

# Cohort state-transition Modeling in R

Decision Modeling for Public Health Workshop

November 15, 2022

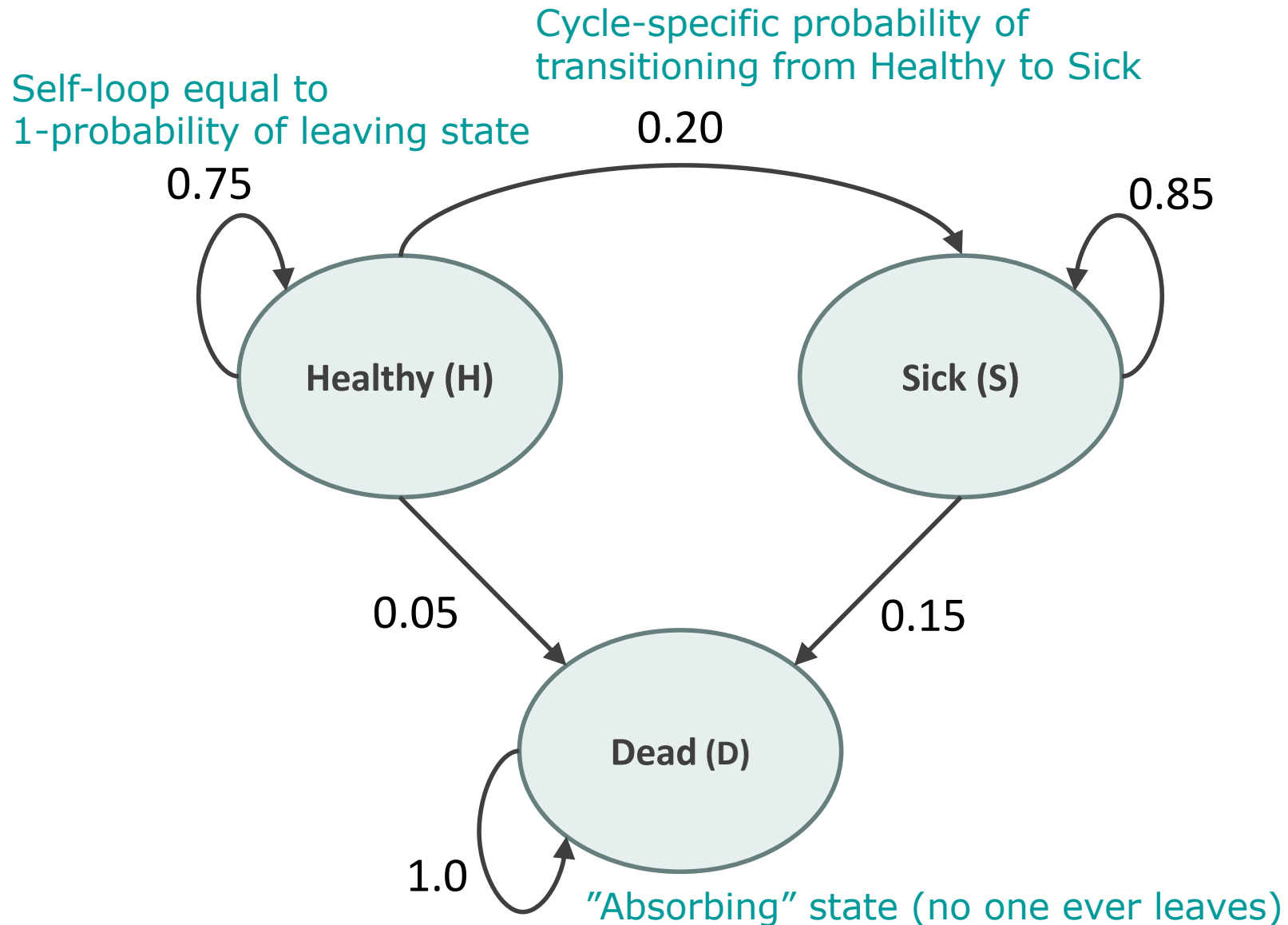
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# Cohort State-Transition Models

- Describes a cohort of patients across a set of health states over time
  - Collectively exhaustive and mutually exclusive
- Transitions allowed between health states with some probability
- Transitions occur in discrete time cycles (months, years, etc.)

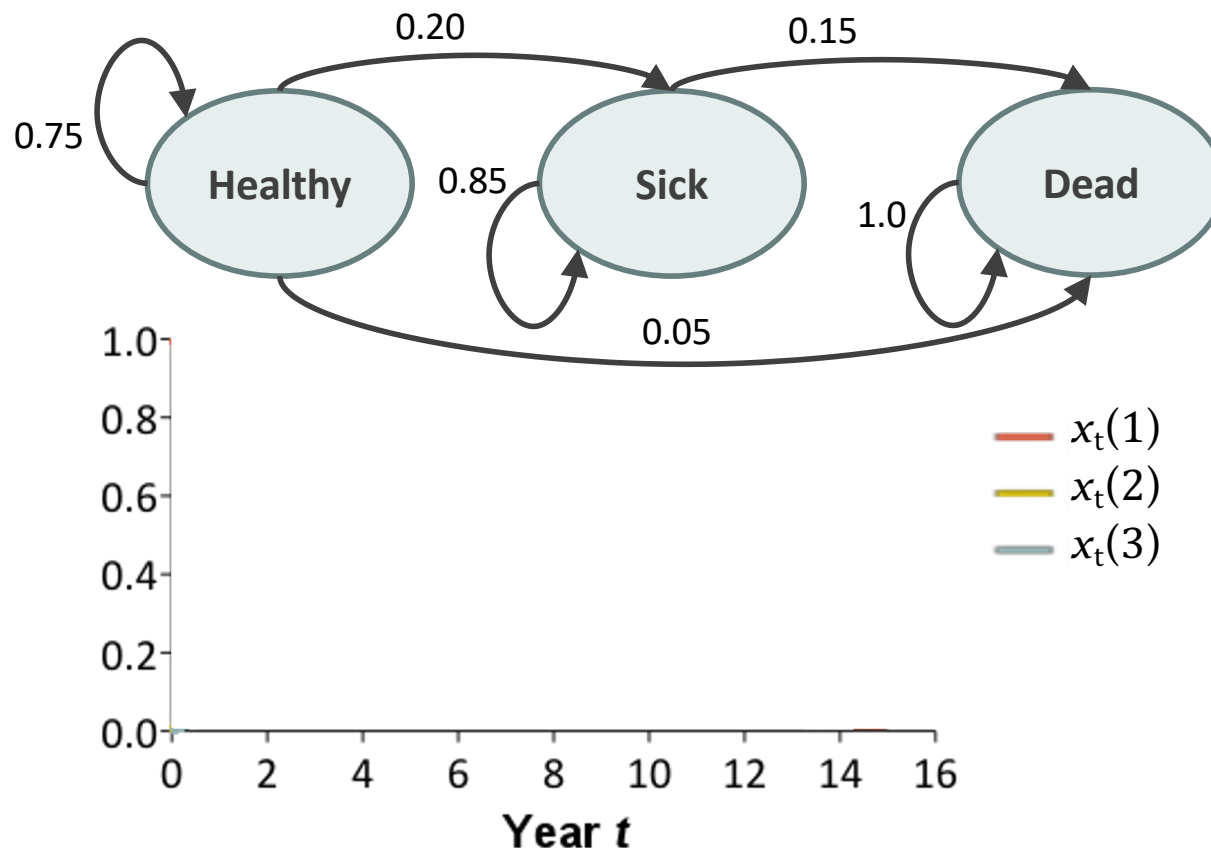
# State-Transition Diagram



# Simulate Cohort Over Time

- Reflects the distribution of a cohort of patients over a set of health states over time

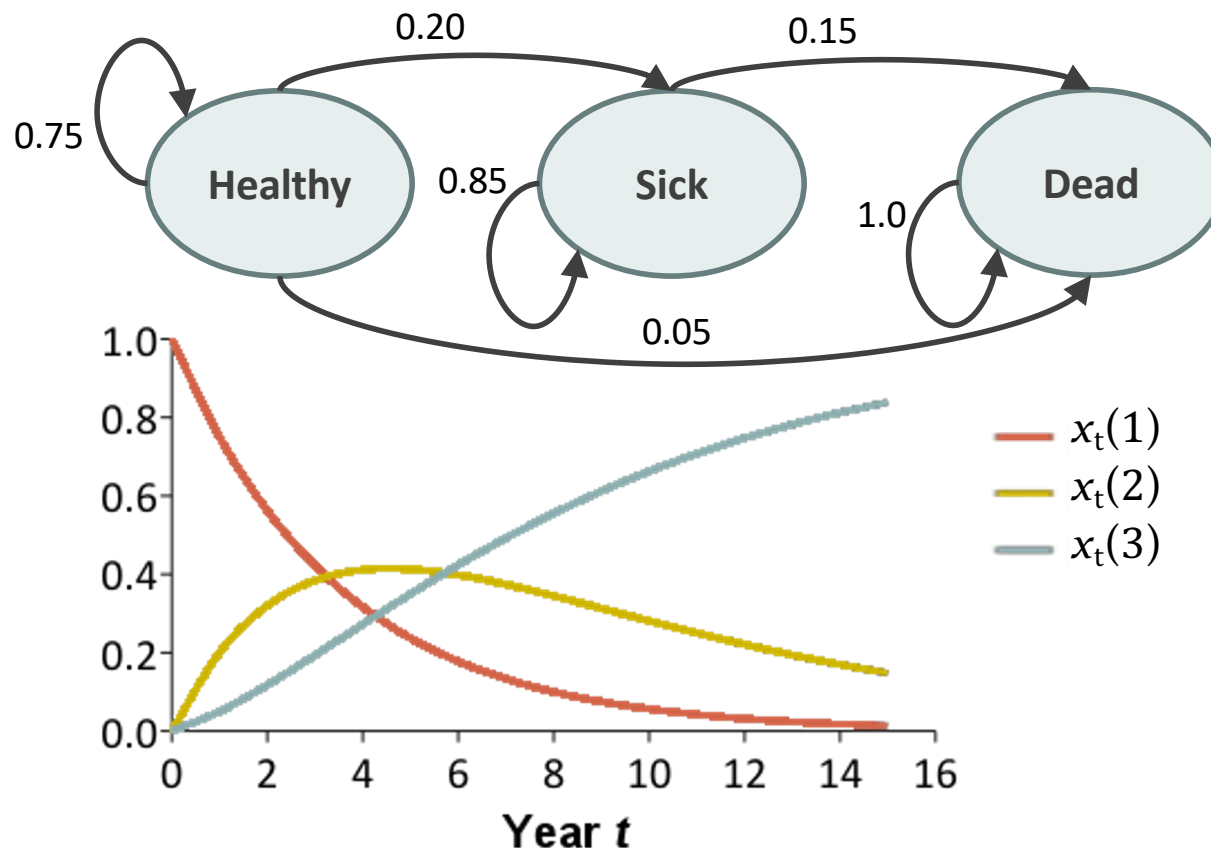
$$x_{10} = [0.06 \quad 0.28 \quad 0.66]$$



# Simulate Cohort Over Time

- Reflects the distribution of a cohort of patients over a set of health states over time

$$x_{15} = [0.01 \quad 0.15 \quad 0.84]$$



# Transition Matrix Calculations

- Summarize transition probabilities as a matrix

		To:				
		Healthy	Sick	Dead		
From:	Healthy	0.75	0.20	0.05	=	A
	Sick	0	0.85	0.15		
	Dead	0	0	1.0		

- Cohort distribution at next time step calculated through matrix multiplication

$$\begin{bmatrix} \text{---} x_{t+1} \text{---} \end{bmatrix} = \begin{bmatrix} \text{---} x_t \text{---} \end{bmatrix} \begin{bmatrix} A \end{bmatrix}$$

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# Transition Matrix Calculations

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- Cohort distribution at next time step calculated through matrix multiplication

$$\begin{array}{c} x_1 \\ \left[ \begin{array}{ccc} 0.75 & 0.20 & 0.05 \end{array} \right] \end{array} = \begin{array}{c} x_0 \\ \left[ \begin{array}{ccc} 1.0 & 0.0 & 0.0 \end{array} \right] \end{array} \begin{array}{c} A \\ \left[ \begin{array}{ccc} 0.75 & 0.20 & 0.05 \\ 0 & 0.85 & 0.15 \\ 0 & 0 & 1.0 \end{array} \right] \end{array}$$



# State-Transition Model Outcomes

- Outcomes (life-years, QALYs, costs, etc.) accrued by the cohort at each time step depend on the distribution across health states
- Each state assigned a value reflecting one cycle of residence
  - Cost per cycle
  - Utility
- At each cycle, multiply state-specific outcome by proportion of cohort in each state
- In CEA, outcomes are discounted to reflect time preferences
  - Prefer benefits now, costs later
  - Typical discount rate of 3% per year in US

# Calculating Outcomes

- Multiply cohort distribution by state-specific values to calculate expected value at each time
  - Sum expected values over time (discount if desired)

Life-Years:      1.0                  1.0                  0.0                   $r = 0.03$

Time	Healthy	Sick	Dead	E[LYs]	
0	1.0	0.0	0.0	--	
1	0.75	0.20	0.05		$* 1/(1+r)$
2	0.56	0.32	0.12		$* 1/(1+r)^2$
3	0.42	0.38	0.19		$* 1/(1+r)^3$
	...	...	...		

Sum  
↓

Total discounted life years: 6.77 years  
(Remaining life expectancy)

# Calculating Outcomes

- Multiply cohort distribution by state-specific values to calculate expected value at each time
  - Sum expected values over time (discount if desired)

Costs:	\$500	\$2,500	\$0		$r = 0.03$
Time	Healthy	Sick	Dead	E[Costs]	
0	1.0	0.0	0.0	--	
1	0.75	0.20	0.05		$* 1/(1+r)$
2	0.56	0.32	0.12		$* 1/(1+r)^2$
3	0.42	0.38	0.19		$* 1/(1+r)^3$
	...	...	...		

Sum  
↓

Total discounted costs: \$11,557


(Total remaining lifetime costs)

# Calculating Outcomes

- Multiply cohort distribution by state-specific values to calculate expected value at each time
  - Sum expected values over time (discount if desired)

Utilities	1.0	0.8	0		$r = 0.03$
Time	Healthy	Sick	Dead	E[QALYs]	
0	1.0	0.0	0.0	--	
1	0.75	0.20	0.05		$* 1/(1+r)$
2	0.56	0.32	0.12		$* 1/(1+r)^2$
3	0.42	0.38	0.19		$* 1/(1+r)^3$
	...	...	...		

Sum



Total discounted QALYs: 5.95 QALYs  
(Total remaining QALYs)

# Designing a Cohort State-Transition Model

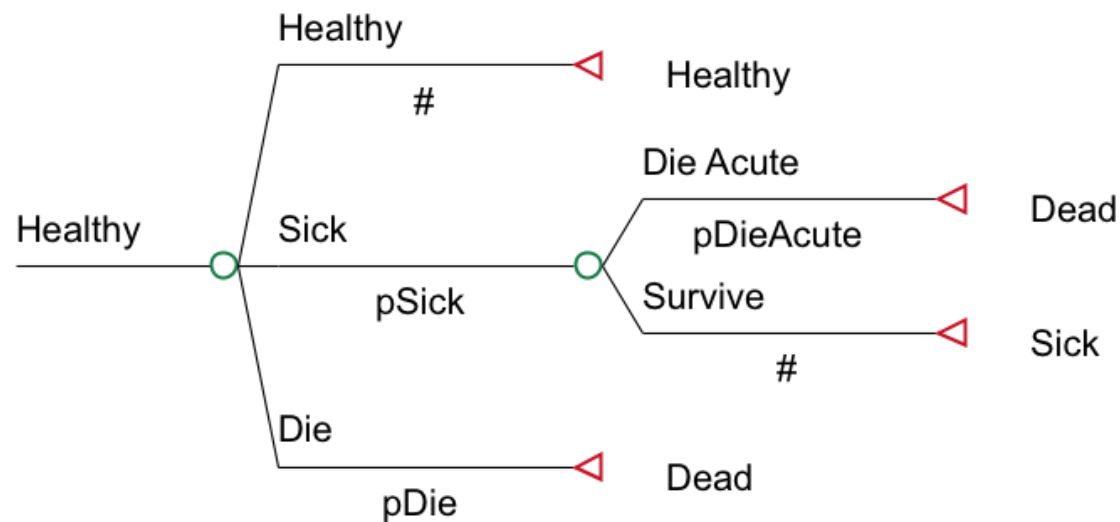
- Specify health states
- Define allowed transitions
- Choose cycle length
- Estimate transition probabilities
- Estimate state-specific values per cycle for outcomes of interests (costs, QALYs, etc.)



# Additional Complexity in Cohort State-Transition Models

# Within-Cycle Events

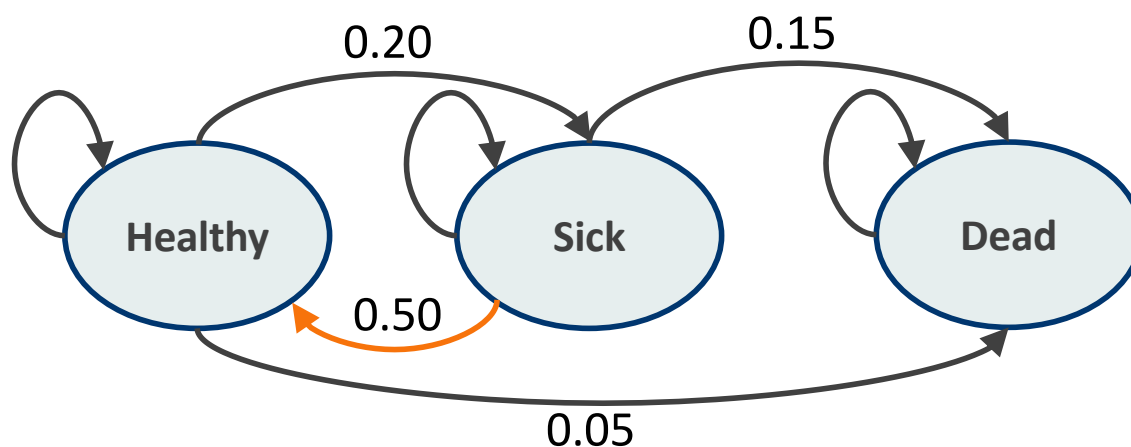
- $\Pr(\text{Healthy} \rightarrow \text{Dead})$  may be conceptualized as a sequence of events within a cycle (“cycle tree”)



- $\Pr(\text{Healthy} \rightarrow \text{Dead}) = p\text{Die} + p\text{Sick} * p\text{DieAcute}$

# Adding “Memory” Into States

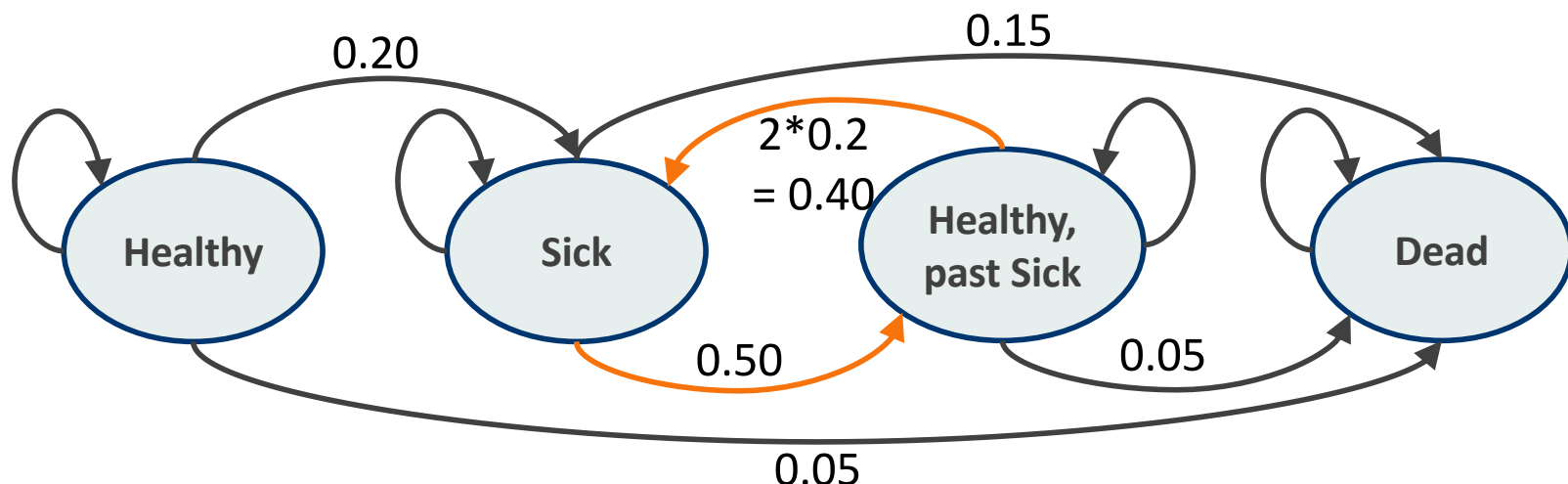
- Same example as before, except can now recover from Sick and return to Healthy
  - Annual probability of recovery = 0.50
- But, for this illness, having been Sick in the past makes you more likely to get Sick in the future
  - Twice as likely to get Sick than those without history
- Track history of illness with additional Markov state





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  - Annual probability of recovery = 0.50
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  - Twice as likely to get Sick than those without history
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# Time-dependency

## **Since start of the simulation**

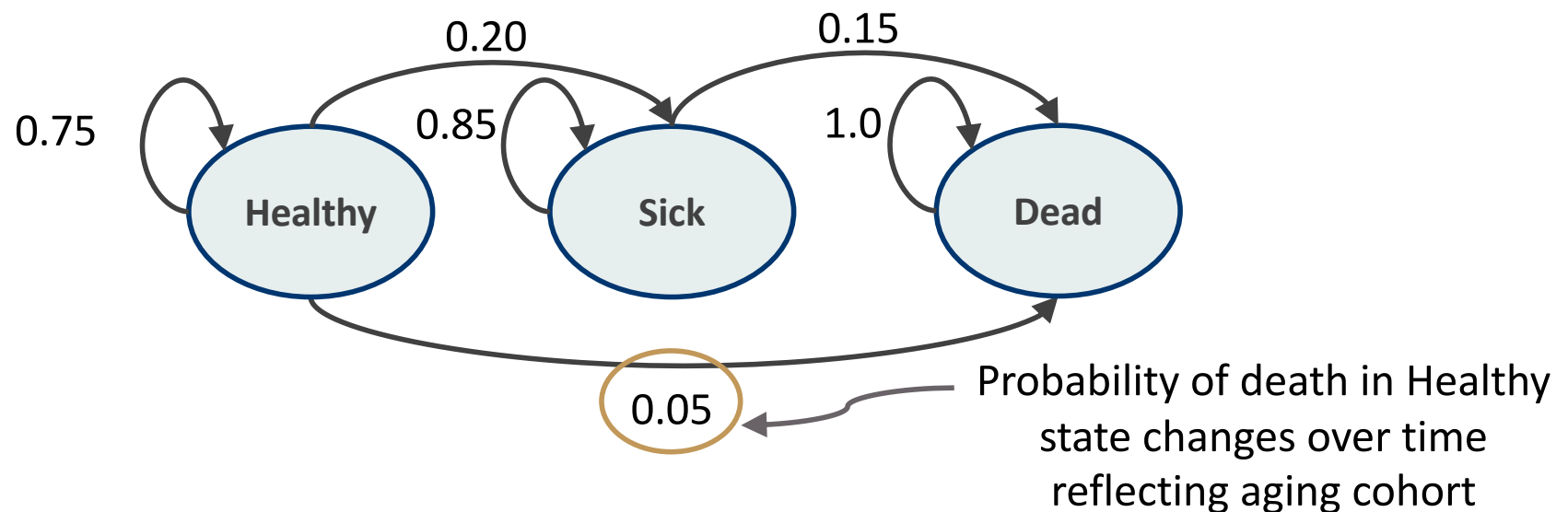
- Parameters vary by cycle
- Most often reflects probabilities that vary by age
  - Background mortality
  - Risk of disease onset

## **Depending on state residence time**

- Some transition probabilities depend on time since an event
  - e.g., risk of developing recurrence among newly diagnosed cancer patients declines with time
- Cost or utility could vary over time spent in a health state

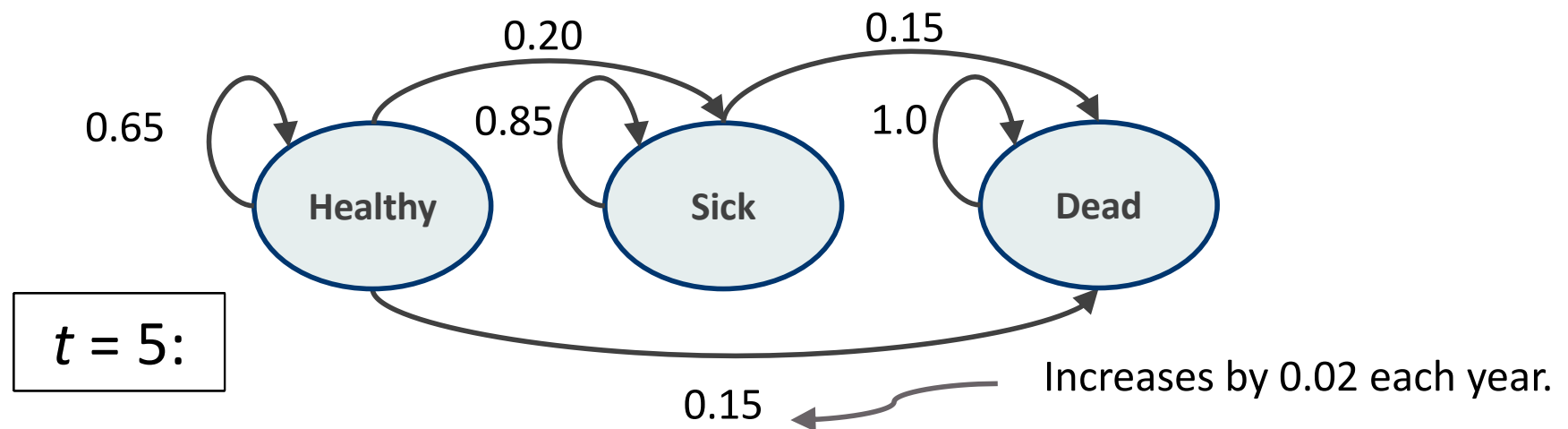
# Simulation Time Dependency

- Some transition probabilities change every cycle
  - Transition matrix  $A$  is not constant over time



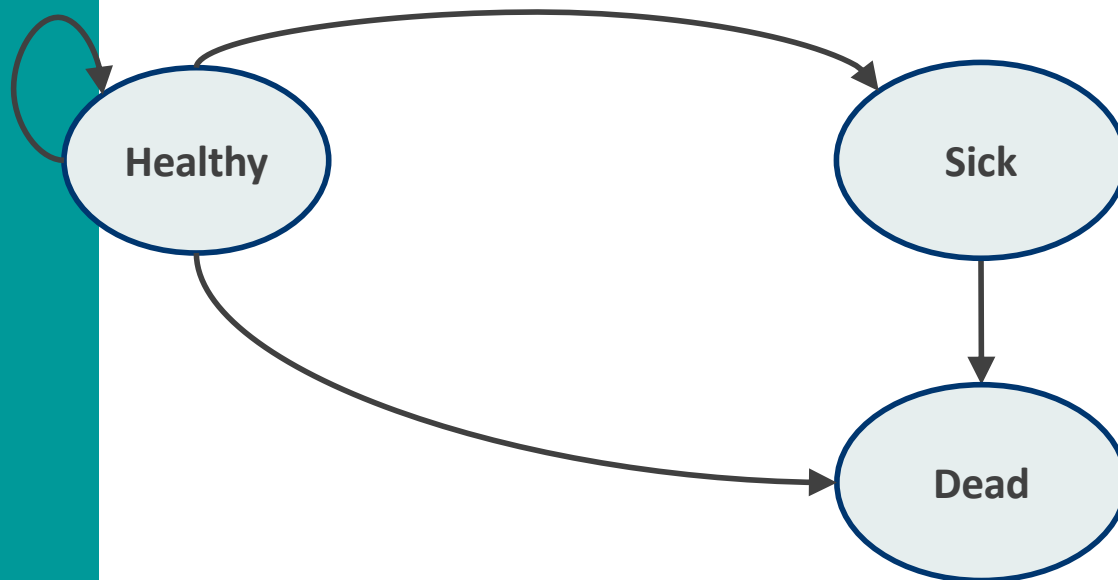
# Simulation Time Dependency

- Some transition probabilities change every cycle
  - Transition matrix  $A$  is not constant over time
- Replace matrix  $A$  with matrices  $A_t$ , where  $t$  is time since simulation start



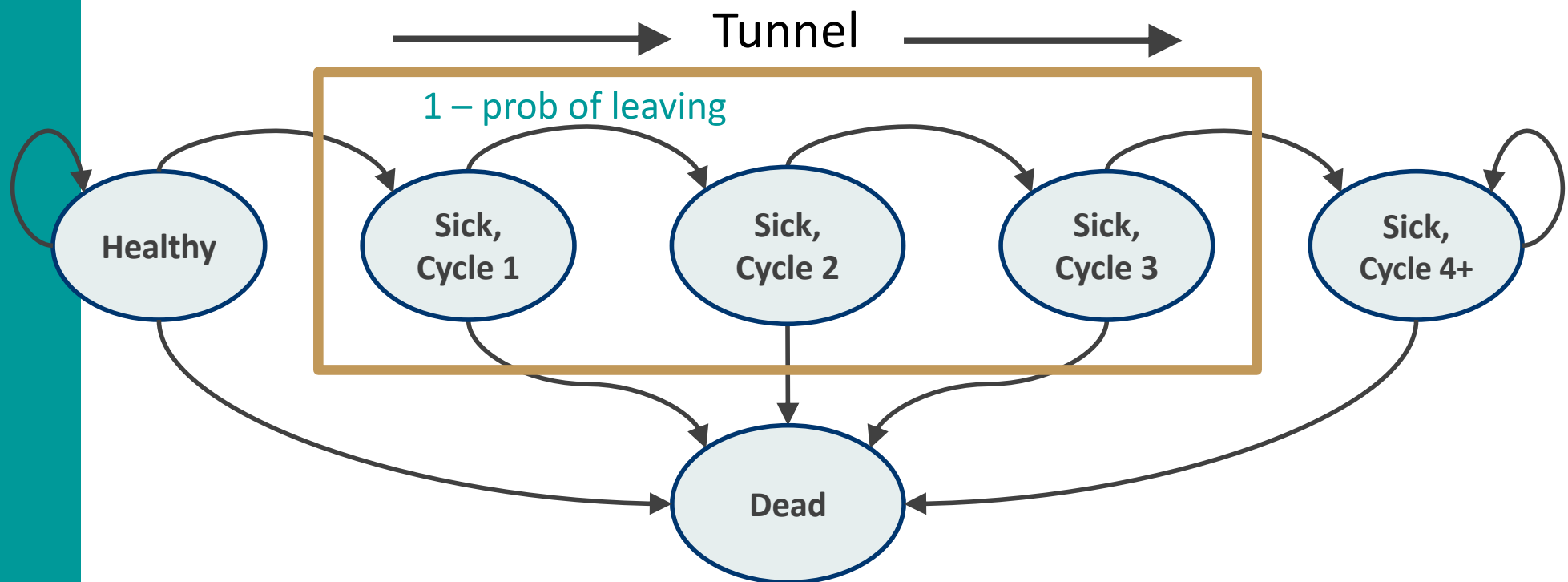
# Residence Time Dependency

- Time spent in a state can be tracked using a series of “tunnel” states



# Residence Time Dependency

- Time spent in a state can be tracked using a series of “tunnel” states
- Transition from one tunnel state to the next each time step (no self loops)





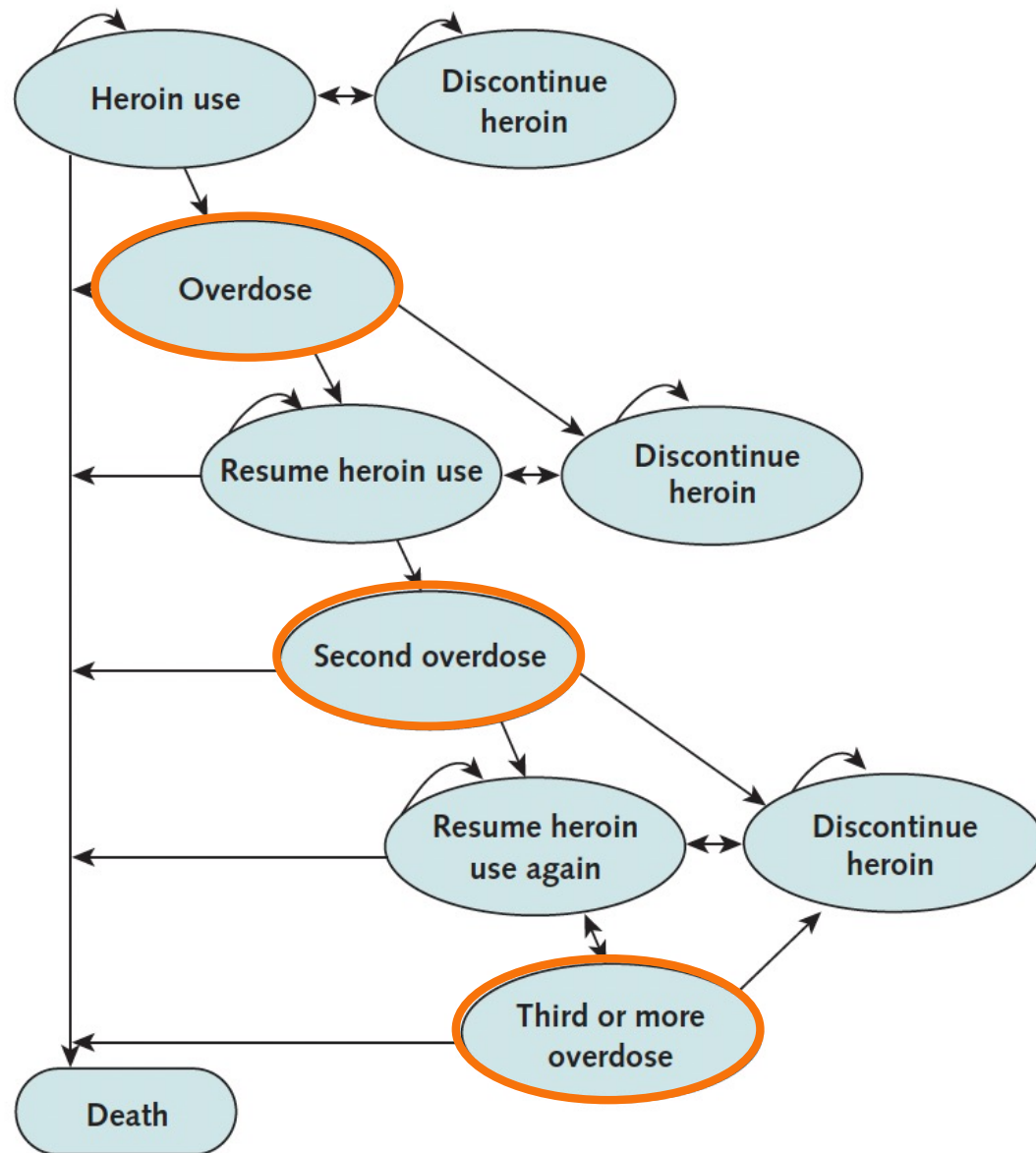
# State-Transition Model CEA: Naloxone Distribution for Overdose Prevention

# Study Context and Design

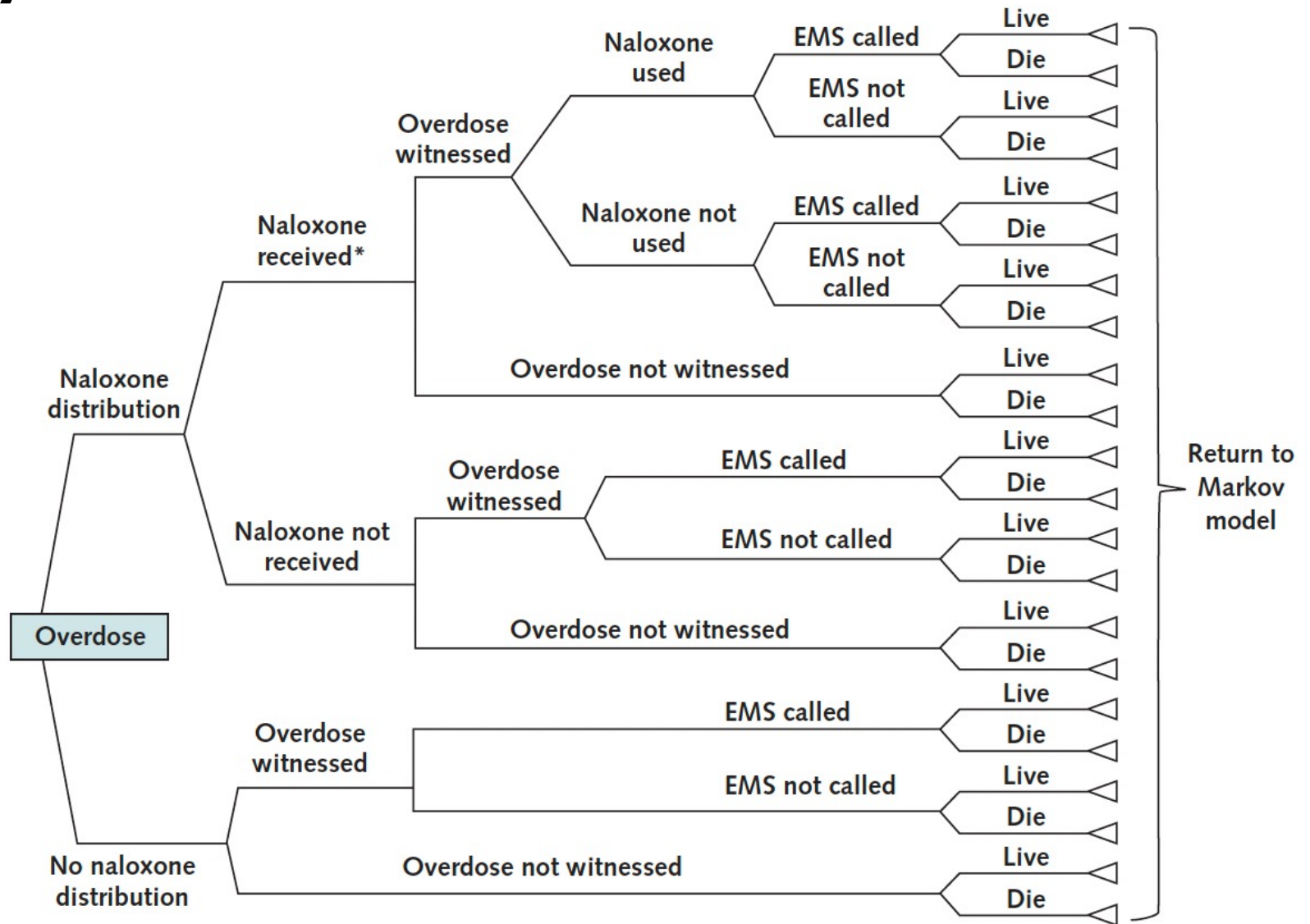
- Cost-effectiveness analysis of distributing naloxone in case of heroine overdose
  - Status quo: no distribution
  - Intervention: distribute naloxone to 20% of people who use heroine
- Population: Cohort of people who use heroine, starting at age 21
- Health outcomes: QALYs, overdose deaths averted
- Costs: naloxone kits, emergency transportation, emergency medical care
  - Sensitivity analysis including “costs to society”
- Time horizon: Lifetime



# State-Transition Diagram



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 5. **Discussion**  
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# Results

- Naloxone distribution ICER of \$421 / QALy gained vs. no naloxone
- Highly cost-effective under many different assumptions, even worst case

# Designing a model-based cost-effectiveness analysis

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# Choosing your model type

# Decision Trees

- Schematic representation of uncertain events/consequences of different alternatives
- Advantages:
  - Relatively simple; intuitive, clear visual representation
- Best for decisions made over a short time horizon
  - Clinical decisions (test, treat, etc.) for acute illness
  - Lifetime consequences can be quantified by using (pre-computed) life-expectancy as terminal value
- Not as appropriate in applications where there are repeated decisions or events
- Can be used to represent upfront strategy decisions, followed by a dynamic model for longer-term outcomes

# Cohort State-Transition Models

- Dynamic model that reflects disease progression and other events in a cohort
- Advantages:
  - Represents dynamic processes
  - Still relatively simple and so computationally efficient
- Best for dynamic processes that
  - Can be represented with a reasonable number of states
  - Don't dependent too much on individual heterogeneity (e.g., homogeneous cohort is a good approximation)
  - Minimal dependence on clinical history or time-in-state
- Usually deterministic (generate mean outcomes), but can be simulated stochastically

# Quick Note: Compartmental Models

- Dynamic models similar to state-transition models, with key differences:
- Open population (not a cohort)
- Transition probabilities or rates can depend on population state → ***infectious processes***
  - e.g., risk of infection depends on prevalence of infection in the population



# Microsimulation

- Stochastic dynamic model that simulates individuals, usually as a closed population
- Advantages:
  - Represents ***stochastic*** dynamic processes
  - Most flexible model type
  - Can capture ***complex dependencies*** on individual features, clinical history, time-since-event
  - Can capture interactions (agent-based model, network model)
- Best when a state-transition model is not sufficient
- Disadvantages
  - Computationally intensive, but can leverage parallel computing
  - Data intensive

# Agent-Based Models

- Stochastic dynamic model that simulates individuals with interactions
  - Infectious processes
  - Behavioral influences
- Advantages:
  - Same advantages as microsimulation (flexible!)
- Disadvantages
  - Especially computationally intensive, requires simulating an entire population at once
  - Data intensive, including parameters governing interactions

# Components of a Model-Based CEA

- Use the model to evaluate the costs and benefits of different strategies
- Strategy ← What you are choosing between
  - Clinical guidelines, treatment, new health technology, intervention, program, or policy
  - Consider combinations where relevant
- Costs ← What is included depends on perspective
  - Intervention costs, formal health care costs
  - Informal health care costs, societal costs
- Benefits ← Benefit depends on decision criteria
  - Infections averted, cases averted, disease-specific metrics
  - Life-years saved, quality-adjusted life-years saved

# Decision criteria

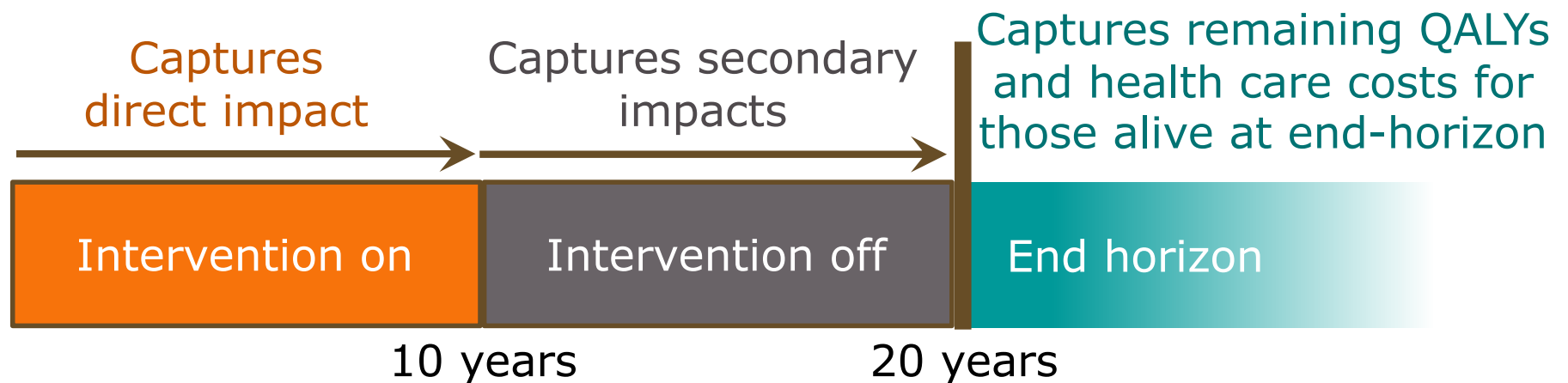
- How will you decide which strategy is optimal?
- Cost minimization
  - Strategy with lowest cost is optimal
  - Benefit is measured only in terms of averted costs (usually health care costs)
- Cost-effectiveness analysis
  - Strategy that maximizes health gains at a "reasonable" cost is optimal
  - "Reasonable cost" means less than a cost-effectiveness threshold
  - Cost per QALY gained, cost per life-year gained, cost per infection/case averted

# Cycle length

- For discrete-time, dynamic models, must select a cycle length
- Shorter cycle lengths better approximate continuous time and more accurately reflect event timing
- Longer cycle lengths reduce computational burden
- Timing of disease progression, screening, treatment, etc. influence appropriate cycle length

# Time horizon

- Time frame over which costs and benefits will be aggregated
- Sufficiently long to capture strategy impacts
- Cohort / closed population: Generally, use lifetime
- Population models: need to define



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