Models for Understanding and Controlling Global Infectious Diseases HUMBIO 154D / HRP 204

Session 11

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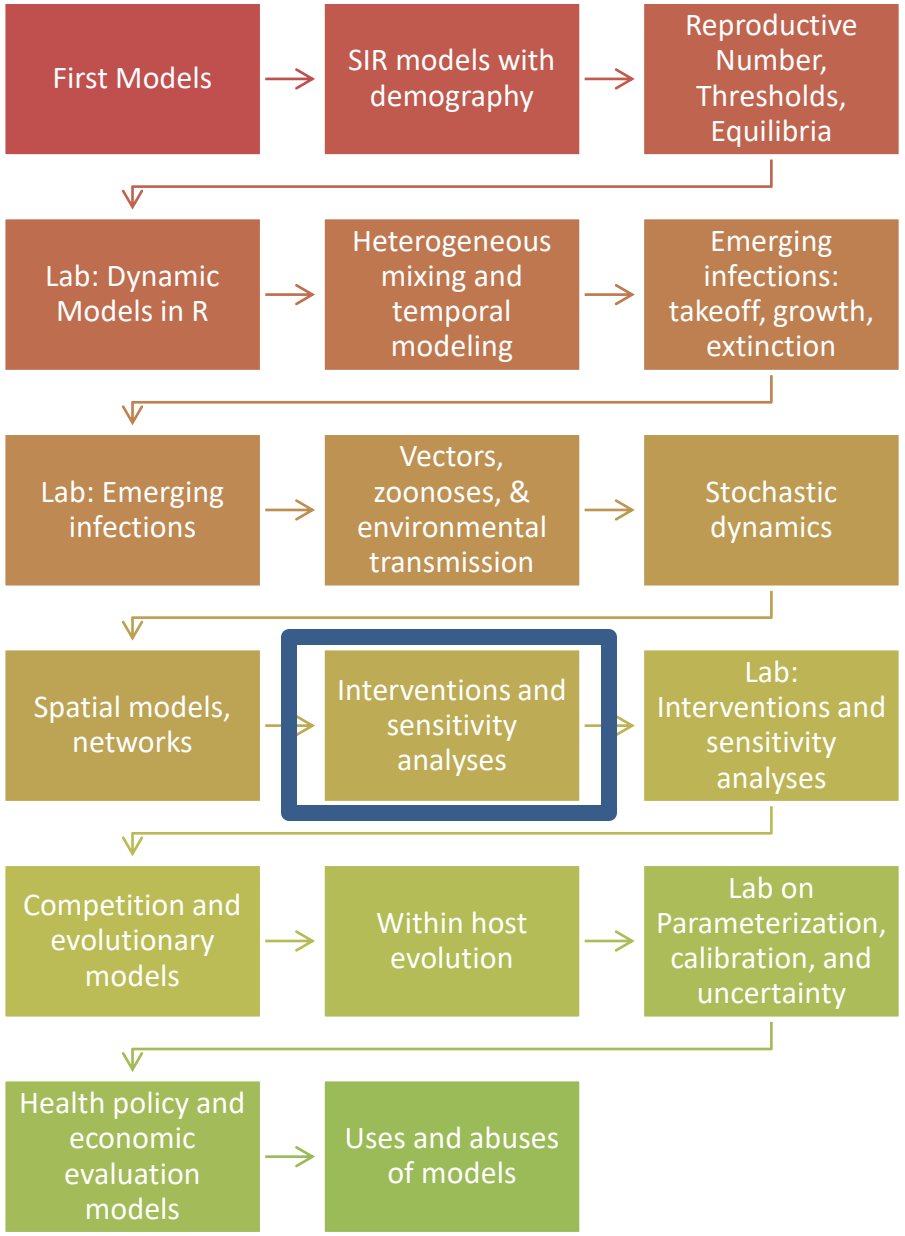
2020

Course Roadmap



Practical Questions

How do we explore how sensitive our model outcomes, projections, and assessments of preferred interventions are to alternative reasonable assumptions?

How do we introduce a range of common interventions into our infectious disease models? What needs to change? What assumptions are needed?

Learning Objectives

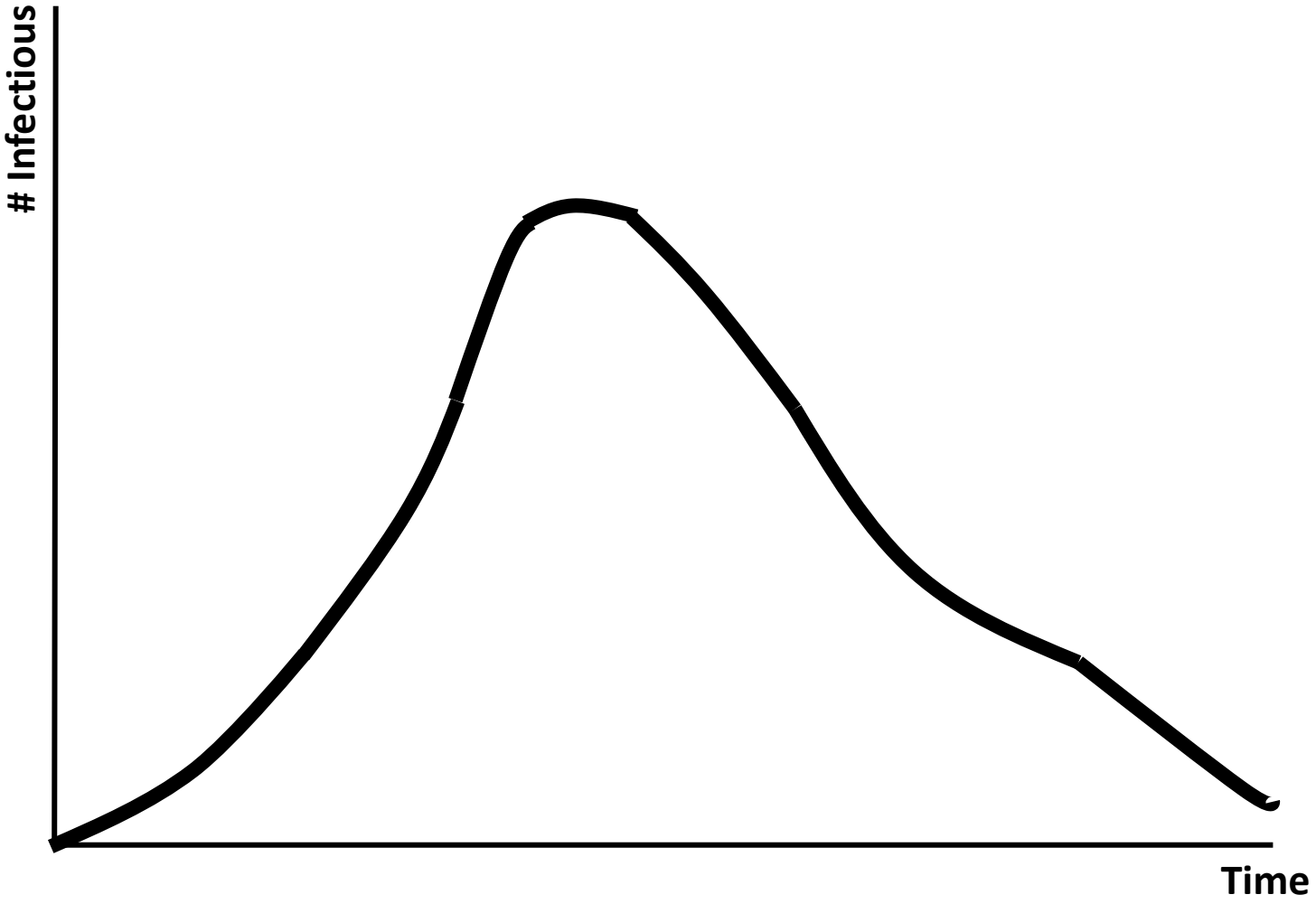
- Define sensitivity analysis
- Differentiate sensitivity analysis from uncertainty analysis
- Explain what our model parameters represent
- Appreciate computational requirements of n-way sensitivity analyses
- List a range of interventions relevant for infectious disease models
- Define the types of parameter and structural changes and additions needed for interventions like vaccination
- Explain the vaccine critical threshold and herd immunity
- Relate vaccination to social/physical distancing
- Describe a model for quarantine/isolation
- Discuss case identification rate in relation to test sensitivity and specificity
- Describe community quarantine/isolation and compare/contrast it with individual-level quarantine/isolation
- Describe contact tracing

WHAT IS A SENSITIVITY ANALYSIS?

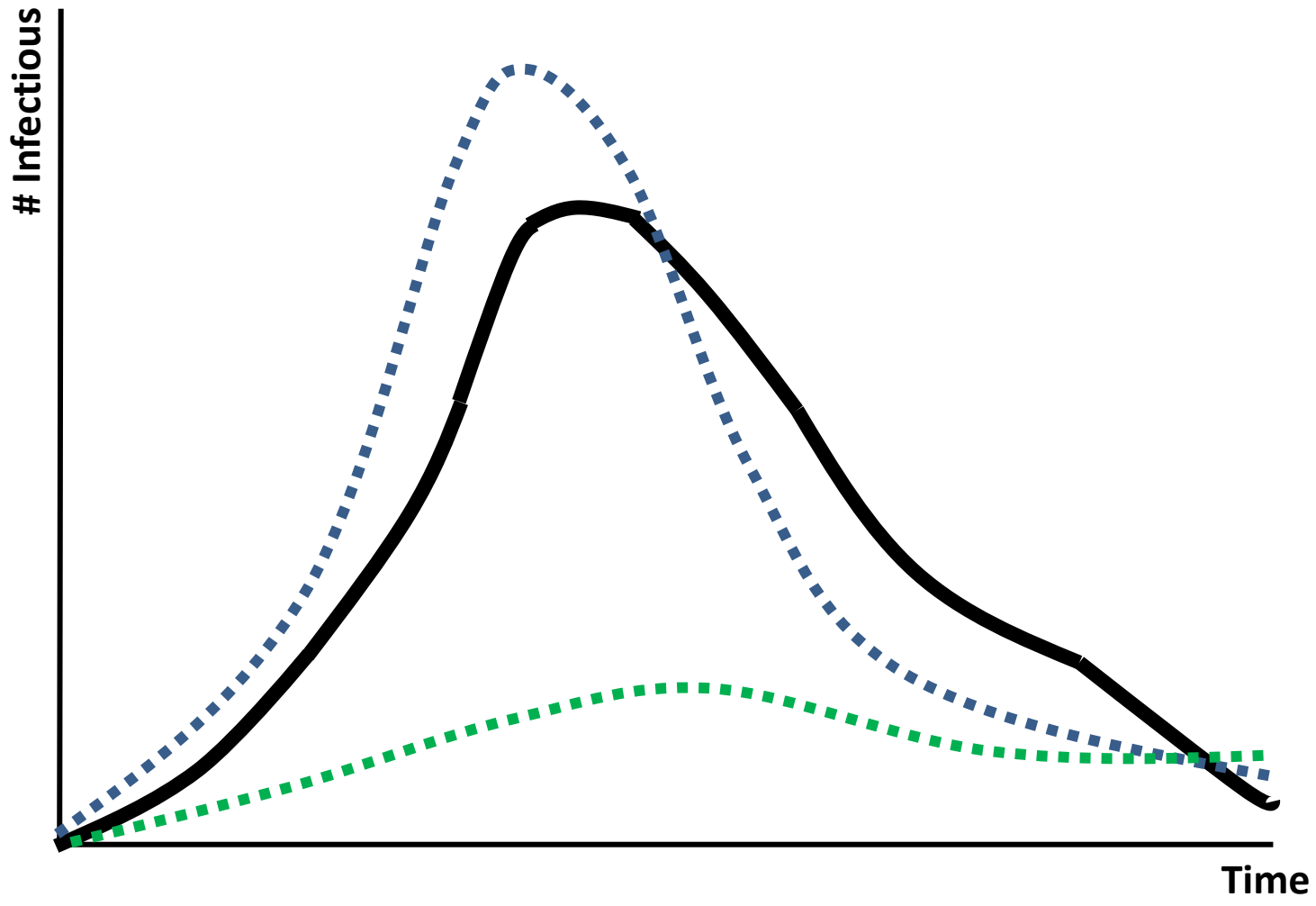
Sensitivity Analysis: Definition #1

- A set of computations that examines how systematic changes in a model's structure and/or parameters alter the conclusion of the analysis

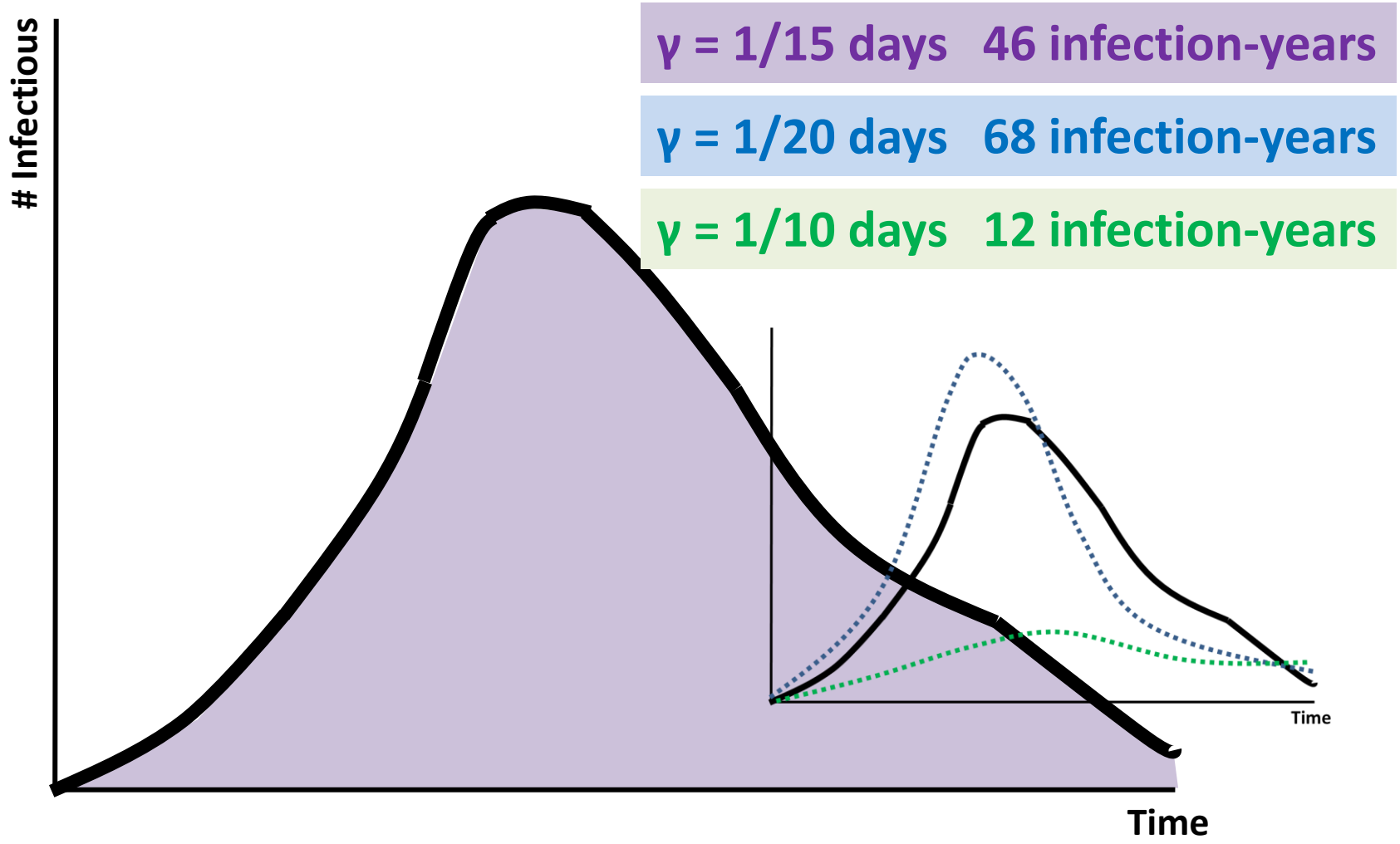
Example: An analysis might examine the prevalence of a disease over time



Example: If we change one of the parameters (e.g., gamma), how does the prevalence curve change?



Example: To simplify things for teaching today, we could focus on a single numeric quantity and how it changes with different values of gamma



Sensitivity Analysis and Interventions

- The second half of today's lecture is about interventions, which means, at minimum, we are interested in a model's predicted outcomes with and without intervention
- This is often connected to deciding making: choosing the intervention that we expect to provide us with the most of a good outcome or the least of a bad outcome
  - Examples: minimizing infections/year; maximizing life expectancy
- We can refine our sensitivity analysis definition accordingly

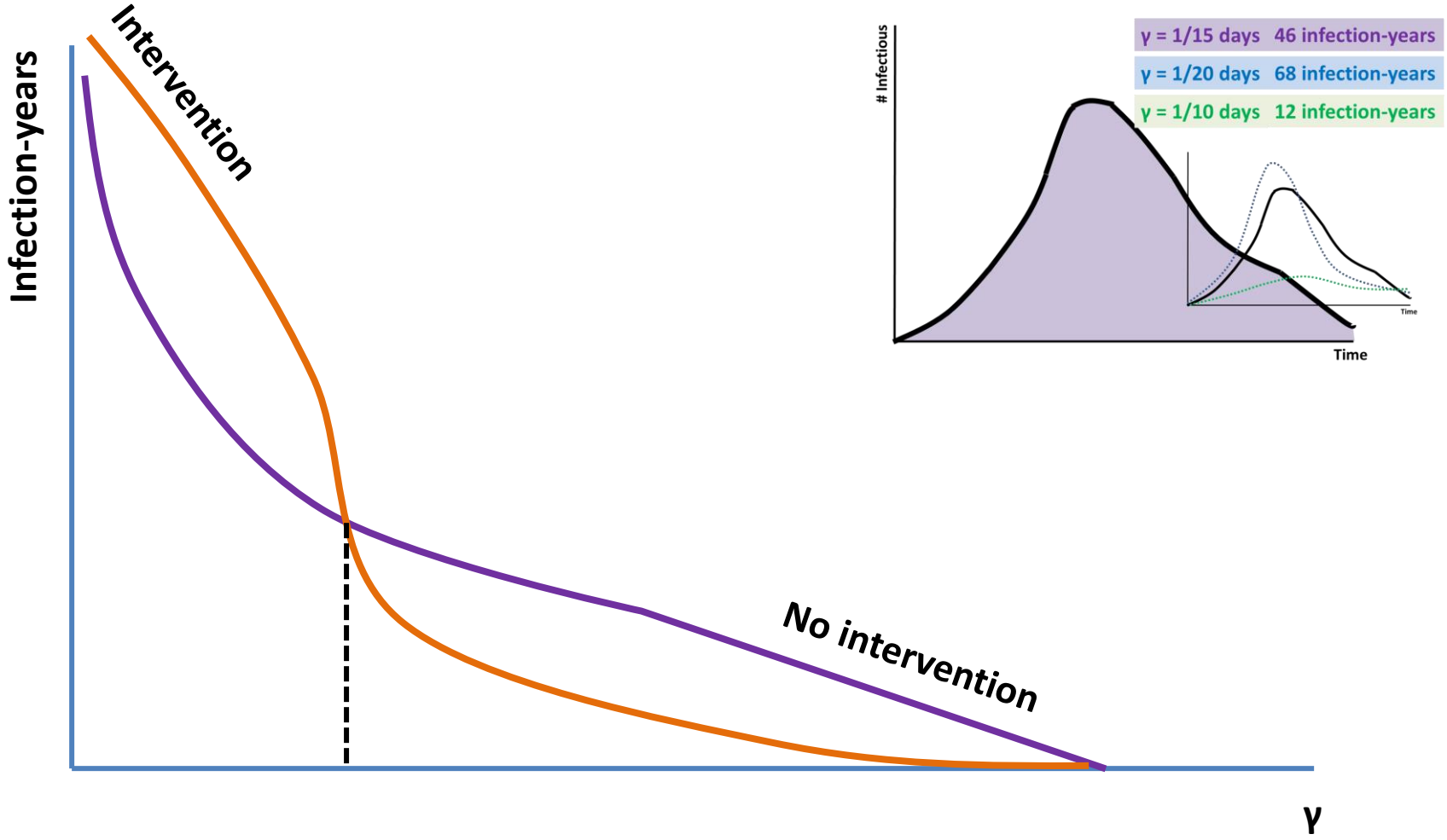
Sensitivity Analysis: Definition #2

- A set of computations that examines how systematic changes in a model's structure and/or parameters alter outcomes under alternative interventions and whether such changes are sufficient to change our preferred intervention and hence the conclusion of the decision analysis (e.g., cost-effectiveness analysis, cost-benefit analysis, etc.)

Types of sensitivity analyses

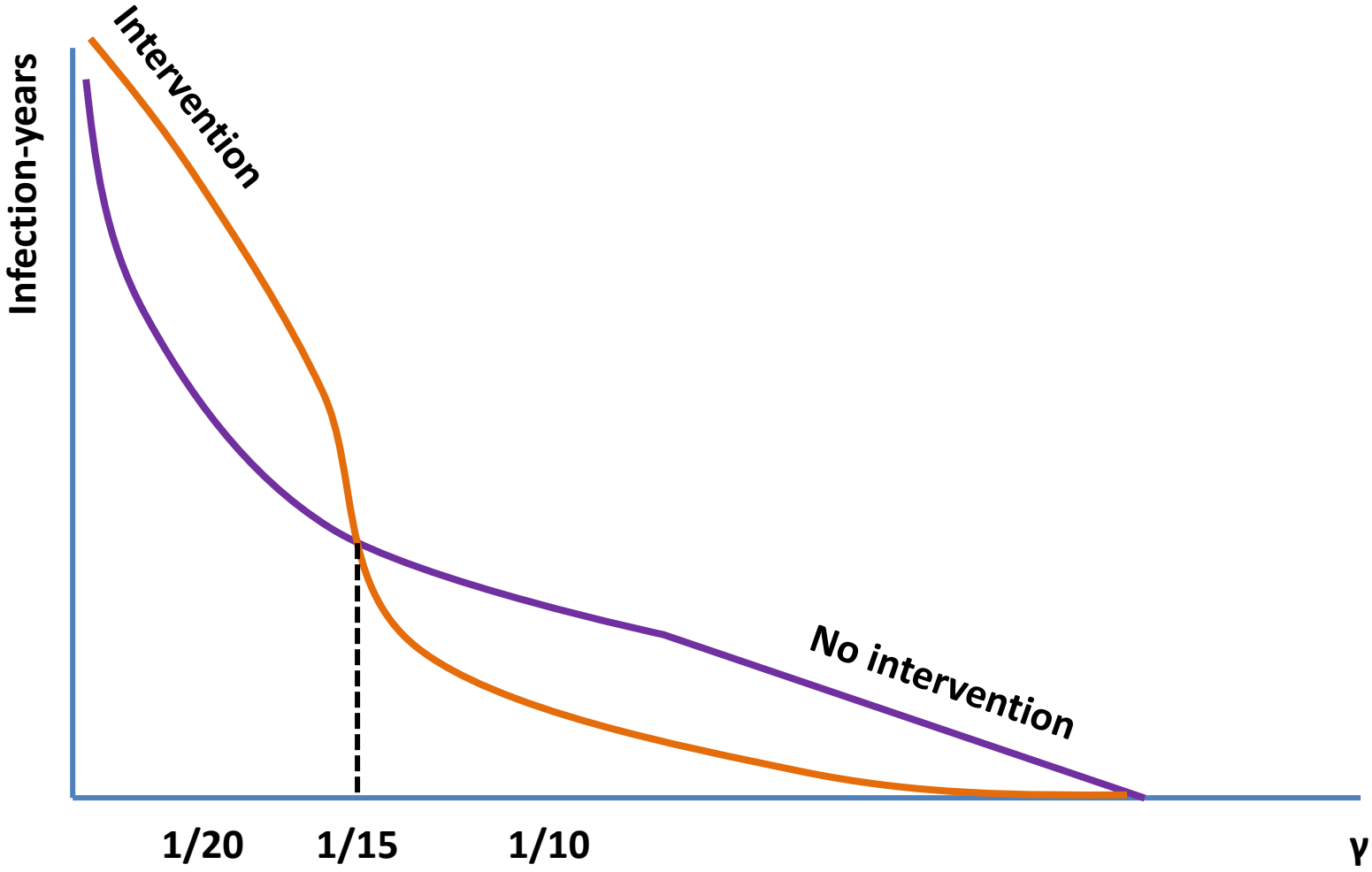
- Threshold analysis
- One-way sensitivity analysis (OWSA)
- Multi-way sensitivity analysis (MWSA)
- Probabilistic sensitivity analysis (PSA)

Simple threshold analysis



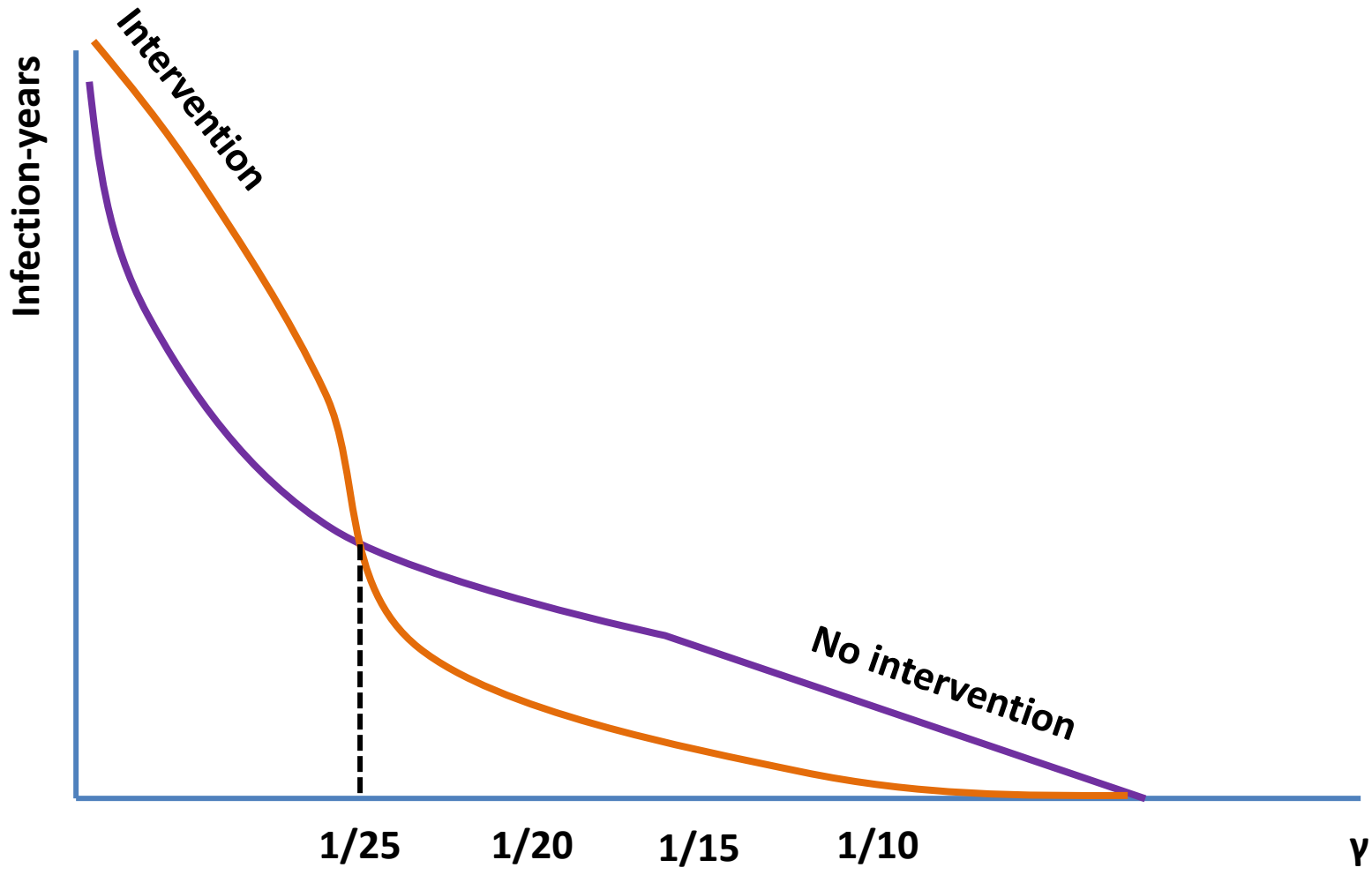
Where is the threshold?

Simple threshold analysis



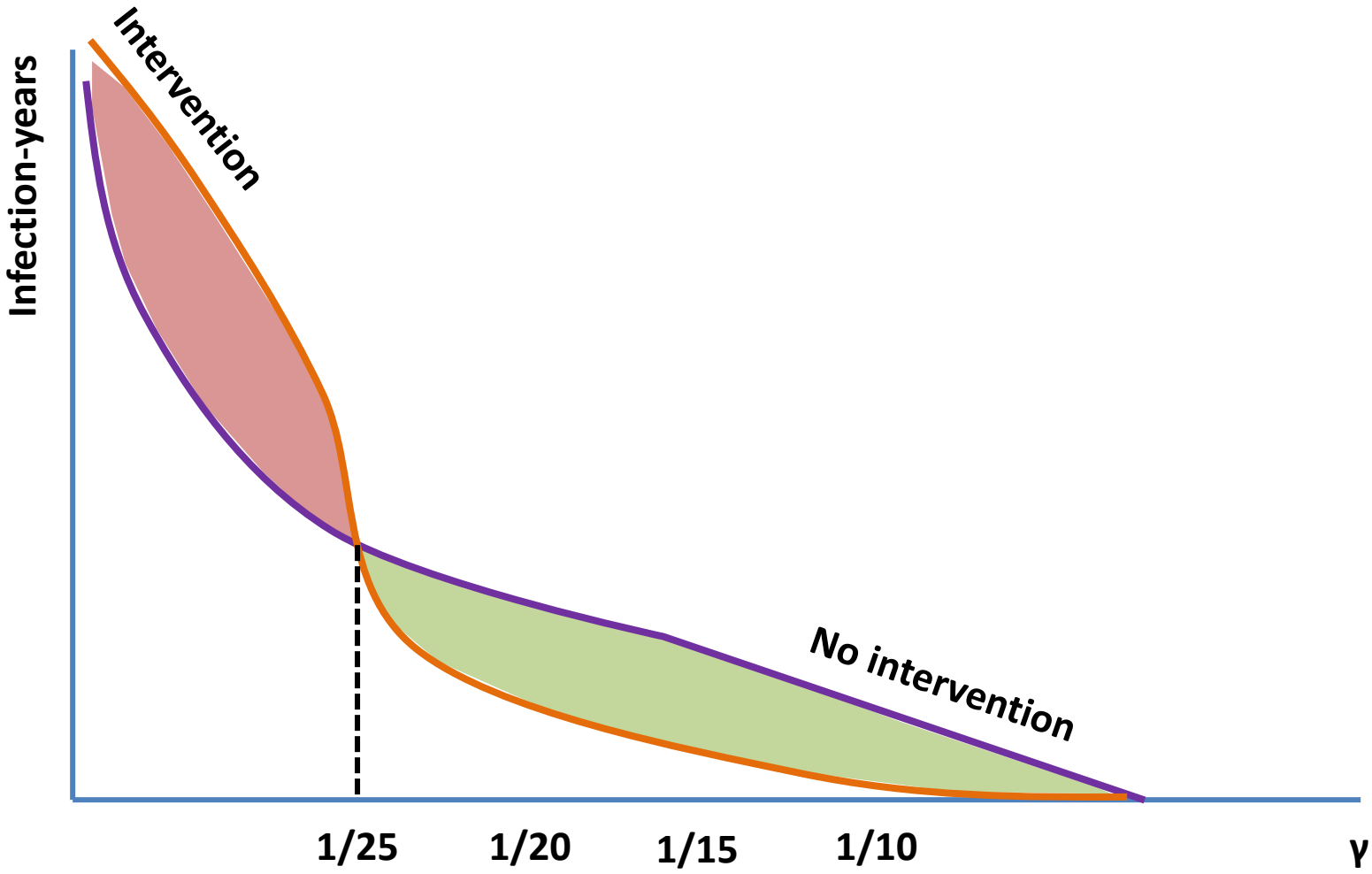
Is the decision sensitive to γ?

Simple threshold analysis



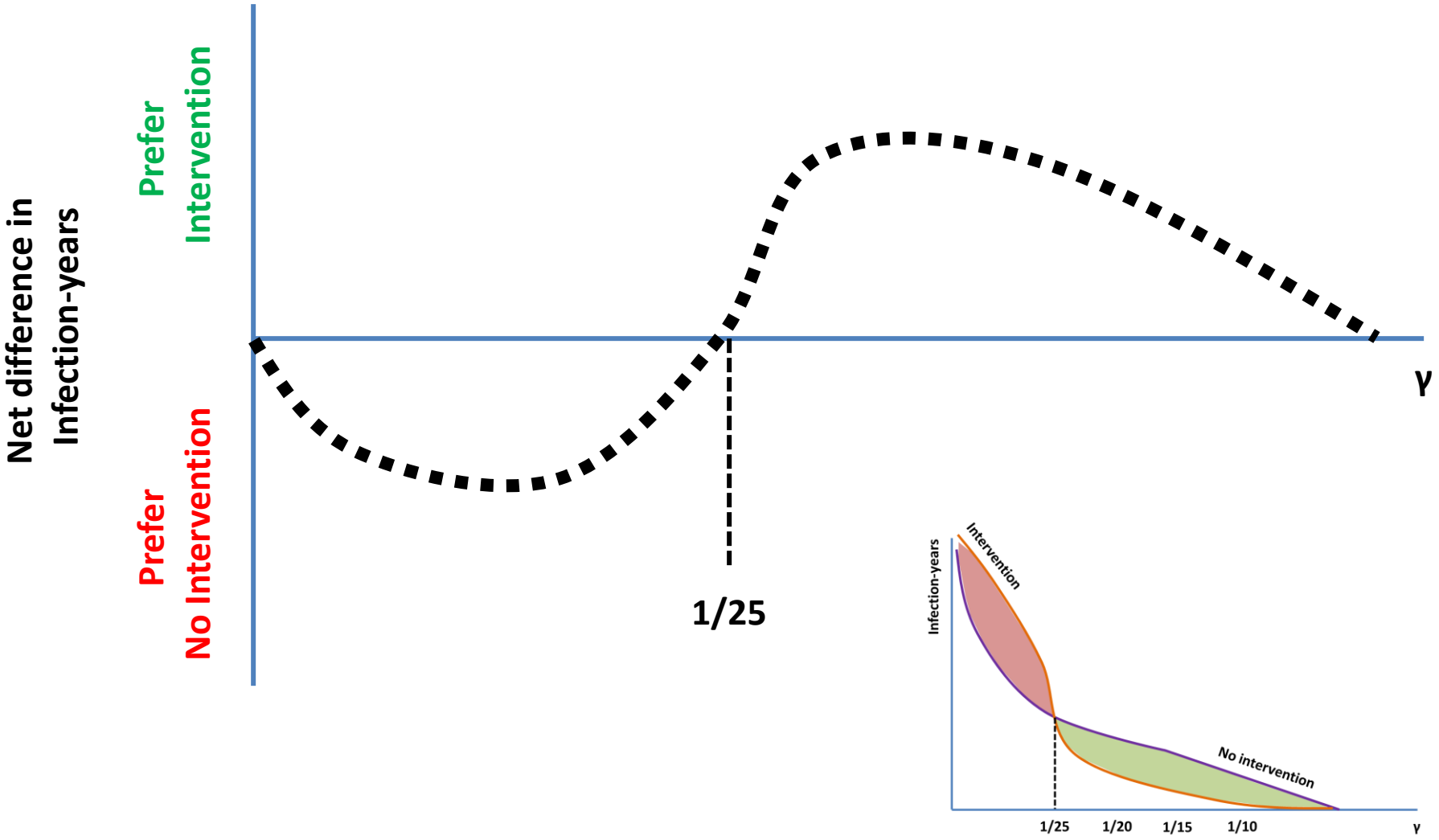
Is the decision sensitive to γ?

Simple threshold analysis

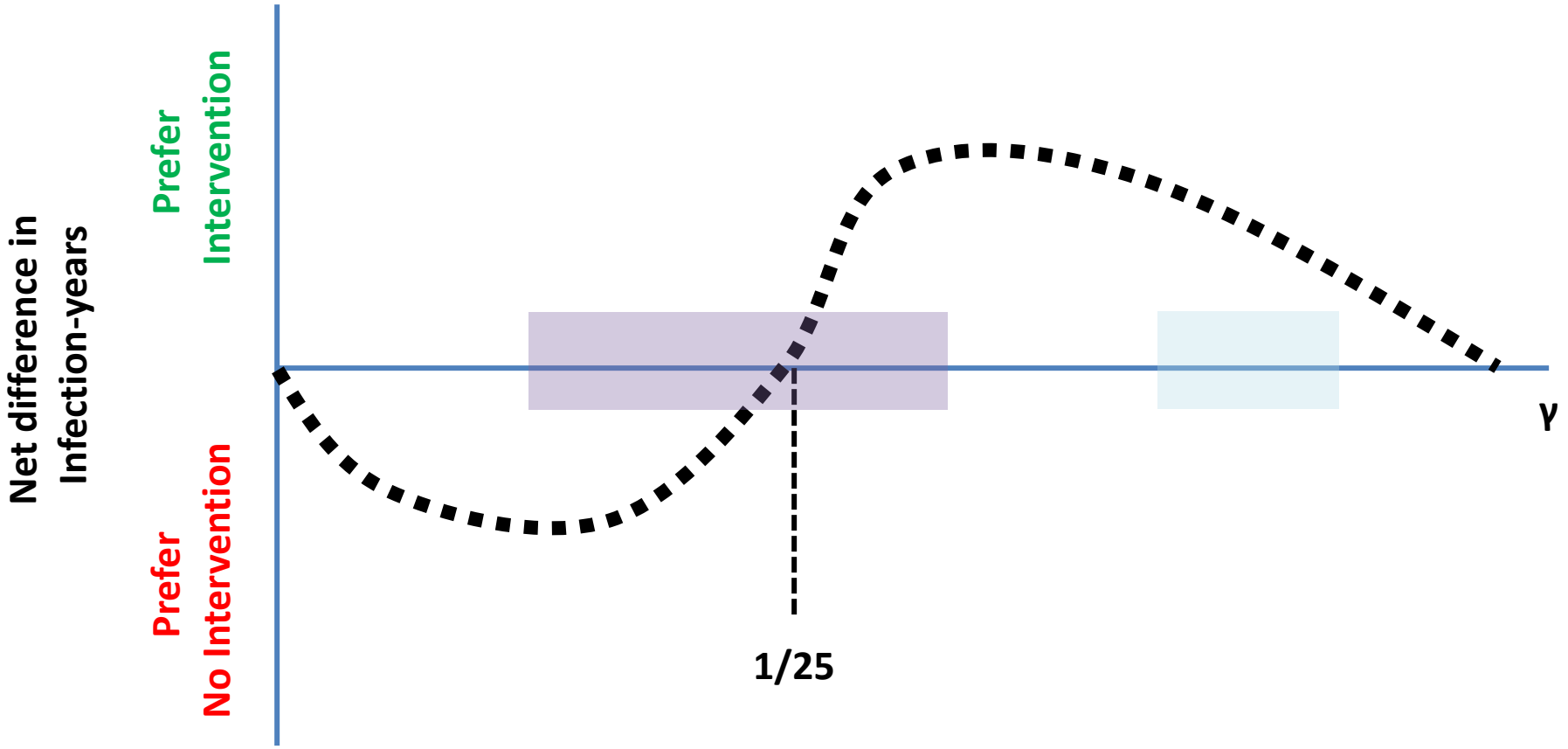


We can think about the decision in terms of the net difference in outcome between Intervention and No Intervention

Simple threshold analysis



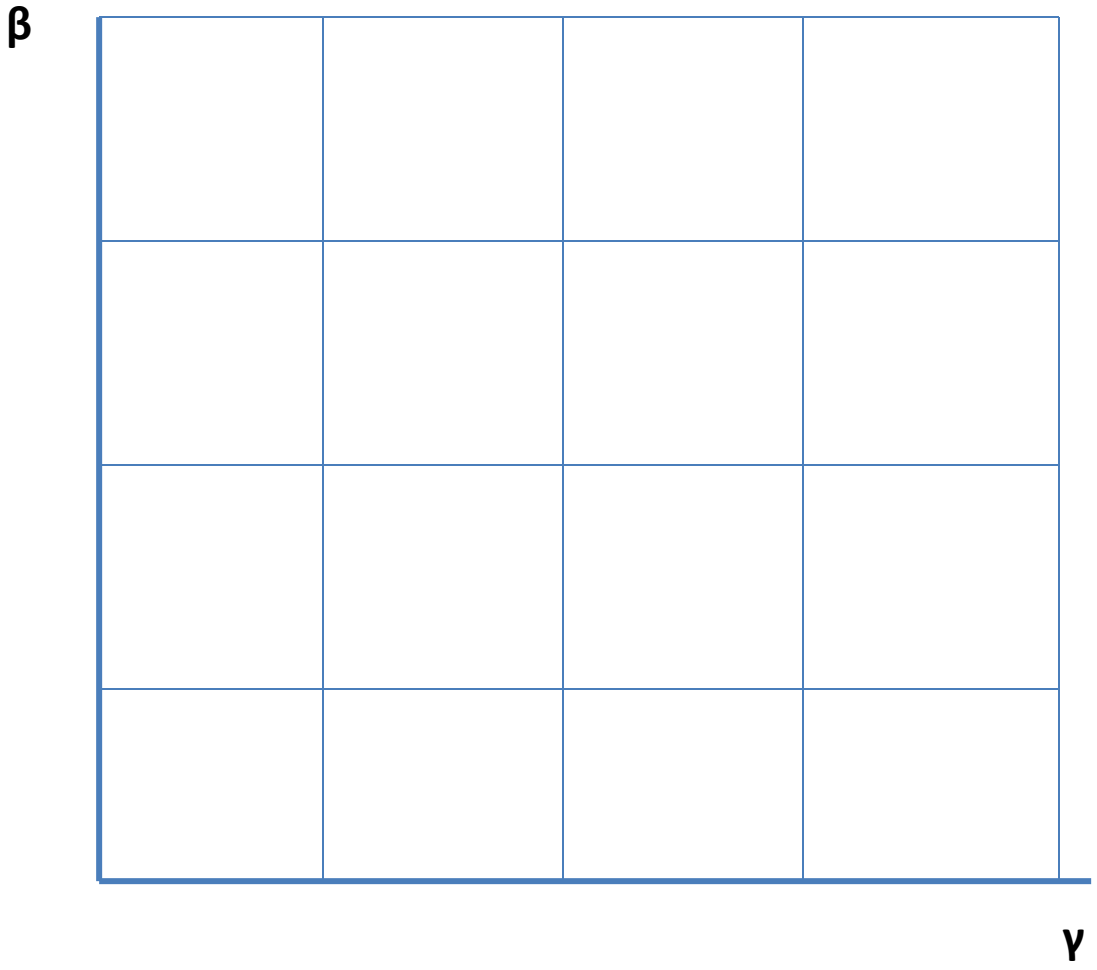
Extension to one-way sensitivity analysis



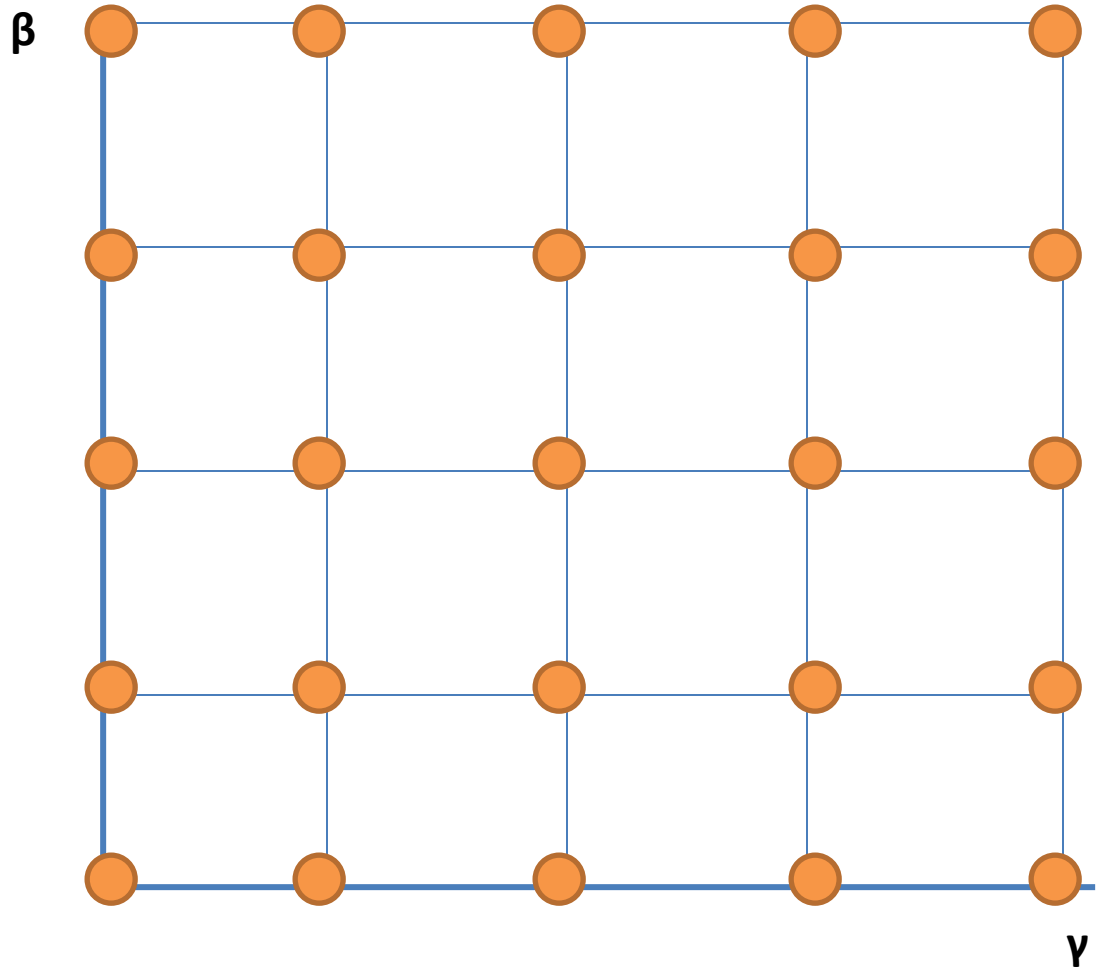
For an OWSA, we define a plausible range of one of our parameters and examine how the outcomes change and whether our decision would change

Extension to 2-way sensitivity analysis

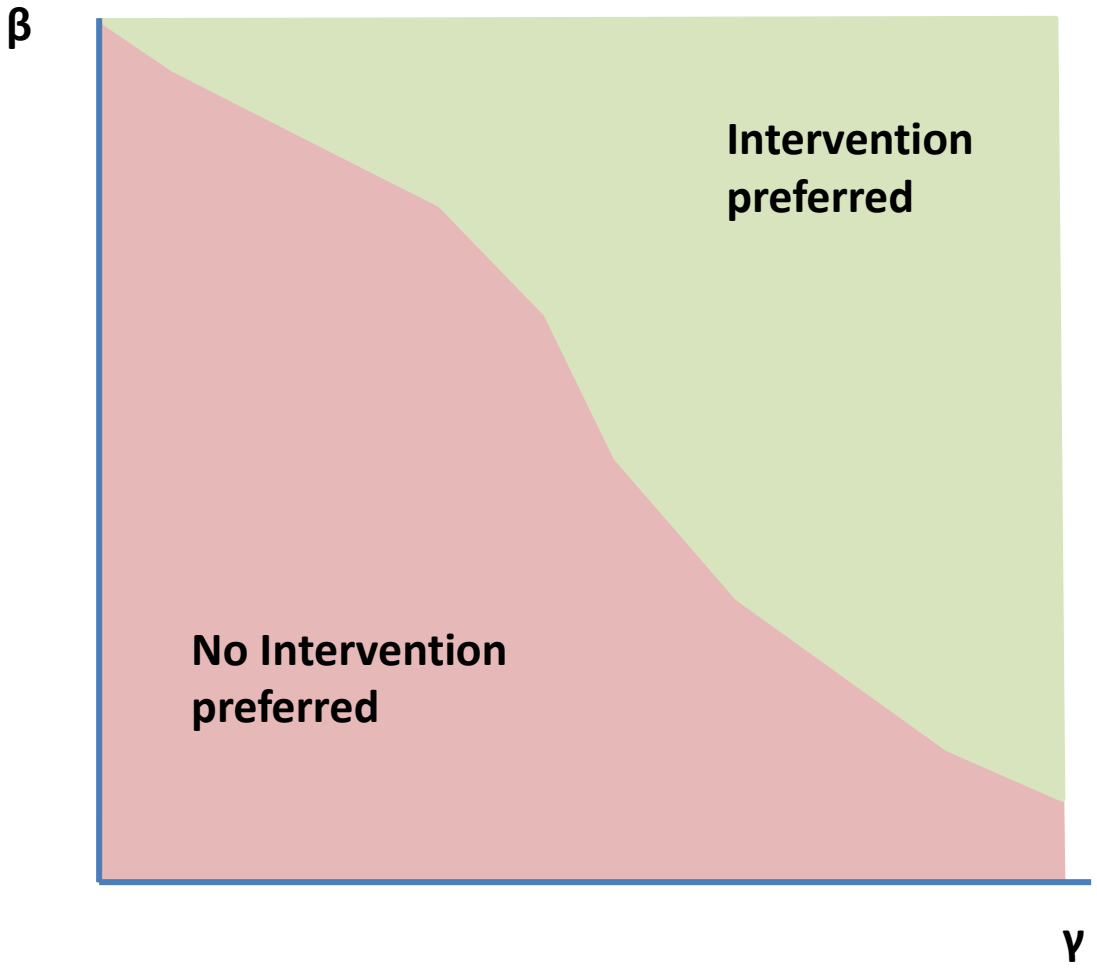
Extension to 2-way sensitivity analysis



Extension to 2-way sensitivity analysis



Extension to 2-way sensitivity analysis



How many model runs?

- Model with n total parameters
- MWSA with k parameters (e.g., k=2 for {β,γ})
- Assume we want to explore the k parameters across a range with a min and max
- Denote # of levels of each parameter explored as "a"
  - When a parameter is not in k, we hold it at its mean value

$$\text{per parameter n}-\text{tuples \# of runs} = a^k \Rightarrow \text{total \# for all parameters} = \binom{k}{n} a^k$$

- Doing MWSA for lots of different parameters is computationally intensive

Moment of reflection

- What do the parameters in our models represent?
  - They are population means (e.g., average rate of recovery for people with a given infection) (How to measure this?)
- What is a sensitivity analysis doing?
  - It asks: Across a range of plausible population mean values of our parameters, would our conclusions change?
  - What it does not ask:
    - How does individual variation from the mean impact our conclusions? (How would we do this?)
    - How uncertain are we about our conclusions give our uncertainty in the population means? (how uncertain are we about those means?)
- For uncertainty analyses: We need probabilistic sensitivity analysis (PSA) (see calibration lecture)

HOW DO WE MODEL INTERVENTIONS?

Types of Interventions

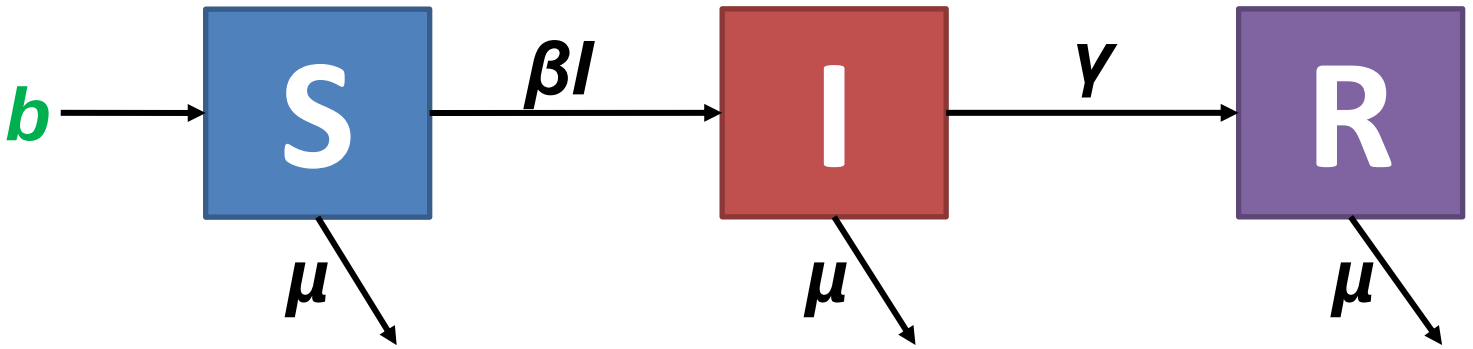
Policy	*Benefits*	*Drawbacks*
Quarantine and Isolation Sequester suspect and confirmed cases	Highly effective at reducing transmission	Requires rapid and high levels of compliance
Movement Restrictions Close schools, airports, and other transport	Potentially useful as shown during 2003 SARS epidemic	Very costly and difficult to implement
Ring Vaccination Trace and vaccinate contacts of suspected cases	Optimizes vaccine use and any associated complications	Logistically costly, and needs efficient contact tracing
Targeted Vaccination Immunize specific groups or neighborhoods	Effective locally; no contact tracing needed	Requires high levels of herd immunity
Mass Vaccination Vaccinate entire population under threat	Effective at widespread transmission control	Large numbers need to be rapidly vaccinated; expensive
Prophylactic Vaccination Vaccinate before introduction of disease	Useful to protect "first-responders"; Can prevent rapid spread	High long-term cost; numbers vaccinated

Prophylactic Treatment; Screening and Treatment; Elimination of Zoonoses; Clean-up of environmental reservoirs; Social/Physical Distancing; Combinations of strategies

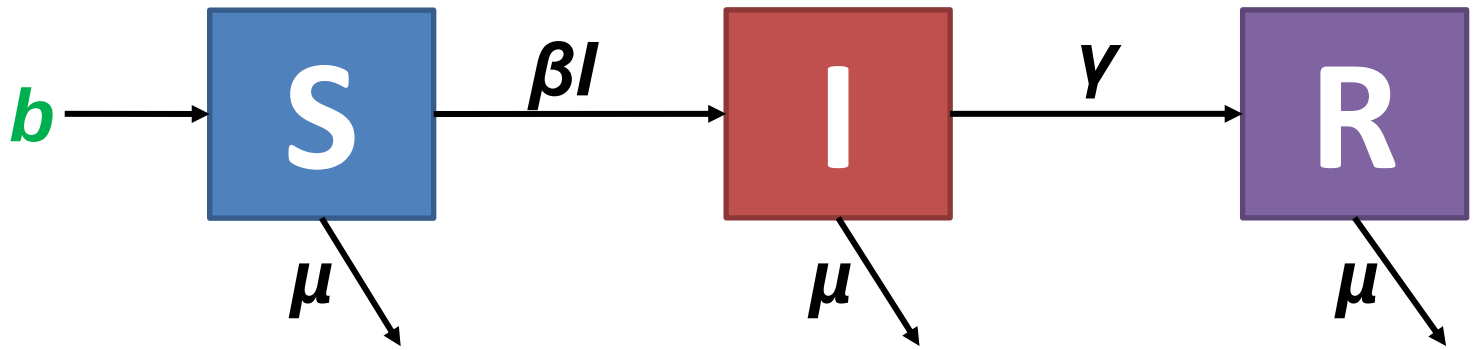
How do we map interventions into our models?

- All interventions will require
  - Either changes to values of parameter(s)
  - Or changes to model structure(s)
  - Or changes to both parameter(s) and structure(s)

Let's start with our SIR model with demography

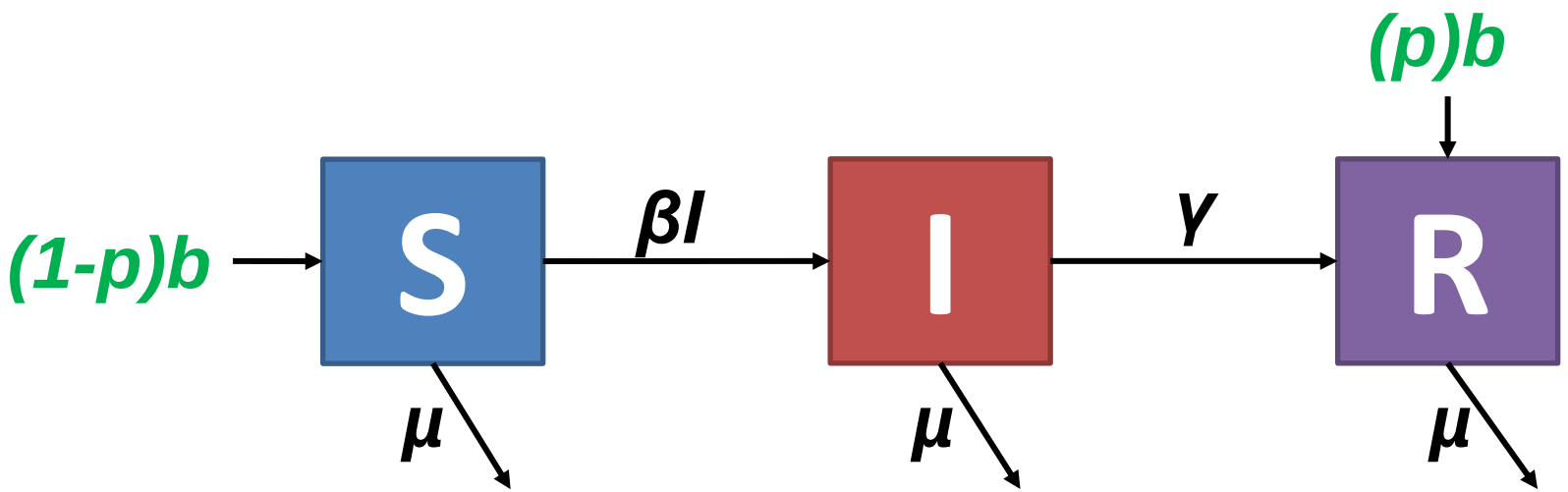


Pediatric vaccination: at birth (or right after maternal immunity wanes), a proportion (*p*) of babies are successfully vaccinated



p = proportion successfully vaccinated; Why do we say "successfully"?
What are the minimum two steps needed for "success"?
Fraction given the vaccine * Fraction that achieve a sufficient immune response conditional on being vaccinated
How does p enter into our model?

Pediatric vaccination: at birth (or right after maternal immunity wanes), a proportion (*p*) of babies are successfully vaccinated



We assume that naturally acquired immunity is like vaccine acquired immunity

Therefore we split the births between susceptibles (those not vaccinated) and the recovereds (those vaccinated)

We also assume the program operates on a continuous constant level

Pediatric vaccination: at birth (or right after maternal immunity wanes), a proportion (*p*) of babies are successfully vaccinated

$$\frac{dS}{dt} = (1-p)b - \beta IS - \mu S \qquad \frac{dS'}{dt} = b - (1-p)\beta I'S' - \mu S'$$

$$\frac{dI}{dt} = \beta IS - \gamma I - \mu I \qquad \frac{dI'}{dt} = (1-p)\beta I'S' - \gamma I' - \mu I'$$

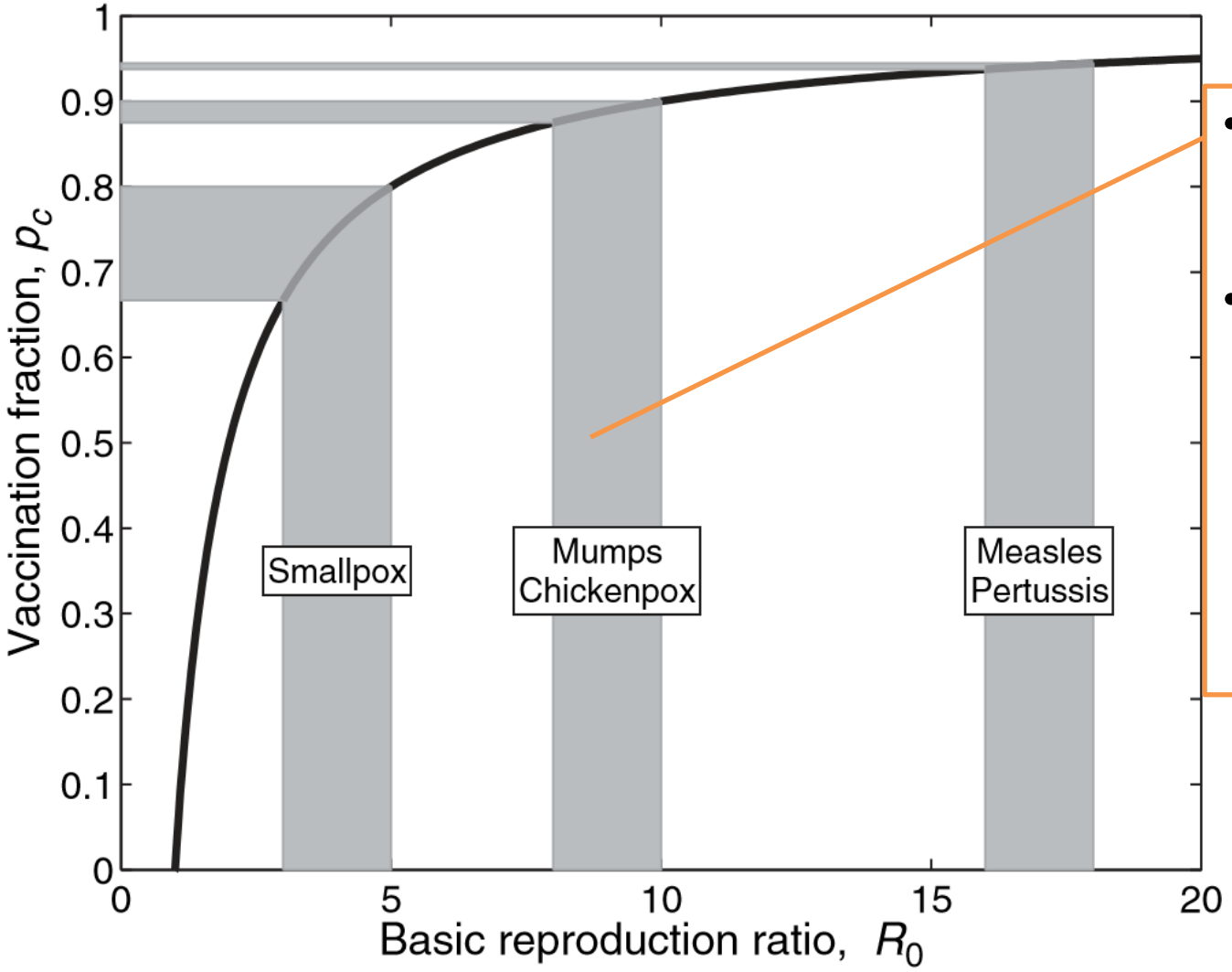
$$\frac{dR}{dt} = \gamma I + (p)b - \mu R \qquad \frac{dR'}{dt} = \gamma I' - \mu R'$$

Keeling and Rohani show that the system on the left is equivalent to the one on the right

The key insight of the one of the right is that the effective reproductive number with vaccination is

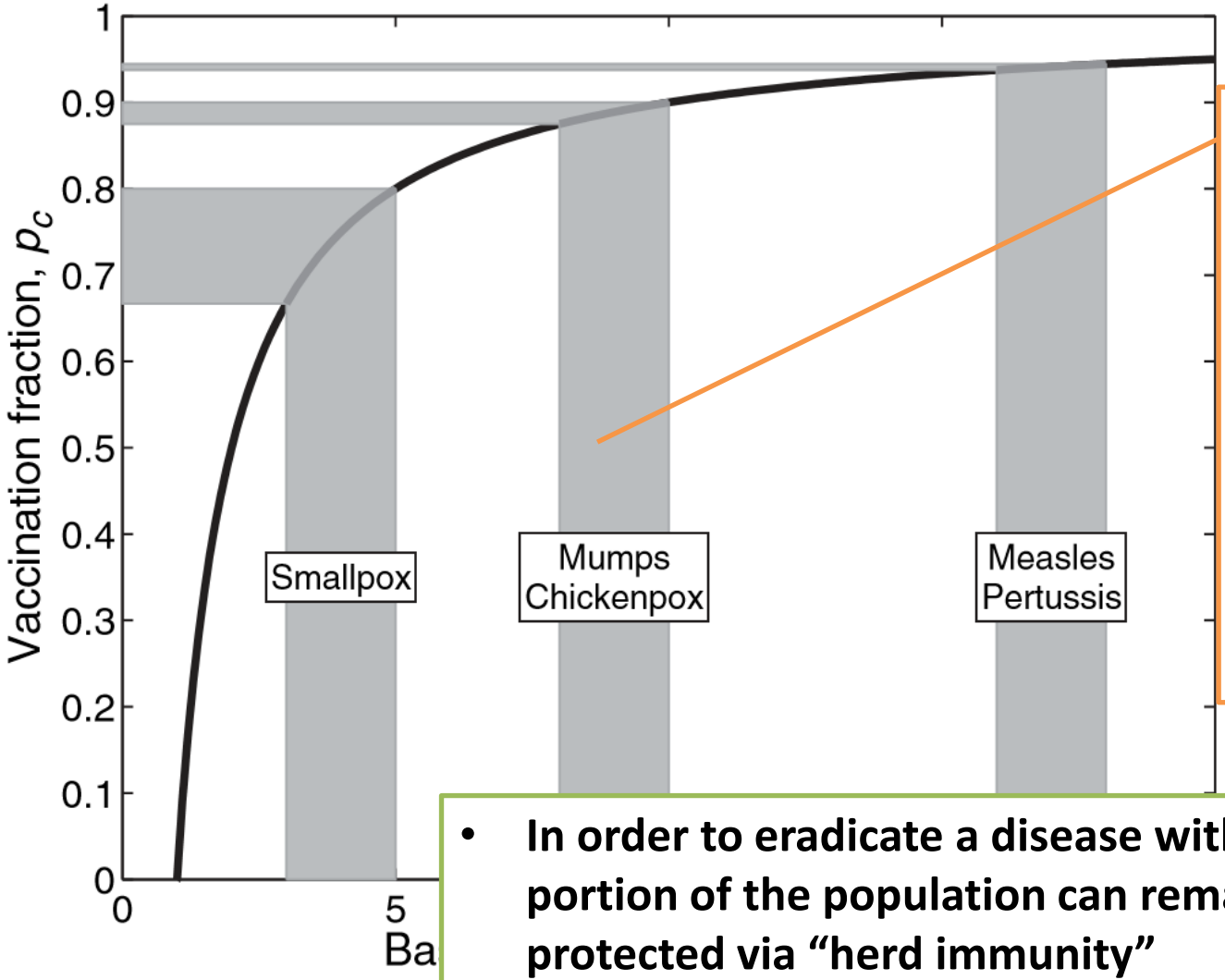
$(1-p)*R_0$ => p_c must be at least $1- 1/R_0$ to achieve eradication

Critical vaccination proportions required for various infectious diseases



- **Why is there a range of R0s for each disease?**
- **If we know that R0 = Beta/(Mu+Gamma), how is this range related to a form of sensitivity analysis?**

Critical vaccination proportions required for various infectious diseases

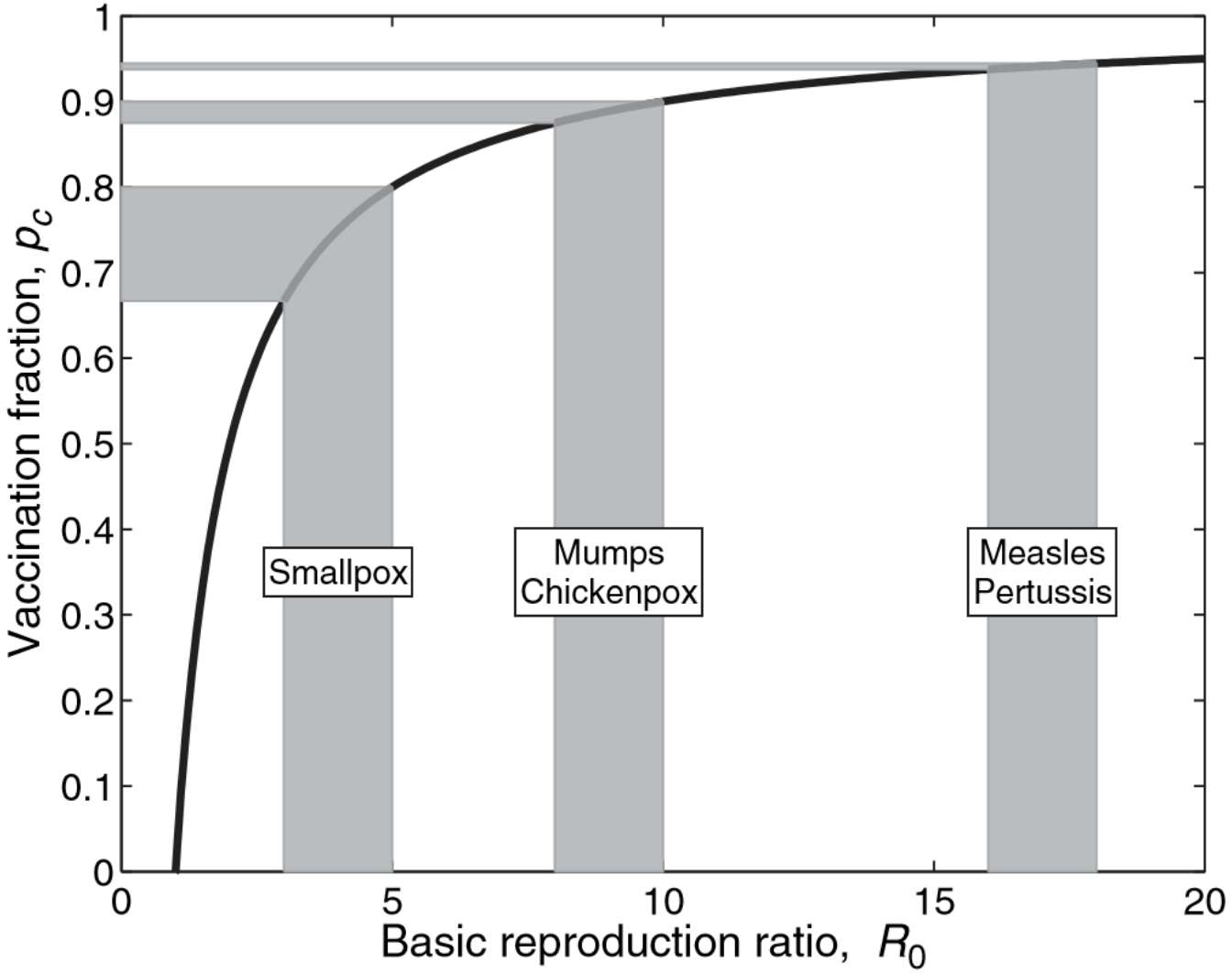


- Why is there a range of R0s for each disease?
- If we know that R0 = Beta/(Mu+Gamma), how is this range related to a form of sensitivity analysis?

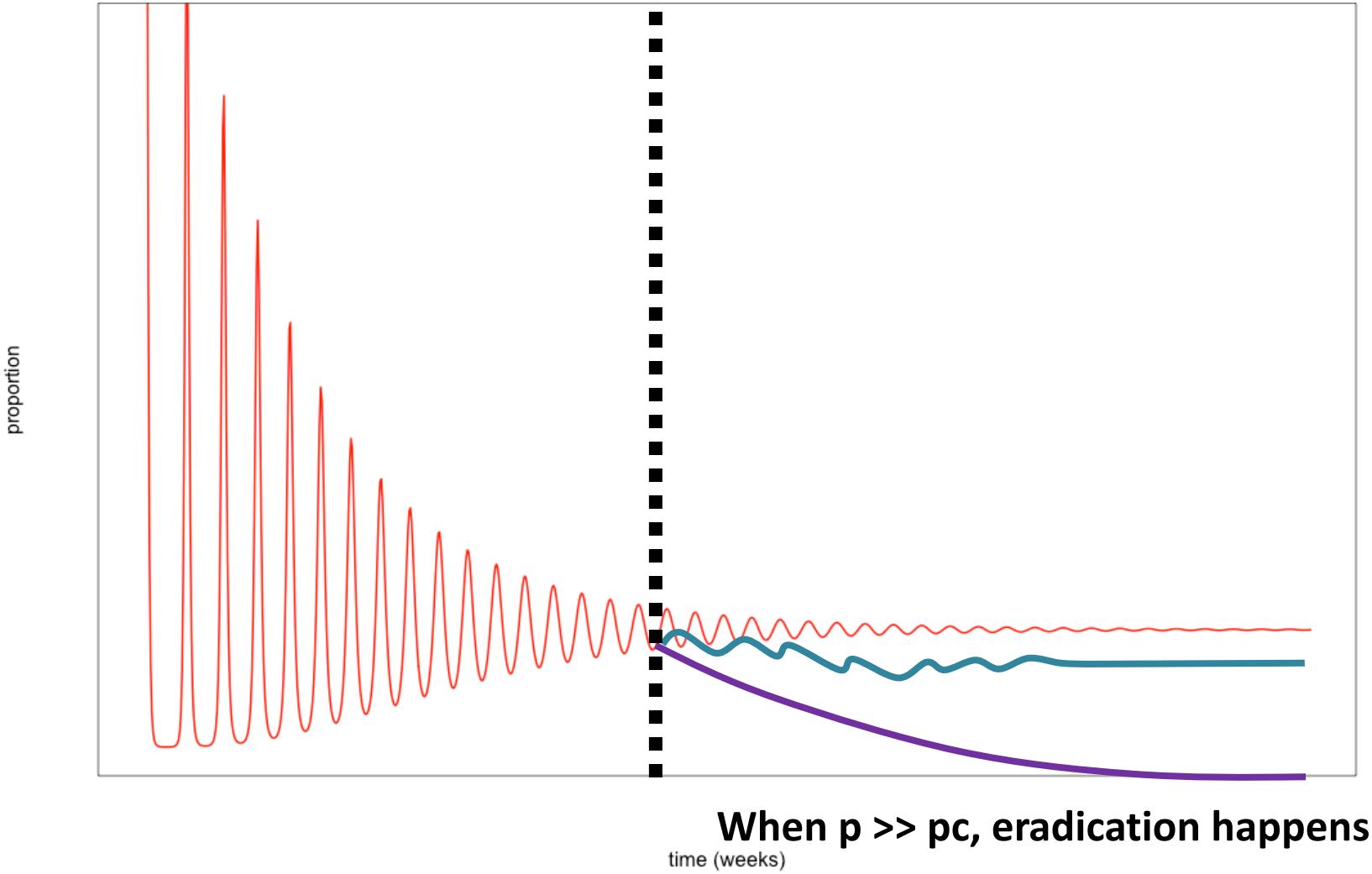
- In order to eradicate a disease with infant vaccination, a portion of the population can remain unvaccinated but protected via “herd immunity”

When we achieve pc, how long does it take for prevalence of I to reach 0?

Even if pc is not achieved, what happens to prevalence of I?

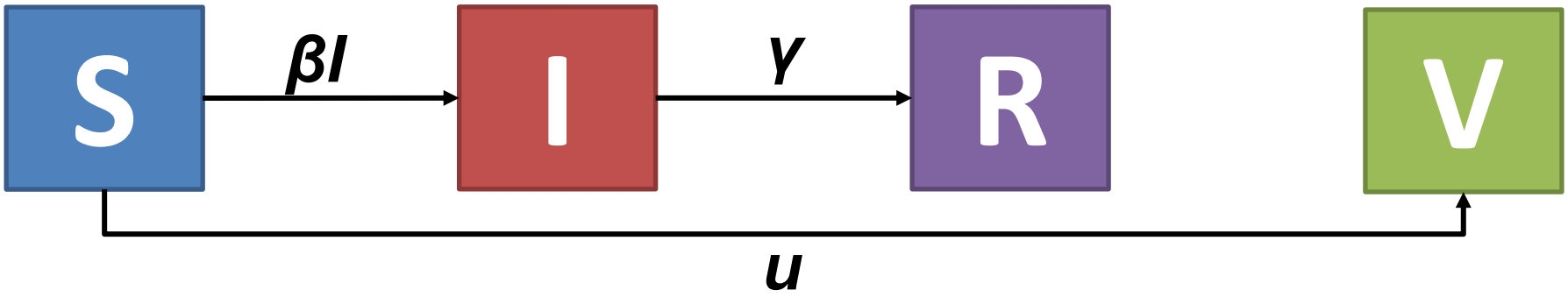


Vaccination Effects: We start vaccination at the dashed black line (>p_c [purple]; <p_c [blue])



When p >> pc, eradication happens faster

Vaccination in an SIR model

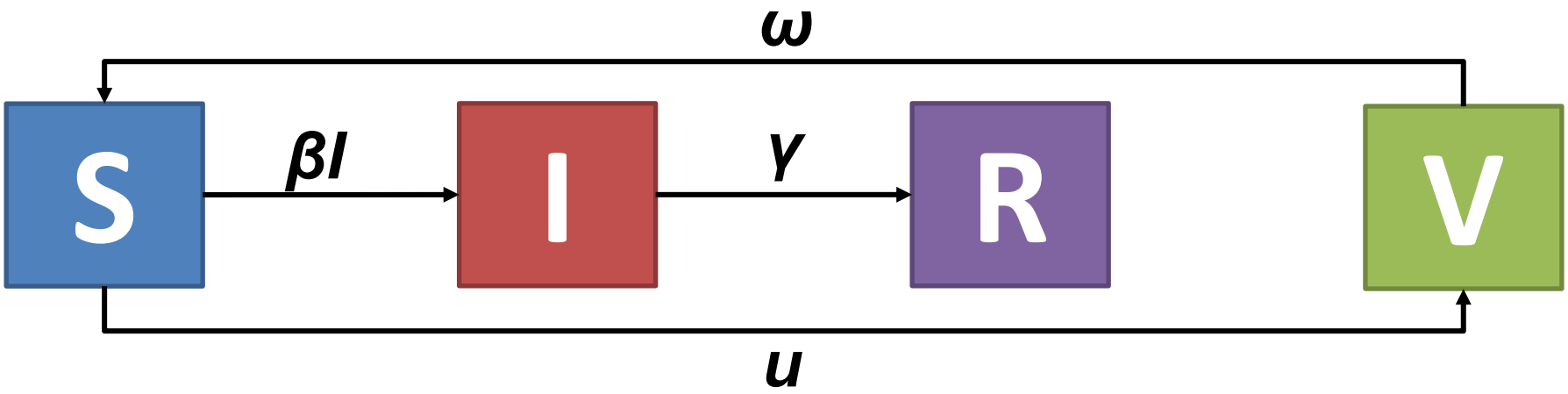


Keeling and Rohani call this "Wildlife Vaccination" but really this is just a model in which a vaccination rate is applied to the susceptibles who enter a vaccinated compartment

First model where we change the structure

Why is there no rate of flow from I's or R's? How do we know whom to vaccinate?

Vaccination in an SIR model



Keeling and Rohani call this "Wildlife Vaccination" but really this is just a model in which a vaccination rate is applied to the susceptibles who enter a vaccinated compartment

The structural change allows for things like waning vaccine-induced immunity even if natural immunity does not wane (e.g., Zoster)

Types of Interventions: Many variants of vaccination which are treated in Keeling and Rohani

Policy	*Benefits*	*Drawbacks*
Quarantine and Isolation		
Sequester suspect and confirmed cases	Highly effective at reducing transmission	Requires rapid and high levels of compliance
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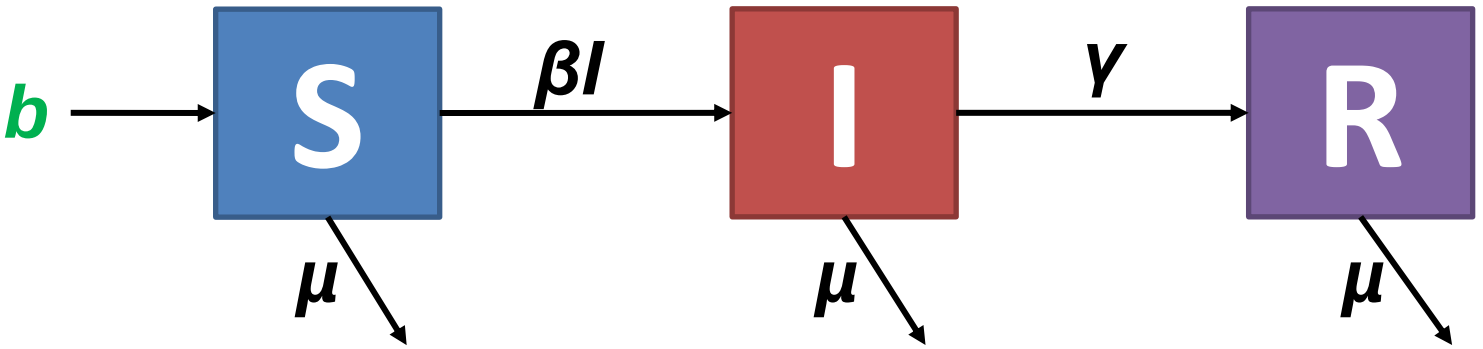
How would we model Social/Physical Distancing? What should change and why?



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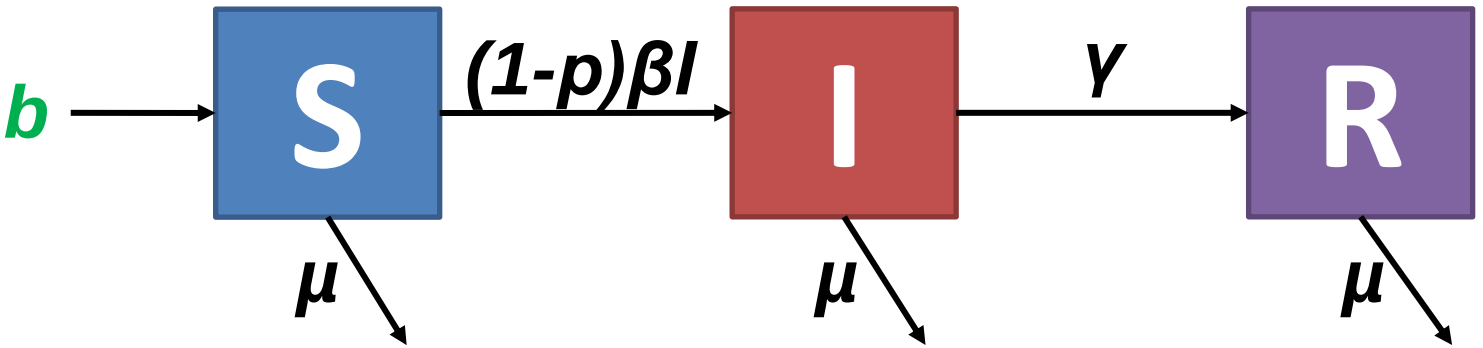


Social/physical distancing reduces the number of contacts we have per unit time and may also change the probability of transmission given a contact if it is accompanied by other hygiene changes (e.g., handwashing, masks) depending on how we define contact
When there are no contacts at all, there is no transmission

Such an approach to Social/Physical Distancing looks like our model of infant vaccination

$$\frac{dS}{dt} = b - (1-p)\beta IS - \mu S$$

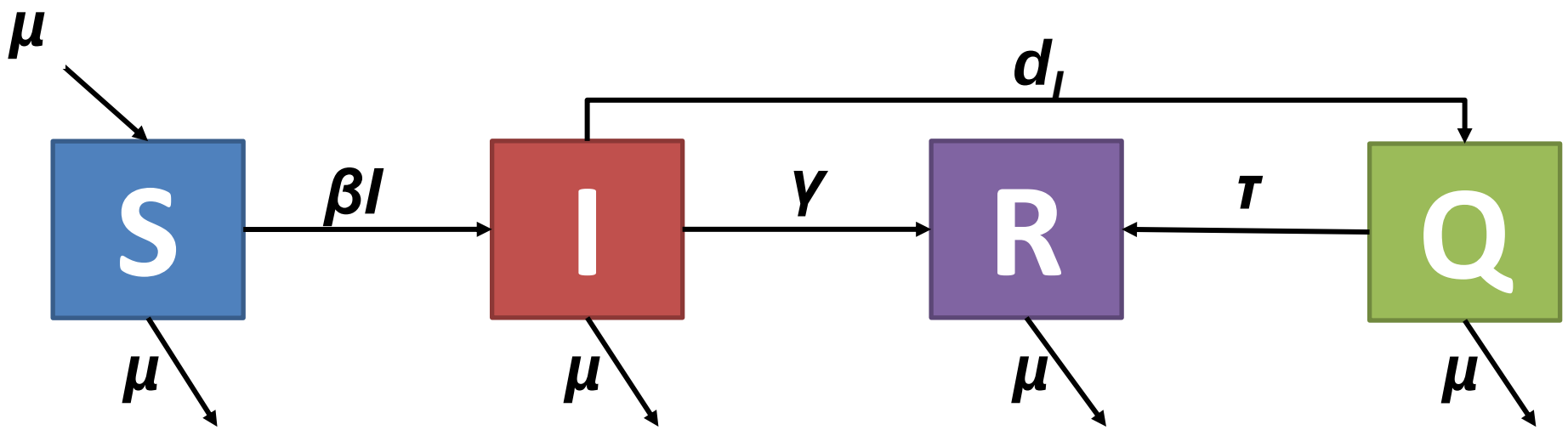
$$\frac{dI}{dt} = (1-p)\beta IS - \gamma I - \mu I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$

Again, the key insight of the one of the right is that the effective reproductive number with social distancing is

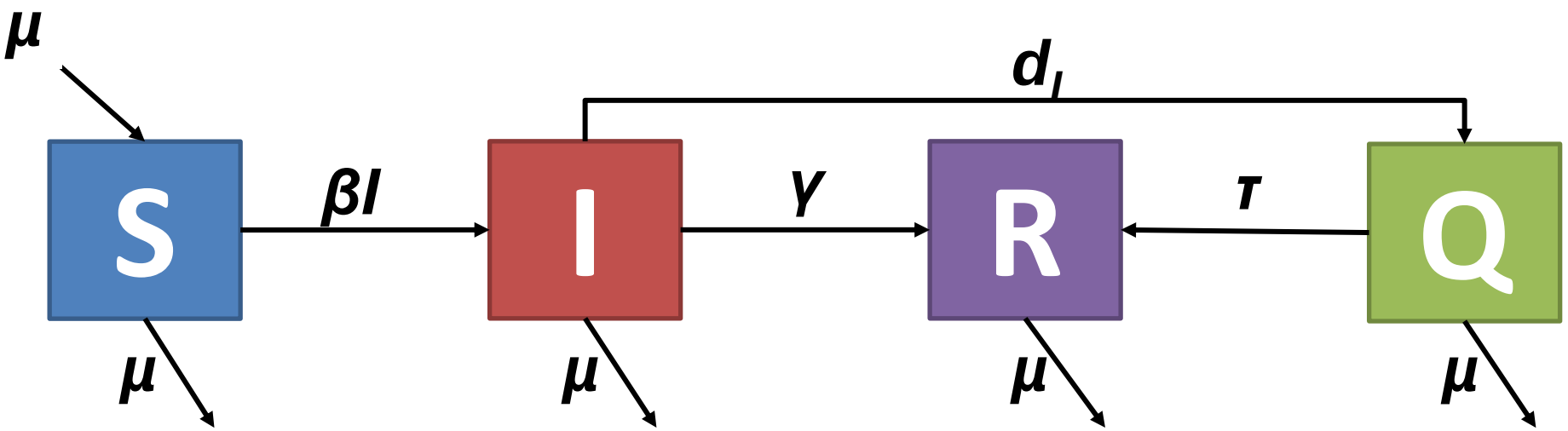
$(1\text{-}p)*R_0 \Rightarrow p_c$ must be at least $1 - 1/R_0$ to achieve eradication

Isolation/Quarantine in an SIR model with demography



- Again, we add a new state (Q) which is the quarantine state
- Infectious individuals who are detected enter the state at a rate d_I
- Individuals leave quarantine at a rate tau after they have recovered
- The critical rate of detection = beta – gamma – mu (to get reproductive number below 1); The rate means that both the fraction & timing matter
- Keeling and Rohani do not have mu leaving quarantine presumably because it is small relative to tau (but I include it here)

Isolation/Quarantine in an SIR model with demography



Let's think a bit more about what d_I means

How does detection occur?

For a disease like measles?

For a disease like COVID-19? What about asymptomatic infectious individuals?

How does testing play in to d_I?

Testing and test results (at a given cutoff)

	Disease+	Disease-	Totals
Test+	a	b	**a+b**
Test-	c	d	**c+d**
Totals	**a+c**	**b+d**	**a+b+c+d=n**

a = # with disease who test positive

b = # without disease who test positive

c = # with disease who test negative

d = # without disease who test negative

Testing and test results (at a given cutoff)

	Disease+	Disease-	Totals
Test+	a	b	**a+b**
Test-	c	d	**c+d**
Totals	**a+c**	**b+d**	**a+b+c+d=n**

What is the probability of people with the disease testing positive?

Sensitivity = a/(a+c) = True Positive Fraction (TPF)

With equal effort but a less sensitive test, d_I will be lower => harder for quarantine to achieve eradication

Testing and test results (at a given cutoff)

	Disease+	Disease-	Totals
Test+	a	b	**a+b**
Test-	c	d	**c+d**
Totals	**a+c**	**b+d**	**a+b+c+d=n**

What is the probability of people without the disease testing negative?

Specificity = d/(b+d) = 1-False Positive Fraction

Since specificity deals with test results for people who do not have disease (not I's), it will not directly impact the effect of quarantine, but lower specificity could fill up quarantine capacity and add substantial costs (more false positives)

Community Quarantine (movement restriction) in conjunction with other interventions

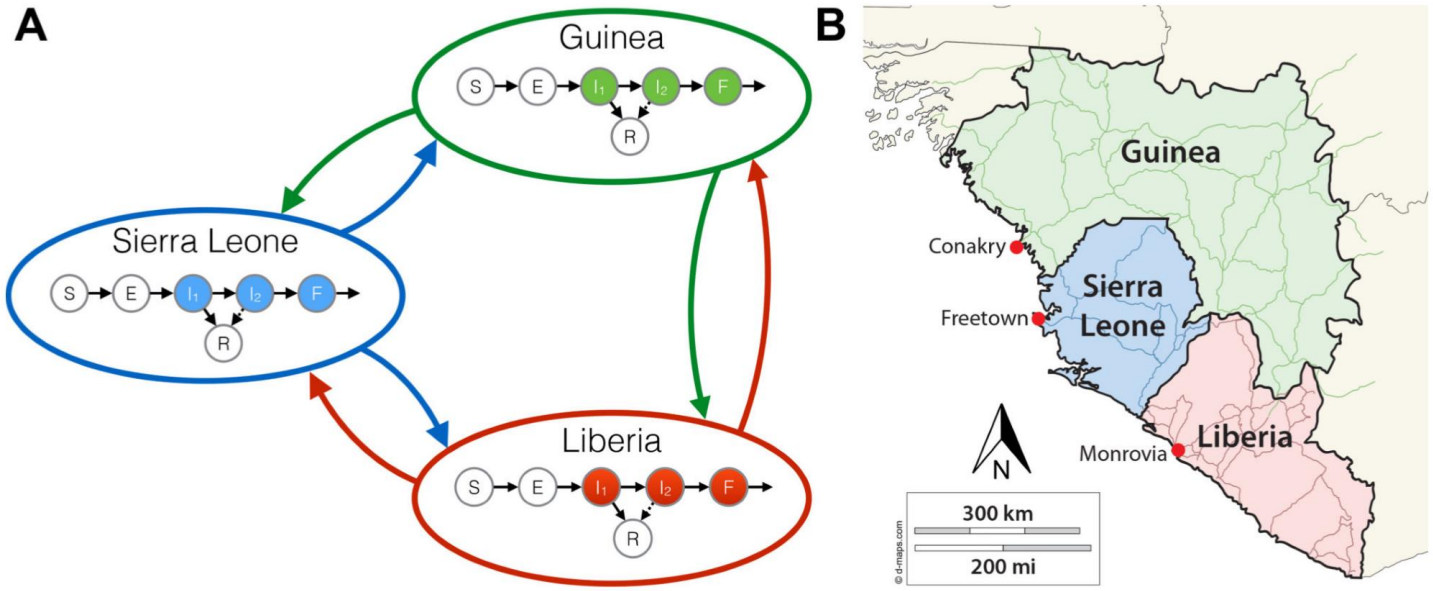


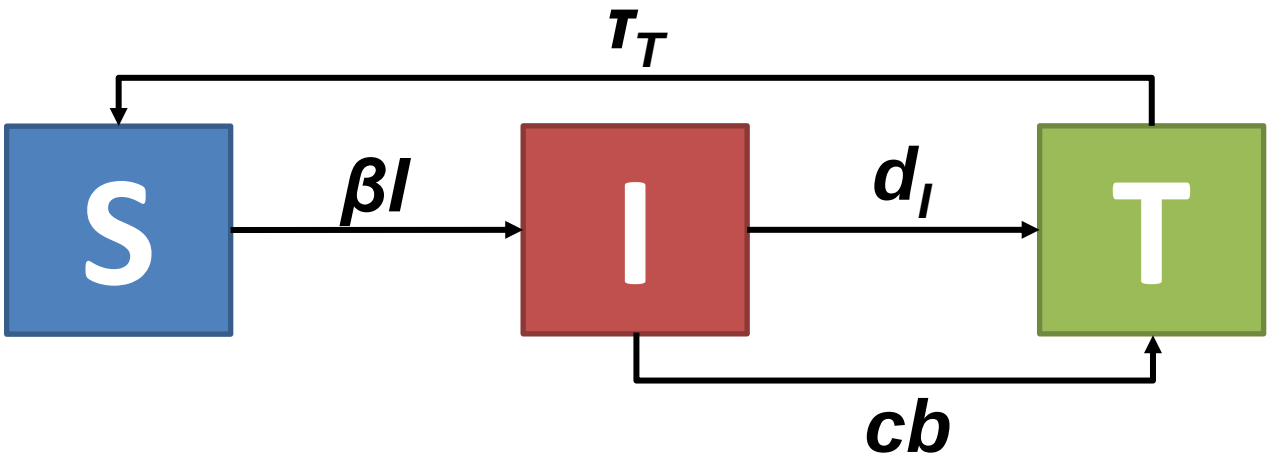
Figure 1.
A diagram of the model structure (left panel) and a map of West Africa showing the locations of each capital used as a population center for each patch (right panel). In each country, the population is compartmentalized into the following categories: susceptible (S), exposed (E), infected in stage one (I_1), infected in stage two (I_2), died but not yet buried (F), and recovered (R). Transmission is possible from persons in compartments I_1, I_2, or F of any country, to persons in compartment S, either within the country or to the other countries.

J Theor Biol. 2017 September 07; 428: 65–75. doi:10.1016/j.jtbi.2017.05.034.

Modeling Spatial Invasion of Ebola in West Africa

Jeremy P D'Silva and **Marisa C. Eisenberg**
Departments of Epidemiology and Mathematics, School of Public Health, University of Michigan, Ann Arbor

Contact Tracing



Contact Tracing in a sexually transmitted infection model (SI[S])
STI treatment + listing out recent sexual partners
Partners are contacted, tested, and if infected, treated and their partners contacted in turn
$1/\tau_T$=avg time in treatment; d_I=rate of treatment seeking; c=rate of contact tracing; b=probability that traced individual is infectious (I,1)
Contact tracing needs to happen at a rate that is faster than the growth rate (related to R0 of the disease) in order to eradicate the disease

Important Announcements