is the proportion of disease in a population that is attributable to the presence of the risk factor in the population.

\[
\frac{\text{Inc}_{\text{total pop}} - \text{Inc}_{\text{unexposed}}}{\text{Inc}_{\text{total}}} \times 100
\]
E.g. PAR for HIV and male circumcision

- Risk factor: not being circumcised
- Expected incidence among 1,000 susceptibles, of which 500 circumcised:

<table>
<thead>
<tr>
<th></th>
<th>Infected</th>
<th>Total population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumcised</td>
<td>6</td>
<td>500</td>
</tr>
<tr>
<td>Not circumcised</td>
<td>10</td>
<td>500</td>
</tr>
</tbody>
</table>

- Using PAR, \( \frac{16/1000 - 6/500}{16/1000} = \frac{2}{10} = 25\% \) of infections in population are due to not being circumcised
- Using a mathematical model, we find 32\% of infections are attributable to not being circumcised.

- Why?
Infectious diseases are non-linear

- PAR is a linear calculation
- Infectious diseases depend on non-linear effects
- Herd immunity—circumcision protections other uncircumcised individuals in population
- PAR does not take prevalence into account
- PAR underestimates effects of risk factors on infectious diseases.
- $R_0$ captures the non-linear dynamics of infectious diseases
The basic and effective reproductive numbers

**$R_o$ The Basic Reproductive Number** - The number of new infections caused by one infection in an entirely susceptible population

**$R_t$ The Effective Reproductive Number** - The number of new infections caused by one infection at a given time

\[ R_0 = D \cdot C \cdot \beta \]

- **Mean length of time infectious**
- **Rate at which sexual contact occurs**
- **Likelihood of transmission on a sexual contact**

\[ R_t = R_0 \cdot x \]

- **Proportion of contacts susceptible**
- **Vaccination**
\( R_0 = 2 \)

- Transmission
- No Transmission
- Infectious
- Susceptible
$R_0 = 2$

$R_t = R_0 \cdot \text{prop susceptible} = 0.5$

Transmission

No Transmission

Infectious

Susceptible

Immune
How do we incorporate these important issues into modeling?

The answer depends on:
- the population to be modeled
- data availability
- the scientific question at hand, and
- the modeler’s preferences
Types of models

- Static models – Decision Trees
- Dynamic models
  - Force of infection can change over time
  - Includes herd immunity
- Both static and dynamic models can be either deterministic or stochastic (constrained random variables)
- Choice of model depends on scientific question
Model classification
…in a simplified scheme…

<table>
<thead>
<tr>
<th>Complexity</th>
<th>Static Deterministic</th>
<th>Dynamic Deterministic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Static Stochastic</td>
<td>Dynamic Stochastic</td>
<td></td>
</tr>
</tbody>
</table>
“Classic epidemic modeling”: uses differential equations to describe how people move through epidemiologically relevant “compartments” over time.
How models are like maps

Like maps, models…

... are abstractions

... have scale

... must trade off realism with generality

The kind of model you use depends on the question you want to answer.
Where do models fit in the path from discovery to implementation?

- Observation
- Clinical Trials
- Implementation Science
- Mathematical Modeling & Health Economic Analyses
- Freezer project
Outline

• Introduction to modeling
• Infectious disease modeling
• How models can be used to estimate health outcomes
  • Example: Potential impact of ART for prevention
  • What study data can you use to parameterize models
• When to use which model
• Primer on Decision
Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model

Reuben M Granich, Charles FGilks, Christopher Dye, Kevin M De Cock, Brian GWilliams

\[ \lambda = \lambda_0 e^{-\alpha t} \quad P = \frac{I}{N} \quad I = \sum_i (I_i + A_i) \quad J = \sum_i (I_i + \varepsilon A_i) \]

Lancet 2008
Models can estimate potential impact of health programs

Treating our way out of the HIV pandemic: could we, would we, should we?  
*Geoffrey P Garnett, Rebecca F Baggaley*

- “HIV prevention is easy in theory – the practice is hard.”
- Need intensive HIV testing and robust linkages to care, even among people who feel well
- Strategies need to be effective and cost-effective
74% ART uptake among eligible participants
(CD4 count ≤350 cells/µL and not on ART at enrollment)
ART Model: Structure

- Mathematical model to evaluate ART scale-up

- Realistic assumptions regarding testing and ART coverage

Roger Ying, Lancet HIV
Using study data for models

- Demographics
- Mixing patterns
- Natural history
- Transmission probability
- Factors that change susceptibility
- Factors that change infectiousness
- Effectiveness of interventions
- Engagement in health care

UNIVERSITY of WASHINGTON

HEIST
Health Economic Impact Studies for Translation
What study data can you use to parameterize models?

- Country specific demographics
- Distribution of CD4 count and viral load
- Intervention (including treatment) coverage and efficacy
- Factors that impact on HIV transmission: viral load, gender, circumcision status, co-infection status
## Cost-effectiveness

<table>
<thead>
<tr>
<th></th>
<th>Change in HIV incidence*</th>
<th>Change in HIV prevalence*</th>
<th>ICER per infection averted</th>
<th>ICER per death averted</th>
<th>ICER per QALY gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home HTC: ART for 48% of all HIV-positive people</td>
<td>−33.8%</td>
<td>−4.7%</td>
<td>Dominated†</td>
<td>$3290</td>
<td>$860</td>
</tr>
<tr>
<td>Home HTC plus CD4: additional ART for CD4 count 350–500 cells per μL</td>
<td>−40.6%</td>
<td>−6.7%</td>
<td>Dominated†</td>
<td>$4070</td>
<td>$900</td>
</tr>
<tr>
<td>Home HTC plus high viral load: additional ART for viral load &gt;10,000 copies per mL</td>
<td>−51.6%</td>
<td>−12.1%</td>
<td>$2960</td>
<td>$5020</td>
<td>$1710</td>
</tr>
</tbody>
</table>

Results are shown for a 10 year time period of 2015–25 with a 6% annual dropout from ART care. Costs and effectiveness are discounted by 3% annually. ICER = incremental cost-effectiveness ratio. QALY = quality-adjusted life-year. HTC = home HIV testing and counselling. ART = antiretroviral therapy. *Relative to a “no ART” counterfactual. †A dominated strategy is more costly and less effective or more costly and less cost-effective than a combination of other interventions.

Table 3: Effectiveness and cost-effectiveness of ART uptake from home HTC with varying ART initiation guidelines
Model: community structure & partnerships

Outside community – no intervention
Community – receives home HTC

Key
- Household
- Woman
- Man
  - Stable partnership
  - Temporary partnership

Incremental cost per DALY averted

- All ICERs per DALY averted are <20% of South African GDP per capita (2012), which by WHO standards are very cost-effective.

- Reducing ART cost to CHAI target reduces ICER per DALY averted by 36-76%.
Outline

• Introduction to modeling
• Infectious disease modeling
• How models can be used to estimate health outcomes
  • Example: Potential impact of ART for prevention
  • What study data can you use to parameterize models
• When to use which model
• Primer on Decision
How to choose the appropriate model for health outcomes

What model should I use?

Is the interaction between patients important (e.g. transmission)?

No → Systems Dynamic Model

Yes → Do you need to model recursive events?

No → Individual sampling model?

Yes → Do you need to model individuals?

No → Decision Tree Model

Yes → Markov Model

Individual sampling model?

Yes → Adapted from Barton et al. 2004

Health Economic Impact Studies for Translation
Summary

• Infectious disease modeling is a useful tool
• Modeling can be used to estimate health outcomes
• Study data can be used to parameterize models
Primer on Decision Trees

James G. Kahn, MD, MPH
Professor of Health Policy, Epidemiology, & Global Health
University of California, San Francisco
Overview

• What is a decision tree?
• When should I use a decision tree?
• How to construct a decision tree
• How to analyze a decision tree
• Software options
What is a decision tree?

• A branching structure that leads from a choice (among competing courses of action) through a probability net of possible consequences (temporary and final) …

• … in which each path of consequences has an associated probability and set of outcomes of interest (e.g., cost and health status) such that …

• … each course of action can be assigned expected values for the outcomes (as the weighted mean of relevant paths) that can be compared and used to guide decisions among the actions.
Decision tree structure to evaluate interventions

<table>
<thead>
<tr>
<th>Population</th>
<th>Decision node / Course of Action / Options</th>
<th>Chance nodes / Consequences</th>
<th>Path Probability</th>
<th>DALYs</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>For terminal nodes</td>
<td>Intermediate product</td>
<td>For terminal nodes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cancer</td>
<td>0.16</td>
<td>10</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>die old</td>
<td>0.04</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no cancer</td>
<td>0.16</td>
<td>8</td>
<td>1.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>die old</td>
<td>0.64</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Young men
(smokers)

Expected value for this option: $8,000
### Decision tree structure to evaluate interventions

<table>
<thead>
<tr>
<th>Population</th>
<th>Decision node / Course of Action / Options</th>
<th>Chance nodes / Consequences</th>
<th>Path Probability</th>
<th>DALYs</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For terminal nodes</td>
<td>Intermediate product</td>
</tr>
<tr>
<td>No intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young men</td>
<td>(smokers)</td>
<td>cancer</td>
<td>0.8</td>
<td>0.16</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>die old</td>
<td>0.2</td>
<td>0.04</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no cancer</td>
<td>0.2</td>
<td>0.16</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>die old</td>
<td>0.2</td>
<td>0.64</td>
<td>0</td>
</tr>
<tr>
<td>Smokers</td>
<td></td>
<td>cancer</td>
<td>0.15</td>
<td>0.12</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>die old</td>
<td>0.2</td>
<td>0.03</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no cancer</td>
<td>0.2</td>
<td>0.17</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>die old</td>
<td>0.2</td>
<td>0.68</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>1.00</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>2.92</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>$8,000</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Expected value for this option:**

- **Difference:** -0.33
- **ICER:** $758

---

Health Economic Impact Studies for Translation
When should I use a decision tree?

- **Conceptualizing: Almost always.** Extremely useful to develop and portray the structure of a cost-effectiveness analysis ... clarify thinking, tighten logic, avoid omissions of possible paths. Can be used in conjunction with other visual portrayals of model dynamics.

- **Operationalizing: Often.** Assures that conceptual approach is reflected in implementation. Often used in conjunction with other calculation tools. Balance of tree & other calculation structures is personal preference.

- **Presenting: Sometimes.** Some analyses done with trees are presented with trees, some not.
How to construct a decision tree

• **Population & context**

• **Decision node (square)** – the question under study, 2 or more action options – all plausible (judgment call). Later decisions brought to front.

• **Chance nodes (circles)** – in each node probabilities sum to 100%. Mutually exclusive & exhaustive. Dichotomous easiest to manipulate. Markov can be incorporated.

• **Terminal node utilities = outcomes** – health, costs (direct, time)

• **Expected values** for health and costs, for each action option as weighted mean of paths.

• **Iterative revision** – unlike RCTs, the approach can (and nearly always does) change with early results and better understanding. The trick is knowing when to stop refining, and balancing completeness with transparency.
How to analyze a decision tree

- **Comparisons across options** – compare expected values for costs and health outcomes … ordered (least to most expensive) & step-wise incremental … then incremental cost-effectiveness ratios (ICERs)

<table>
<thead>
<tr>
<th></th>
<th>Cost</th>
<th>Δ Cost</th>
<th>DALYs</th>
<th>Δ DALYs (averted)</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Option A</td>
<td>$1,000</td>
<td></td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option C</td>
<td>$1,500</td>
<td>$500</td>
<td>8</td>
<td>2.0</td>
<td>$250</td>
</tr>
<tr>
<td>Option B</td>
<td>$1,700</td>
<td>$200</td>
<td>8.5</td>
<td>-0.5</td>
<td>Dominated</td>
</tr>
<tr>
<td>Option D</td>
<td>$2,500</td>
<td>$800</td>
<td>7.5</td>
<td>1.0</td>
<td>$2,000 [vs C]</td>
</tr>
</tbody>
</table>

- **Sensitivity analyses** – 1-way, 2-way, scenarios, thresholds, multivariate (eg Monte Carlo).
• **Excel** – familiar, generic, flexible (e.g., incorporate epidemic and cost models), has sensitivity analysis add-ons (Crystal Ball, @Risk). My favorite. Consider starting with template.

• **TreeAge** – new, specialized, efficient for set CEA tasks, less flexible, quirky manual and implementation.

• **@Risk** – newer, specialized, efficient for set CEA tasks, powerful, complex, narrow market.
**Extra credit: testing analysis**

**Prevalence before test performance**

---

**Tree structure to evaluate diagnostic tests**

<table>
<thead>
<tr>
<th>Population</th>
<th>Decision: Test or not</th>
<th>True disease prevalence (risk of disease)</th>
<th>Test performance*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Why?**

Forces equal disease prevalence in all arms, o/w source of error

Avoid ppv, npv, etc which are more complex (prevalence-dependent)

---

**Test # 1**

- **Disease (prevalence)**
  - True positive (Sensitivity)
  - False negative (1 - sensitivity)
- **No disease (1 - prev)**
  - True negative (Specificity)
  - False positive (1 - specificity)
• Thank you
• Email: rbarnaba@uw.edu