Using Mathematical Models for Health Economic Analyses

Ruanne V. Barnabas, MBChB, D.Phil

Associate Professor, Global Health, Allergy & Infectious Disease

University of Washington

CFAR
FRED HUTCHINSON CANCER RESEARCH CENTER
SEATTLE BIOMED
SEATTLE CHILDREN'S
CENTER FOR AIDS RESEARCH
UNIVERSITY OF WASHINGTON

HEIST
Health Economic Impact Studies for Translation
UNIVERSITY of WASHINGTON

UNIVERSITY OF WASHINGTON
INTERNATIONAL CLINICAL RESEARCH CENTER

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

UNIVERSITY of WASHINGTON

HEIST
Health Economic Impact Studies for Translation

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)

UNIVERSITY of WASHINGTON

Garnett, G. P. (2002). Sex Transm Infect 78(1): 7-12.

HEIST
Health Economic Impact Studies for Translation

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

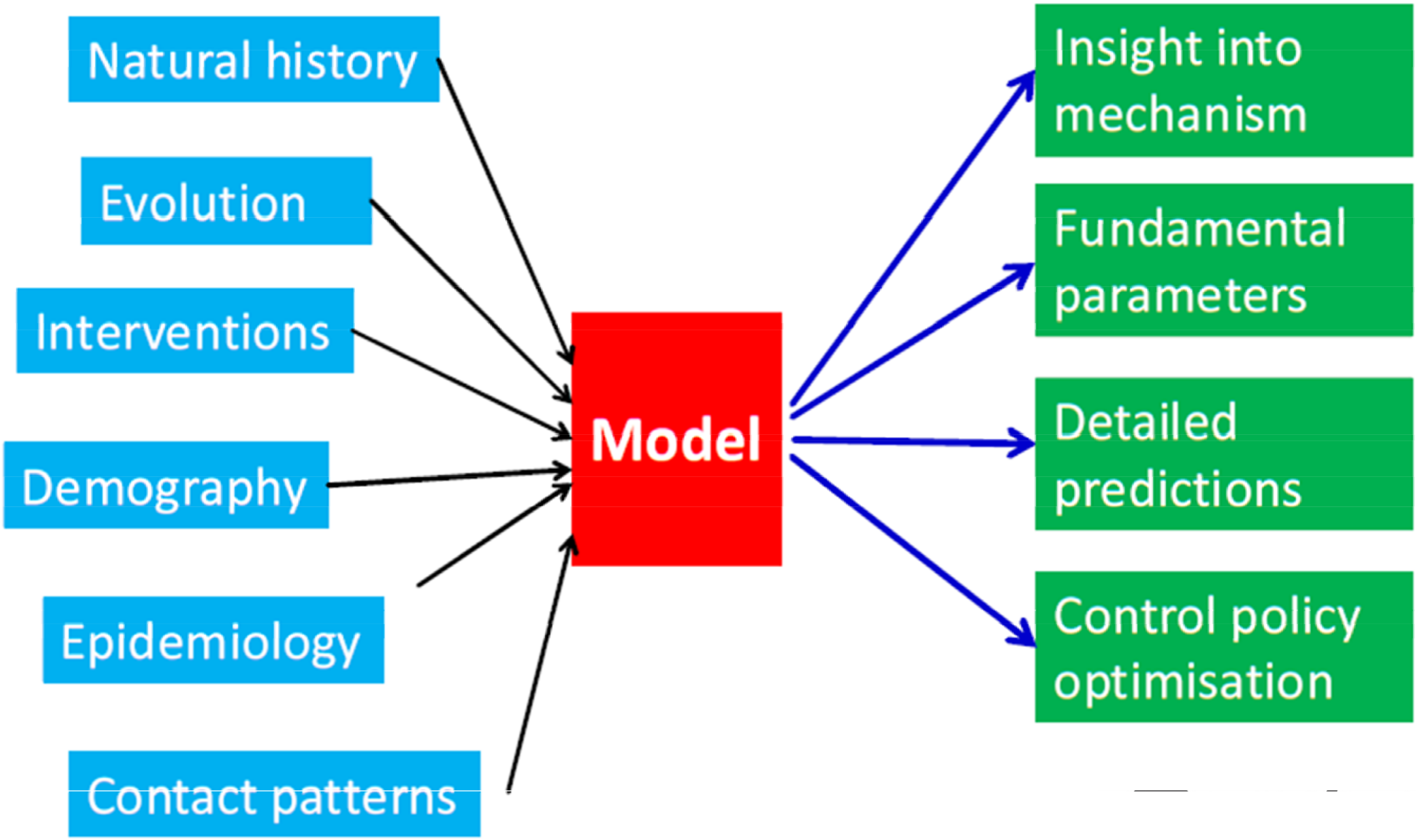
UNIVERSITY of WASHINGTON

HERC short course, Oxford, 2012

HEIST

Health Economic Impact Studies for Translation

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(disease)= b0 + b1AGE + b2SEX … + b3Income

UNIVERSITY of WASHINGTON

HEIST
Health Economic Impact Studies for Translation

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.

  $(\text{Inc}_{\text{total pop}} - \text{Inc}_{\text{unexposed}})/\text{Inc}_{\text{total}} \times 100$

UNIVERSITY of WASHINGTON

HEIST
Health Economic Impact Studies for Translation

E.g. PAR for HIV and male circumcision

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

	Infected	Total population
Circumcised	6	500
Not circumcised	10	500

- Using PAR, (16/1000-6/500)/(16/1000) = 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?

UNIVERSITY of WASHINGTON

HEIST
Health Economic Impact Studies for Translation

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

UNIVERSITY of WASHINGTON

HEIST
Health Economic Impact Studies for Translation

The basic and effective reproductive numbers

R_0 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

$$R_0 = D \, . \, C \, . \, \beta$$

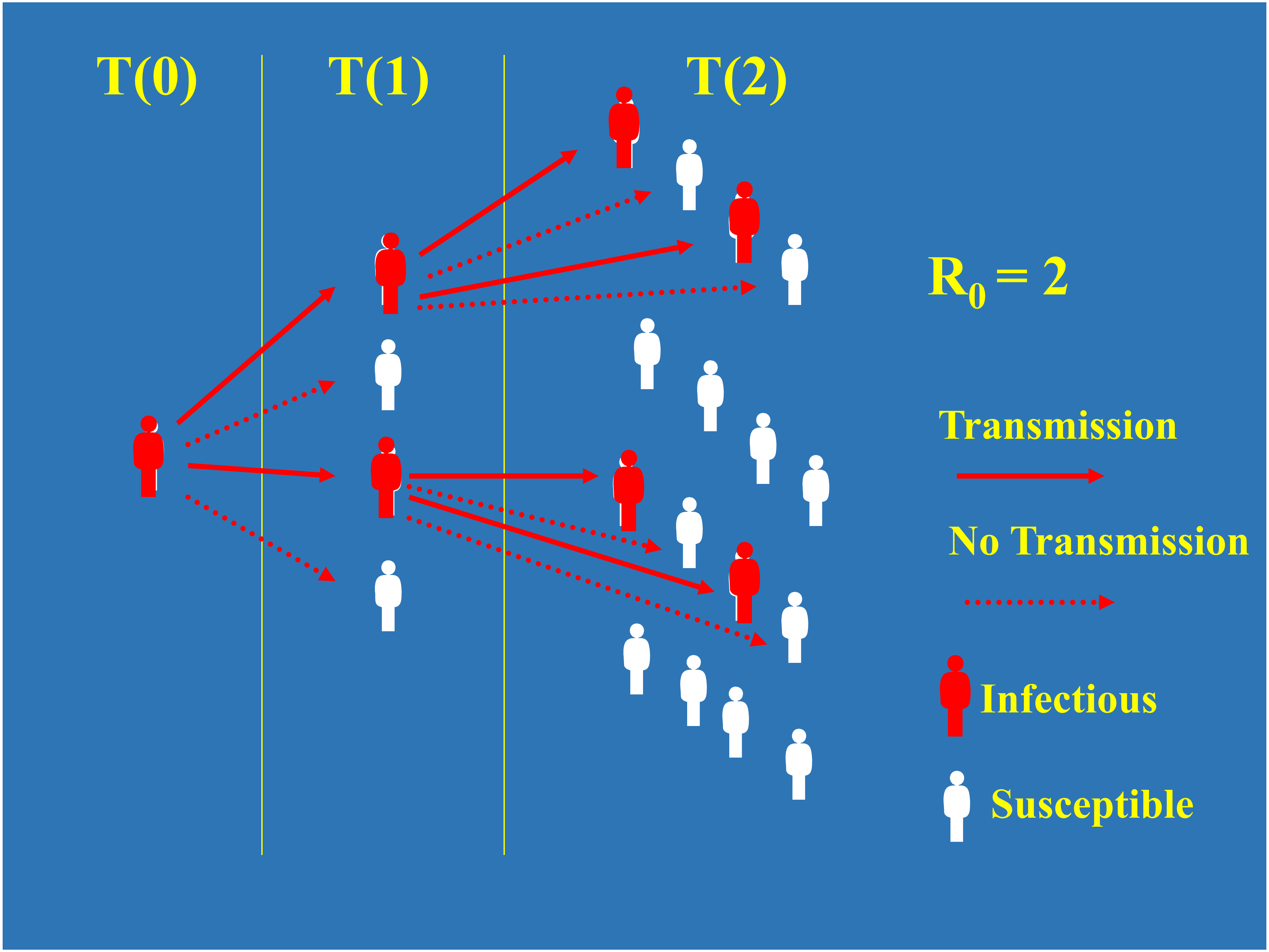
Likelihood of transmission on a sexual contact

Mean length of time infectious

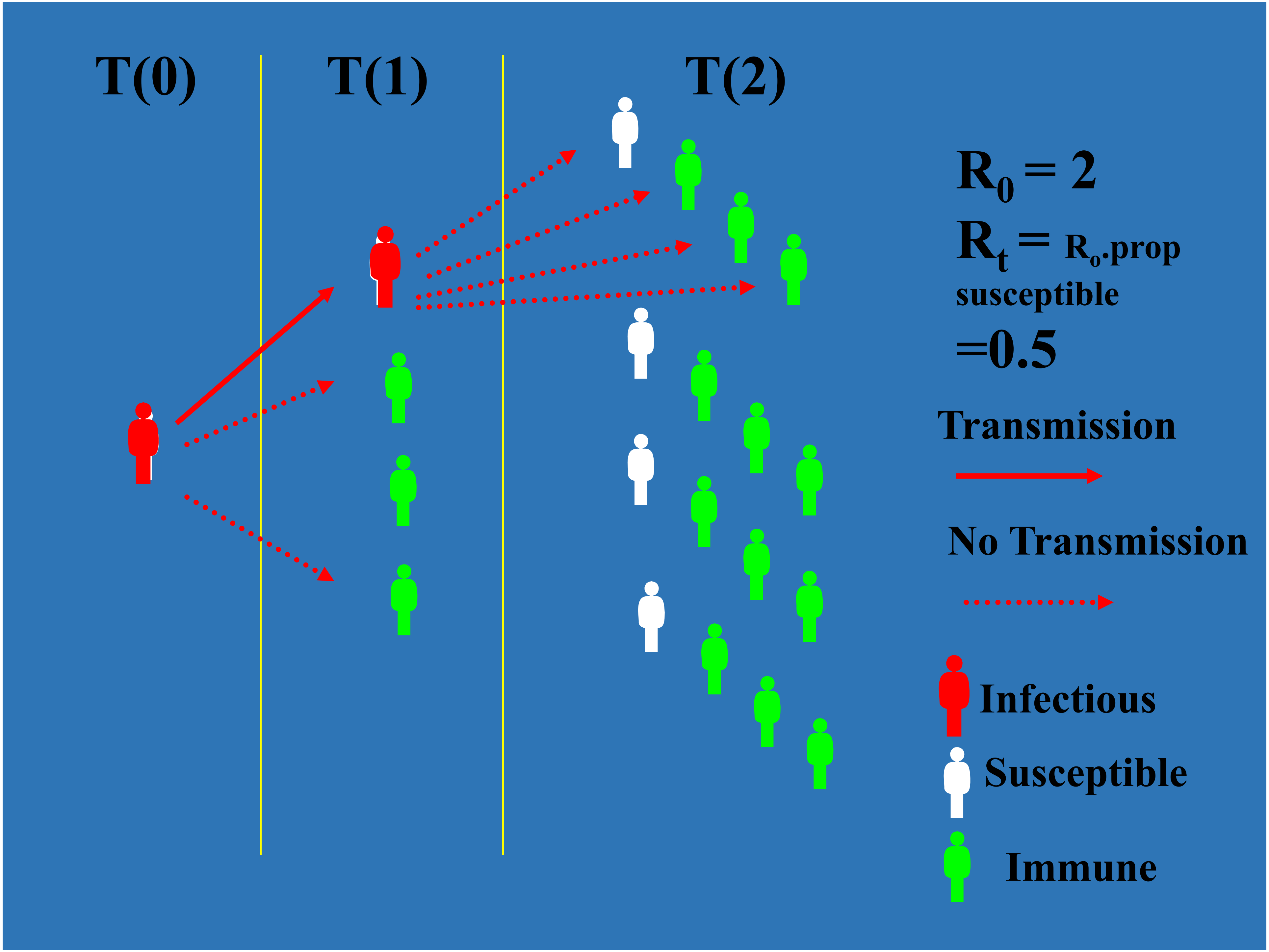
Rate at which sexual contact occurs

$$R_t = R_0 \, . \, x$$

Proportion of contacts susceptible -Vaccination



T(0)
T(1)
T(2)
$R_0 = 2$
Transmission
No Transmission
Infectious
Susceptible


T(0)
T(1)
T(2)
R0 = 2
Rt = Ro.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…

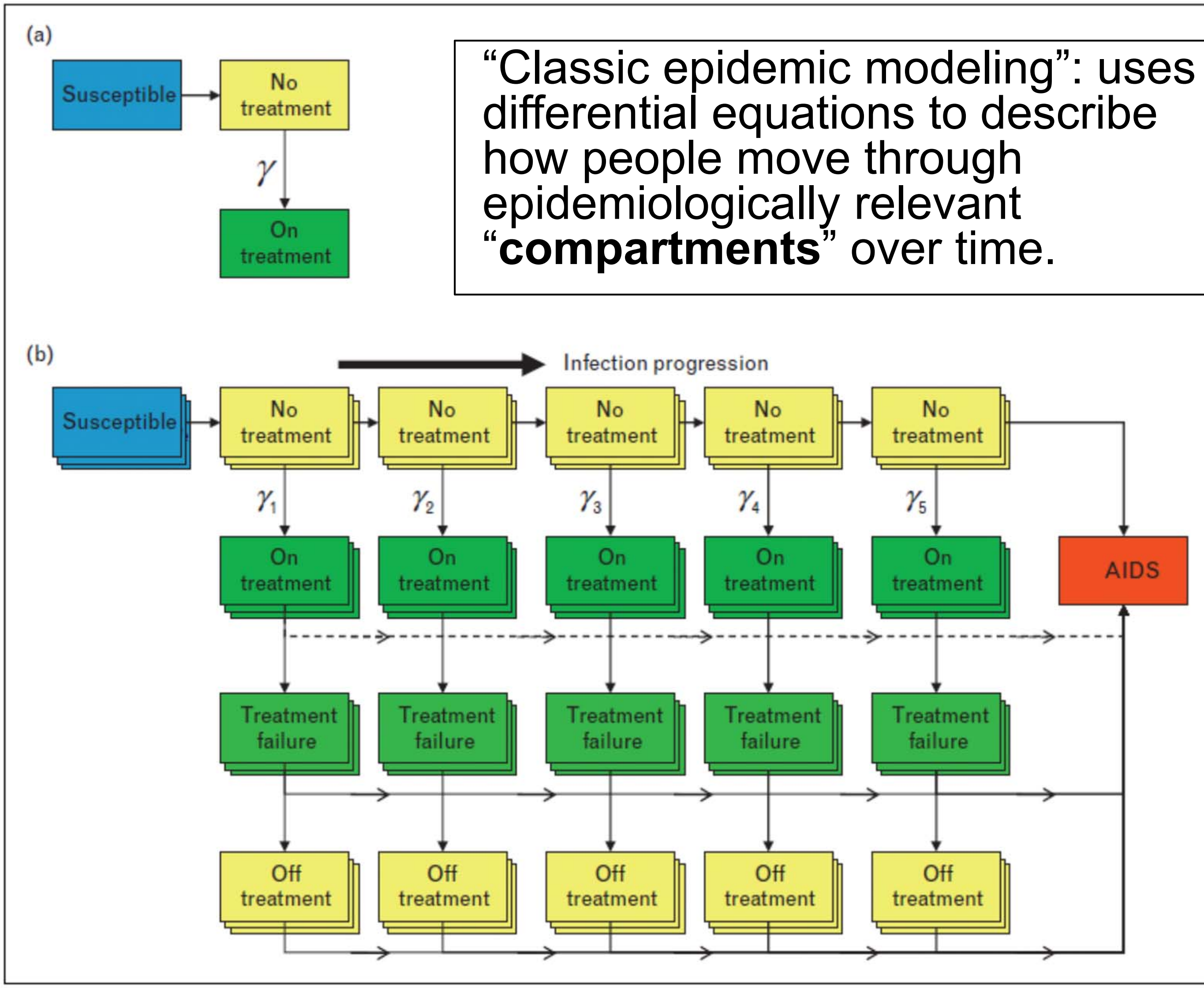
complexity →

Static Deterministic	Dynamic Deterministic
Static Stochastic	Dynamic Stochastic

complexity? ↓

Dynamic, deterministic model

Figure 3 Schematic illustrations of the structure of HIV transmission models incorporating antiretroviral therapy



"Classic epidemic modeling": uses differential equations to describe how people move through epidemiologically relevant "**compartments**" over time.

Baggeley & Fraser. Current Opinion in HIV/AIDS, 2010

es for Translation

How models are like maps

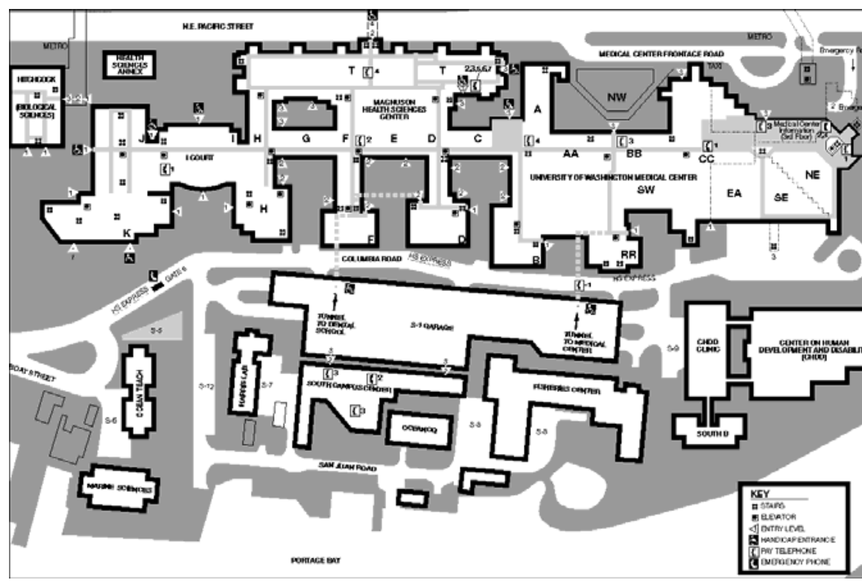
Like maps, models…

… are *abstractions*

… have *scale*

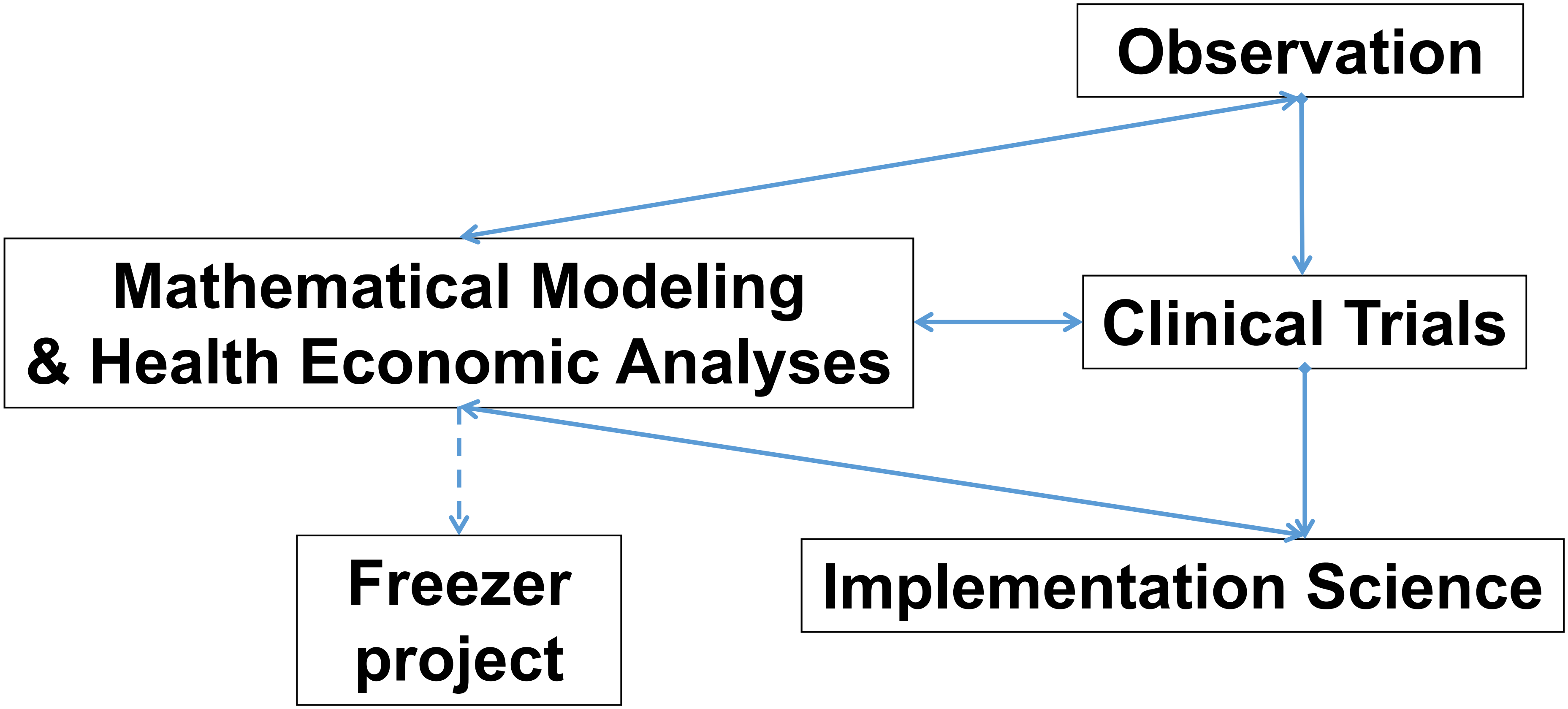
… must trade off *realism* with *generality*

The kind of model you use depends on the question you want to answer.



UNIVERSITY *of* WASHINGTON

Where do models fit in the path from discovery to implementation?



UNIVERSITY of WASHINGTON

HEIST
Health Economic Impact Studies for Translation

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

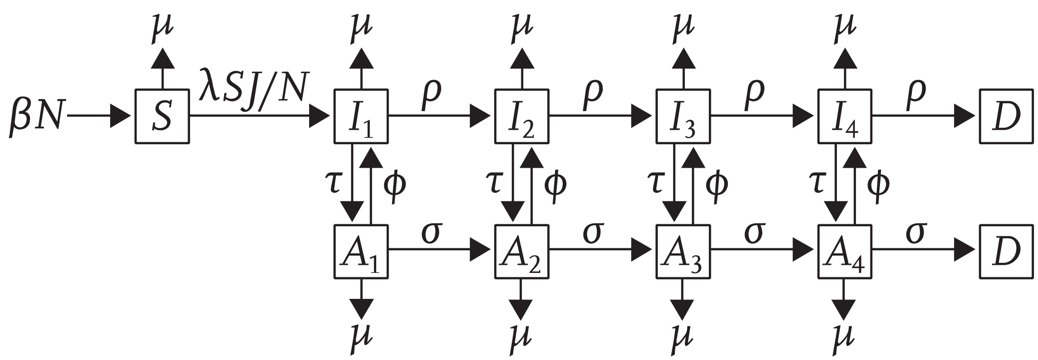
UNIVERSITY *of* WASHINGTON

HEIST
Health Economic Impact Studies for Translation

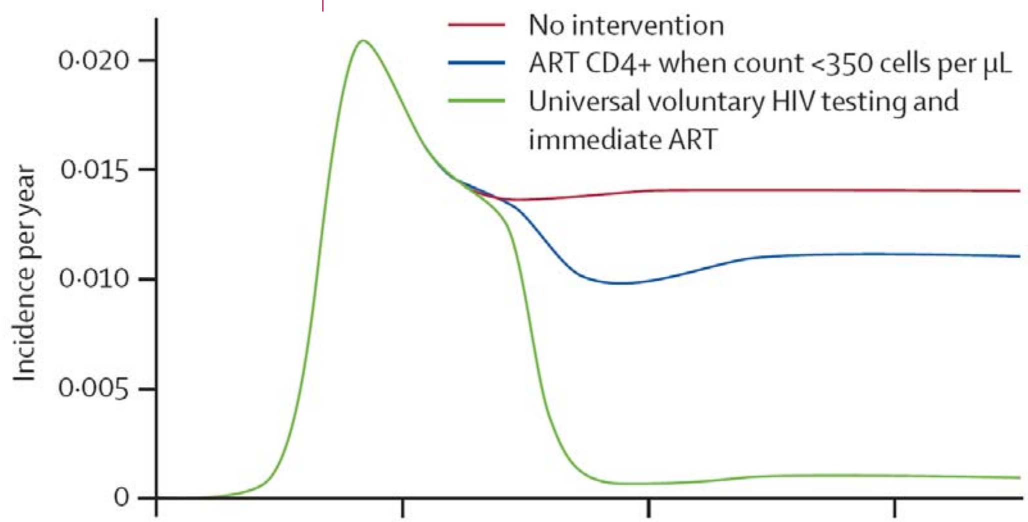
Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model

Reuben M Granich, Charles F Gilks, Christopher Dye, Kevin M De Cock, Brian G Williams

$\lambda=\lambda_o e^{-\alpha P n}$ $P=\frac{I}{N}$ $I=\Sigma_i(I_i+A_i)$ $J=\Sigma_i(I_i+\varepsilon A_i)$



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

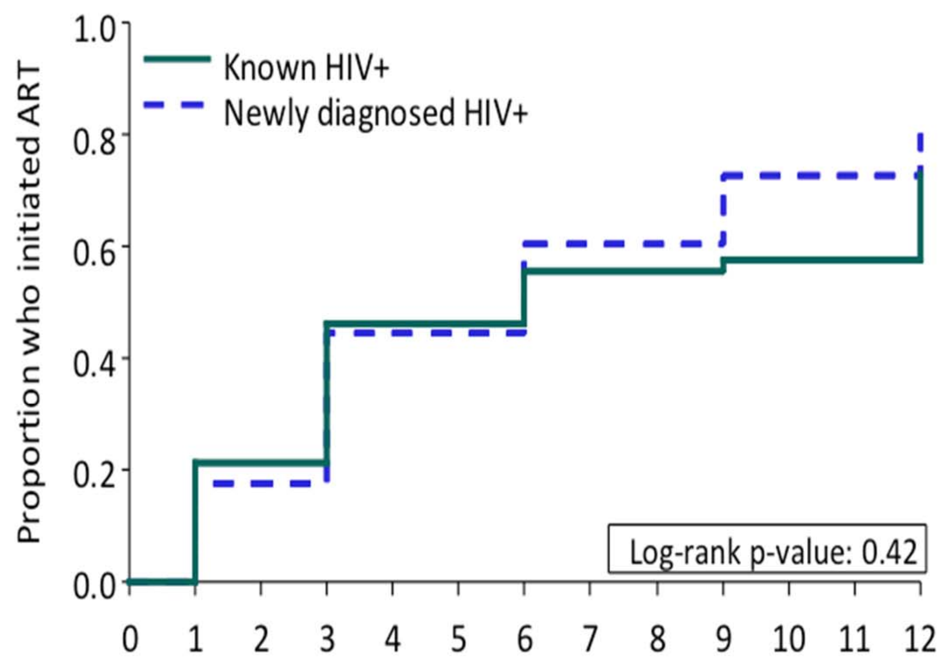
UNIVERSITY *of* WASHINGTON

HEIST
Health Economic Impact Studies for Translation

Initiation of antiretroviral therapy and viral suppression after home HIV testing and counselling in KwaZulu-Natal, South Africa, and Mbarara district, Uganda: a prospective, observational intervention study

Ruanne V Barnabas, Heidi van Rooyen, Elioda Tumwesigye, Pamela M Murnane, Jared M Baeten, Hilton Humphries, Bosco Turyamureeba, Philip Joseph, Meighan Krows, James P Hughes, Connie Celum

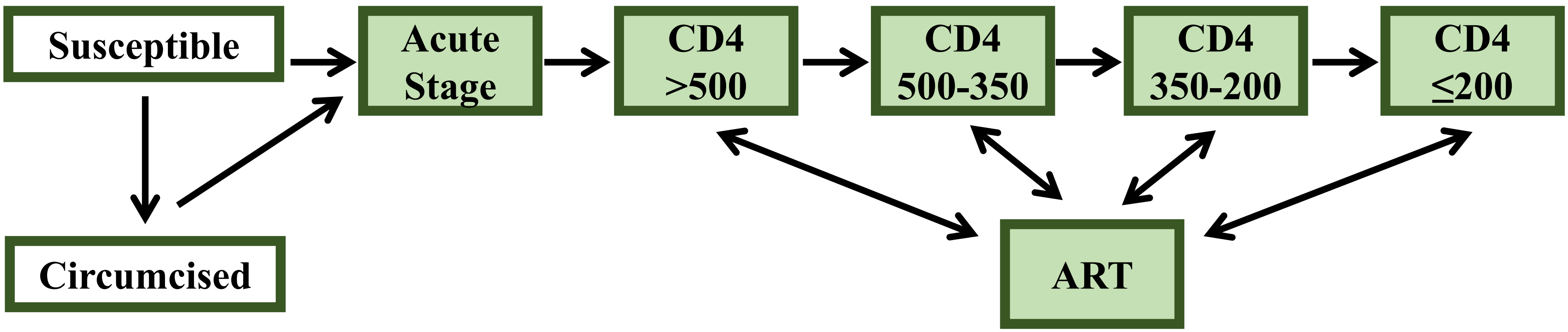
74% ART uptake among eligible participants
(CD4 count ≤350 cells/μL and not on ART at enrollment)



No. in followup:	0	1	3	6	9	12
Known HIV+	52	52	41	28	23	22
Newly diagnosed HIV+	74	74	61	38	26	15

ART Model: Structure

- Mathematical model to evaluate ART scale-up



- Realistic assumptions regarding testing and ART coverage

UNIVERSITY of WASHINGTON

Roger Ying, Lancet HIV

Health Economic Impact Studies for Translation

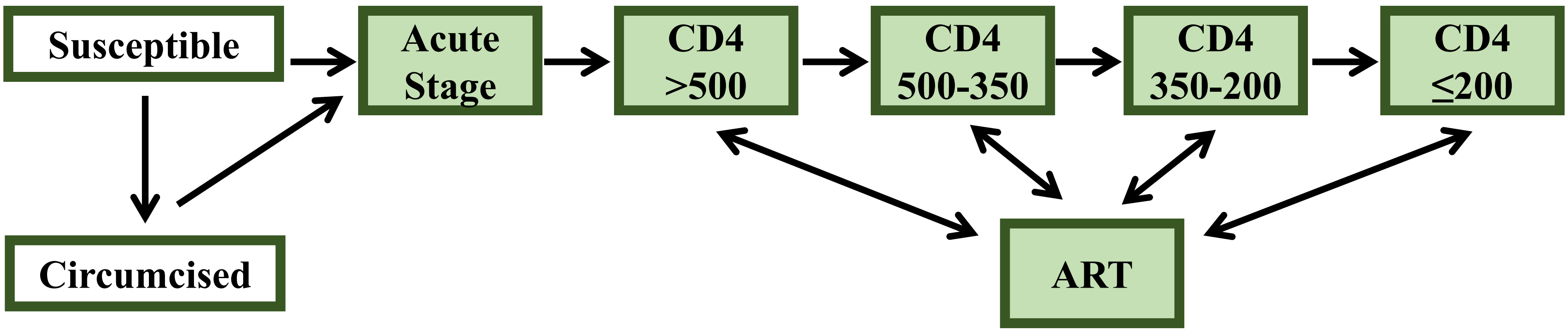
Using study data for models

- 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?

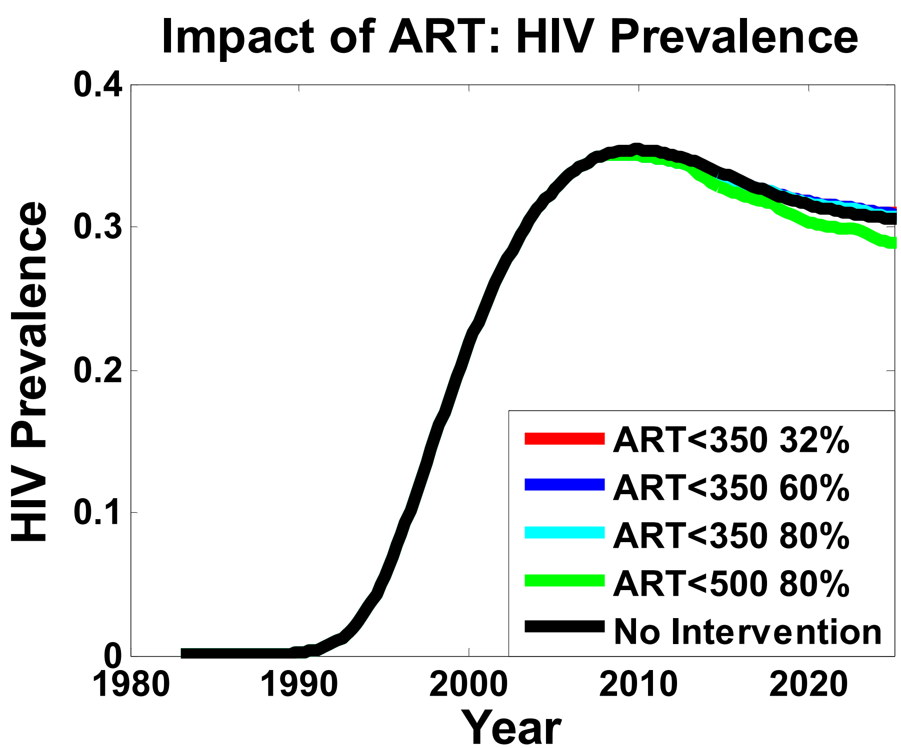


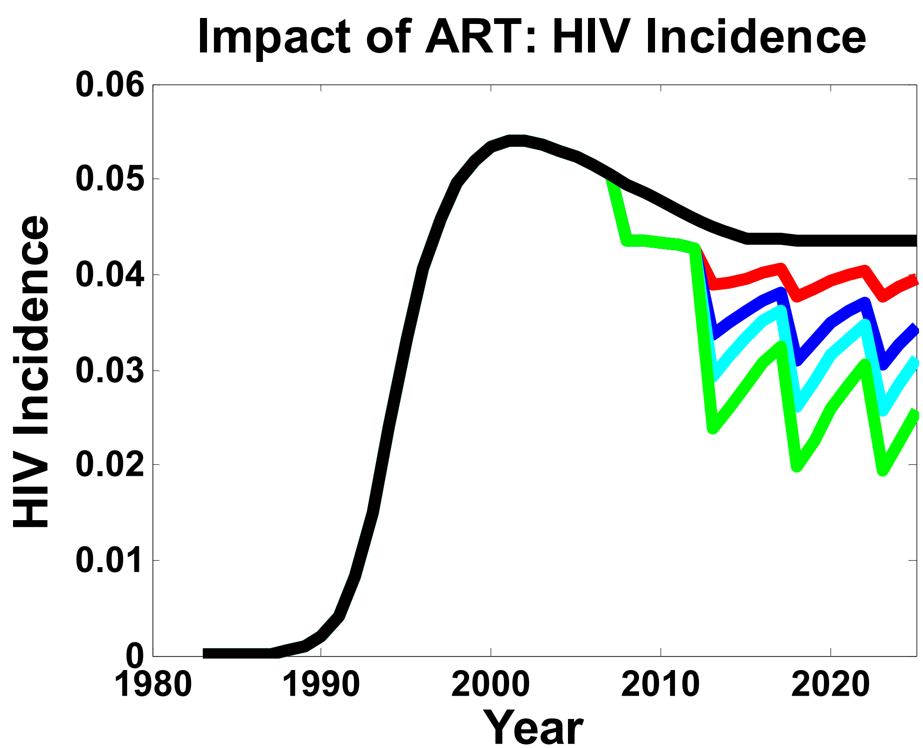
- Country specific demographics
- Distribution of CD4 count and viral load
- Intervention (including treatment) coverage and efficacy
- Factors that impact on HIV transmission: viral load, gender, circumcision status, co-infection status

UNIVERSITY of WASHINGTON

HEIST
Health Economic Impact Studies for Translation

ART Model: Results





W UNIVERSITY of WASHINGTON

Roger Ying, ISSTDR 2013

HEIST

Health Economic Impact Studies for Translation

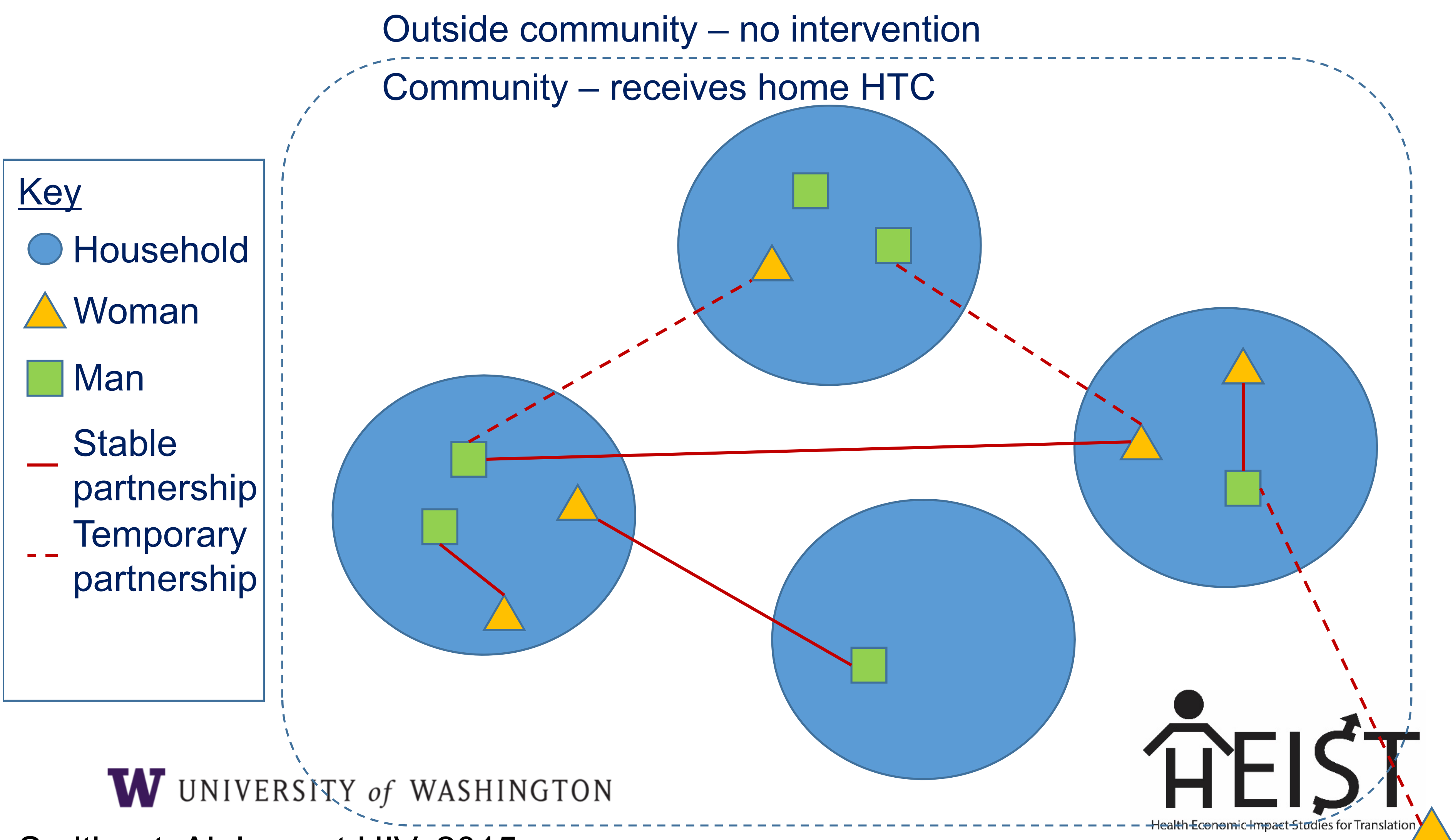
Cost-effectiveness

	Change in HIV incidence*	Change in HIV prevalence*	ICER per infection averted	ICER per death averted	ICER per QALY gained
Home HTC: ART for 48% of all HIV-positive people	–33·8%	–4·7%	Dominated†	$3290	$860
Home HTC plus CD4: additional ART for CD4 count 350–500 cells per µL	–40·6%	–6·7%	Dominated†	$4070	$900
Home HTC plus high viral load: additional ART for viral load >10 000 copies per mL	–51·6%	–12·1%	$2960	$5020	$1710

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

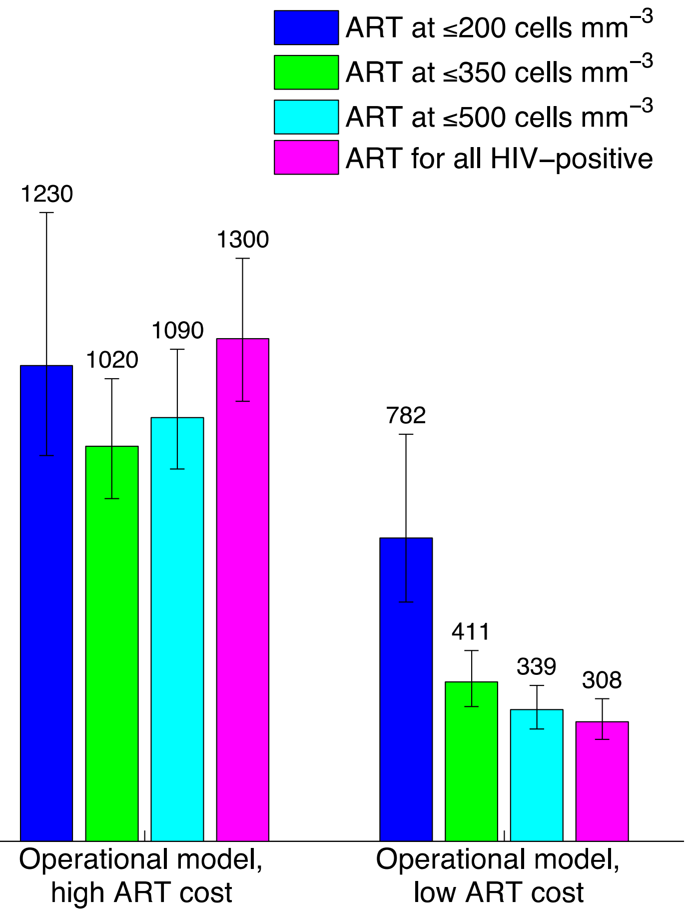


Smith, et. Al, Lancet HIV, 2015

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%**



UNIVERSITY of WASHINGTON

HEIST
Health Economic Impact Studies for Translation

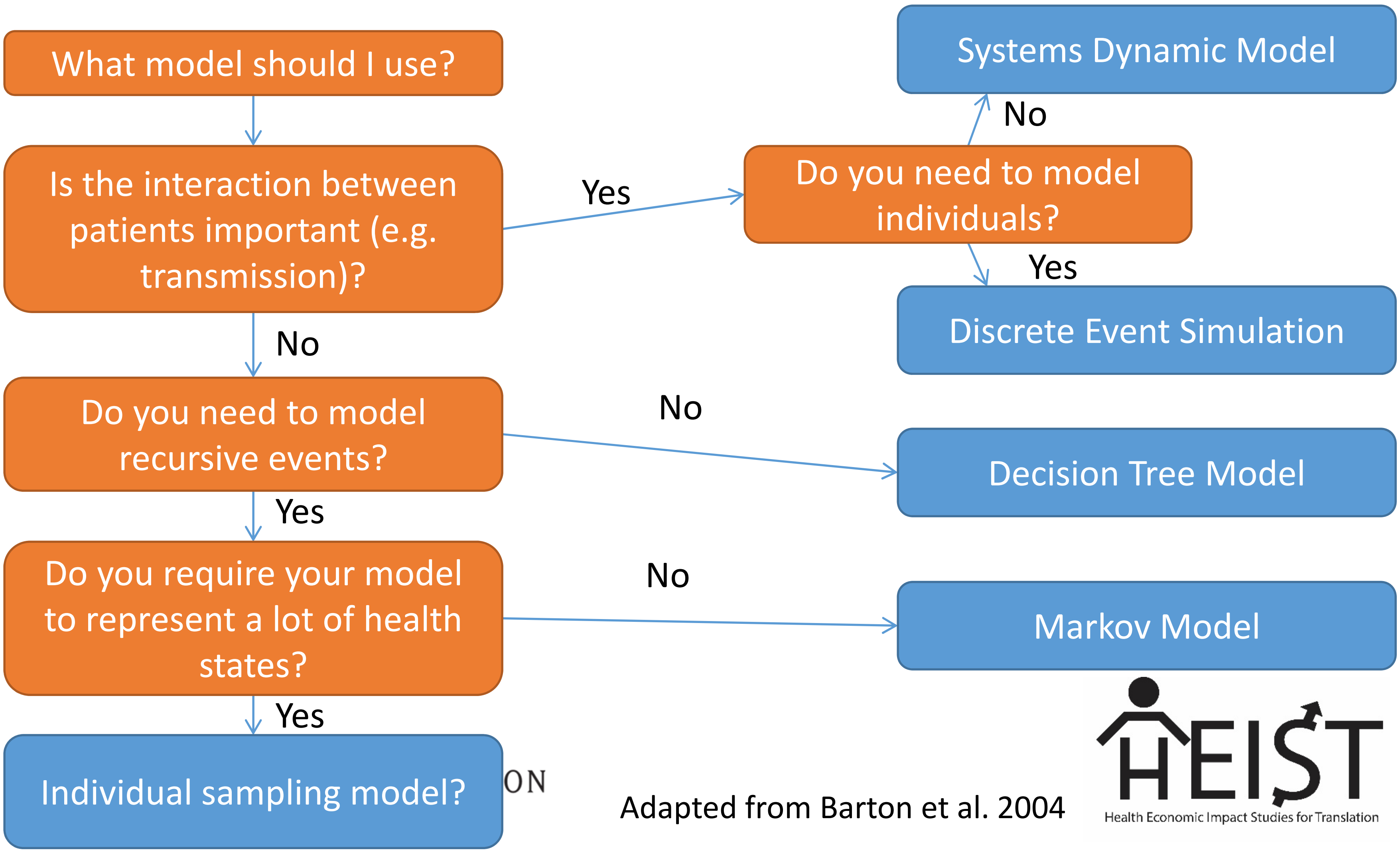
Outline

- 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

UNIVERSITY of WASHINGTON

HEIST
Health Economic Impact Studies for Translation

How to choose the appropriate model for health outcomes



Adapted from Barton et al. 2004

HEIST
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

CFAR
FRED HUTCHINSON CANCER RESEARCH CENTER
SEATTLE BIOMED
SEATTLE CHILDREN'S
CENTER FOR AIDS RESEARCH
UNIVERSITY OF WASHINGTON

HEIST
Health Economic Impact Studies for Translation
UNIVERSITY of WASHINGTON

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.

UNIVERSITY of WASHINGTON

HEIST
Health Economic Impact Studies for Translation

Decision tree structure to evaluate interventions

Population	Decision node / Course of Action / Options	Chance nodes / Consequences		Path Probability	DALYs		Costs	
					For terminal nodes	Intermediate product	For terminal nodes	Intermediate product
Young men (smokers)	No intervention	cancer 0.2	die young 0.8	0.16	10	1.6	$20,000	$3,200
			die old 0.2	0.04	1	0.04	$20,000	$800
		no cancer 0.8	die young 0.2	0.16	8	1.28	$5,000	$800
			die old 0.8	0.64	0	0	$5,000	$3,200
				1.00		**2.92**		**$8,000**

Expected value for this option.

UNIVERSITY of WASHINGTON

HEIST
Health Economic Impact Studies for Translation

Decision tree structure to evaluate interventions

Population	Decision node / Course of Action / Options	Chance nodes / Consequences		Path Probability	DALYs: For terminal nodes	DALYs: Intermediate product	Costs: For terminal nodes	Costs: Intermediate product
Young men (smokers)	No intervention	cancer 0.2	die young 0.8	0.16	10	1.6	$20,000	$3,200
			die old 0.2	0.04	1	0.04	$20,000	$800
		no cancer 0.8	die young 0.2	0.16	8	1.28	$5,000	$800
			die old 0.8	0.64	0	0	$5,000	$3,200
				1.00		**2.92**		**$8,000**
	Smoking cessation program	cancer 0.15	die young 0.8	0.12	10	1.2	$21,000	$2,520
			die old 0.2	0.03	1	0.03	$21,000	$630
		no cancer 0.85	die young 0.2	0.17	8	1.36	$6,000	$1,020
			die old 0.8	0.68	0	0	$6,000	$4,080
				1.00		**2.59**		**$8,250**
					Difference	**-0.33**	**Difference**	**$250**
						ICER	**$758**	

Expected value for this option.

UNIVERSITY of WASHINGTON

HEIST
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)

	Cost	Δ Cost	DALYs	Δ DALYs (averted)	ICER	
Option A	$1,000		10			
Option C	$1,500	$500	8	2.0	$250	
Option B	$1,700	$200	8.5	-0.5	Dominated	
Option D	$2,500	$800	7.5	1.0	$2,000	[vs C]

- **Sensitivity analyses** – 1-way, 2-way, scenarios, thresholds, multivariate (eg Monte Carl0).

UNIVERSITY of WASHINGTON

HEIST
Health Economic Impact Studies for Translation

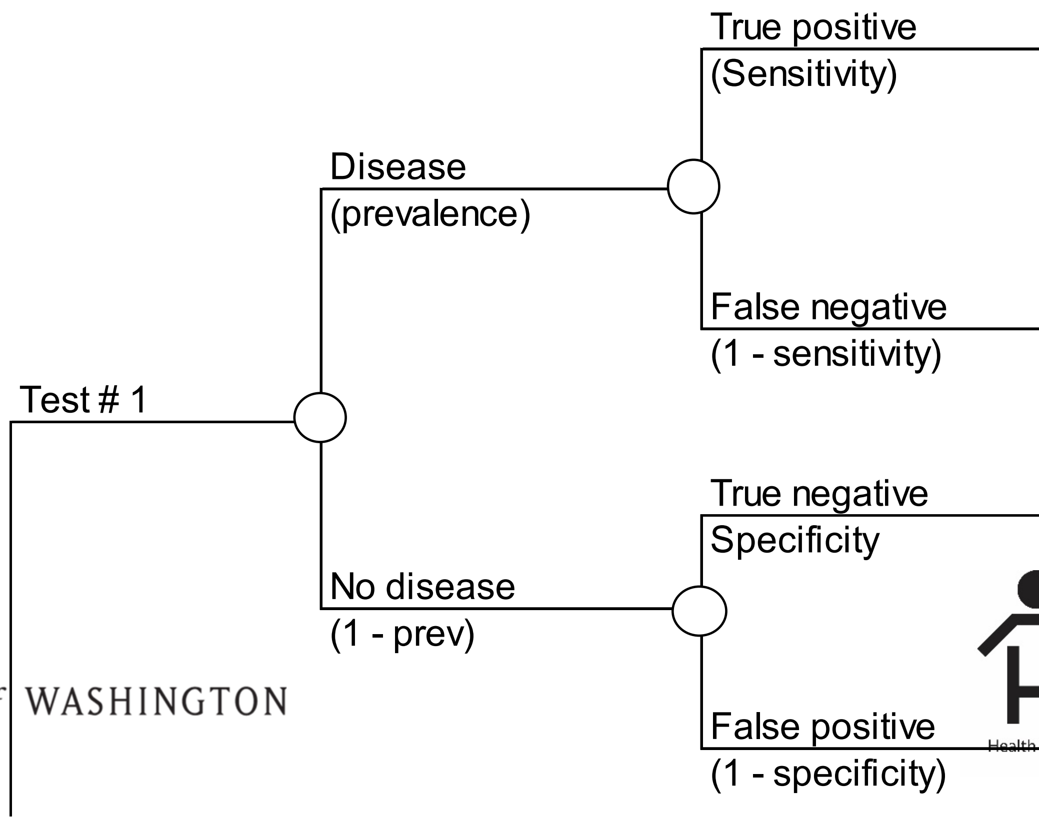
Software

- **Excel** – familiar, generic, flexible (eg 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

Population	Decision: Test or not	True disease prevalence (risk of disease)	Test performance*



Why?

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

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

- Thank you
- Email: rbarnaba@uw.edu

UNIVERSITY of WASHINGTON

HEIST

Health Economic Impact Studies for Translation