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

Session 16

Jason Andrews

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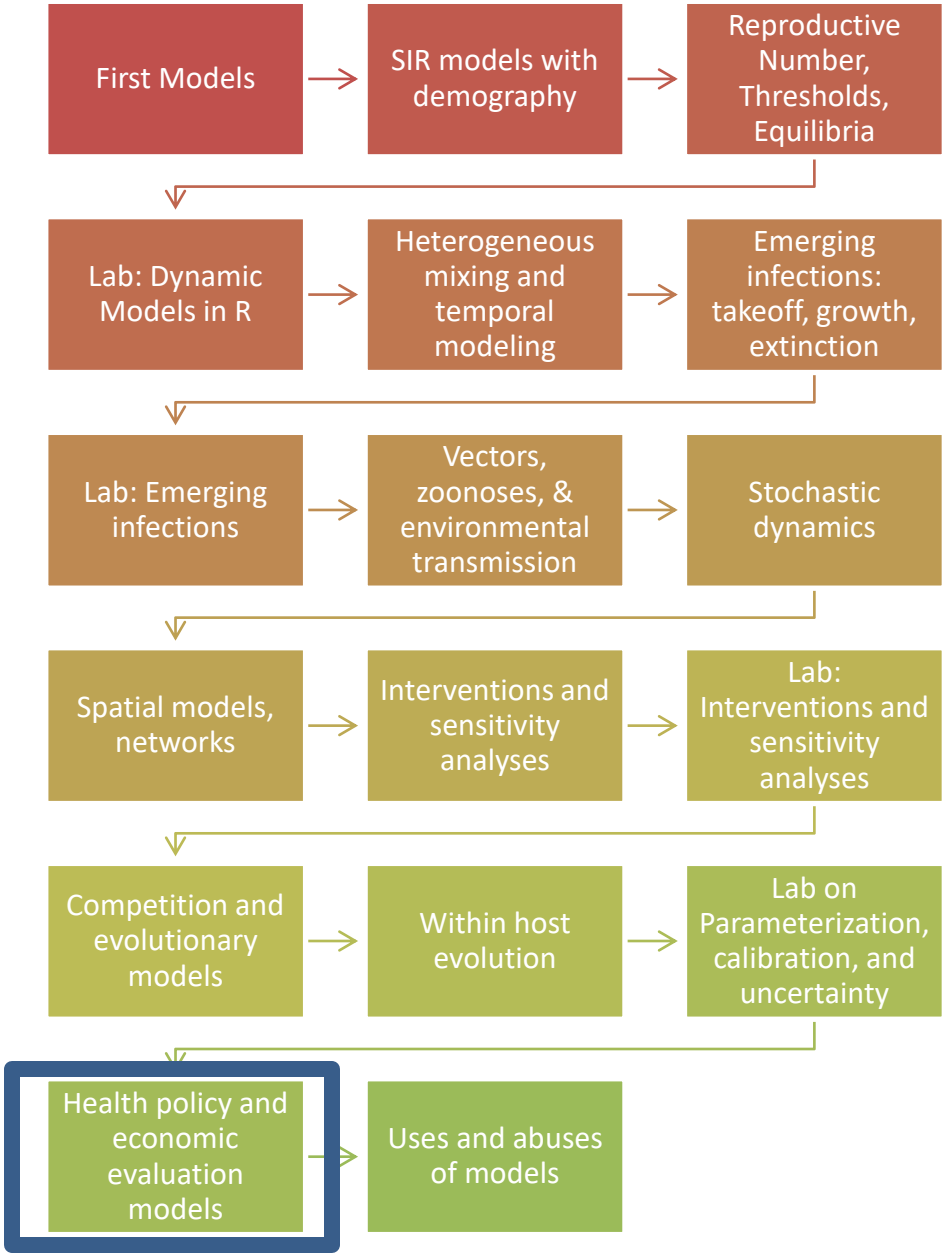
2020

# Course Roadmap



# REAL-WORLD RELEVANCE OF ECONOMIC EVALUATION AND POLICY ANALYSIS

The New York Times

Opinion

# Will Our Economy Die From Coronavirus?

## It will if we keep up our current strategy.

**By Paul Romer and Alan M. Garber**

Paul Romer, who received the Nobel Prize in Economics in 2018, is a professor at N.Y.U. Alan M. Garber, a physician and economist, is the provost of Harvard University.

March 23, 2020

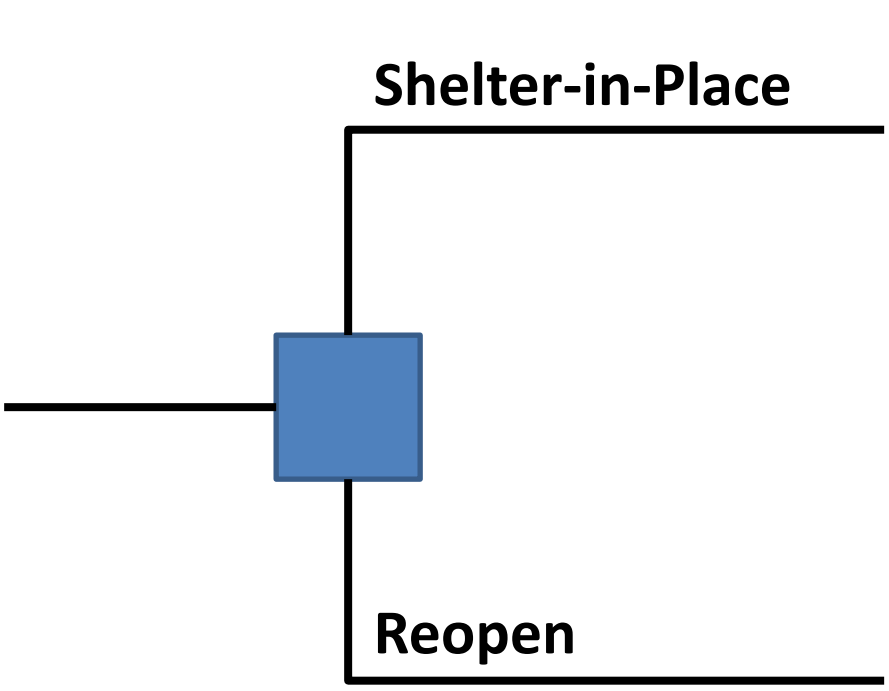
*BMJ* 2020;369:m1496 doi: 10.1136/bmj.m1496 (Published 21 April 2020)

## Opportunity costs

At this point the ugly question that could be asked is whether the value of the benefits (deaths averted or quality of life years (QALYs) saved, say) is more or less than the (opportunity) costs of the interventions. The costs will be measured in economic as well as health and healthcare terms. Opportunity costs will also include mortality and morbidity from conditions other than covid-19 because of reduced use of health services and delays in treatment of other illnesses arising from the NHS prioritising resources on covid-19. Some indication of these from the Office for National Statistic's regular monitoring suggests that for the week ending 3 April for England and Wales, there were 3475 deaths from covid-19 but 6082 more deaths from all causes compared with the five year average for this week.[10] It remains to be seen how many of the "excess" non-covid deaths could be the result of covid-19 interventions and changes in the public's healthcare seeking behaviour.

Despite some early estimates from the US suggesting that there is a net benefit of social distancing and isolation versus the hit on the economy,[11] [12] these estimates come with large uncertainty.

# A debate over a decision argued about what the costs and benefits are and how we weight them




Deaths
Illness
Intervention Costs
GDP decline
…

Deaths
Illness
Intervention Costs
GDP decline
…

Huge simplification of course. Need at least 2 alternatives for a decision but method can accommodate many alternatives

# Practical Questions

For health policy evaluations, how is value defined and calculated?

How do we assess the value of alternative interventions or policies intended to control or eliminate an infectious disease epidemic in a given population?

# Learning Objectives

- Define Value and contrast it with assessments of cost-minimization and health-maximization
- Define a decision problem in terms of alternatives and outcomes
- Characterize interventions on the cost-effectiveness plane
- Identify the areas of the cost-effectiveness plane where incremental analysis is required
- Define the incremental cost-effectiveness ratio and when it connotes higher (lower) value
- Know to ALWAYS avoid using average cost-effectiveness ratios
- Become familiar with dominance to identify the cost-effectiveness frontier (graphical and tabular)
- Consider how total costs and effects are streams of outcomes over a long time horizon
- Become familiar with equations that include discounting
- Become familiar with Quality-Adjusted Life Expectancy and Life Years (QALYs)
- Connect computation of these streams and our simulation models and justify why we would use models to do this
- Examine an applied example (TB and MDR-TB) which illustrates a cost-effectiveness using a dynamic transmission model
- Consider advanced topic 1: How do we consider and report uncertainty in a CEA
- Consider advanced topic 2: CEA with open populations vs. single cohorts

# WHAT IS VALUE?

# Value

# ≠

# Large Health Improvements

# Value

# ≠

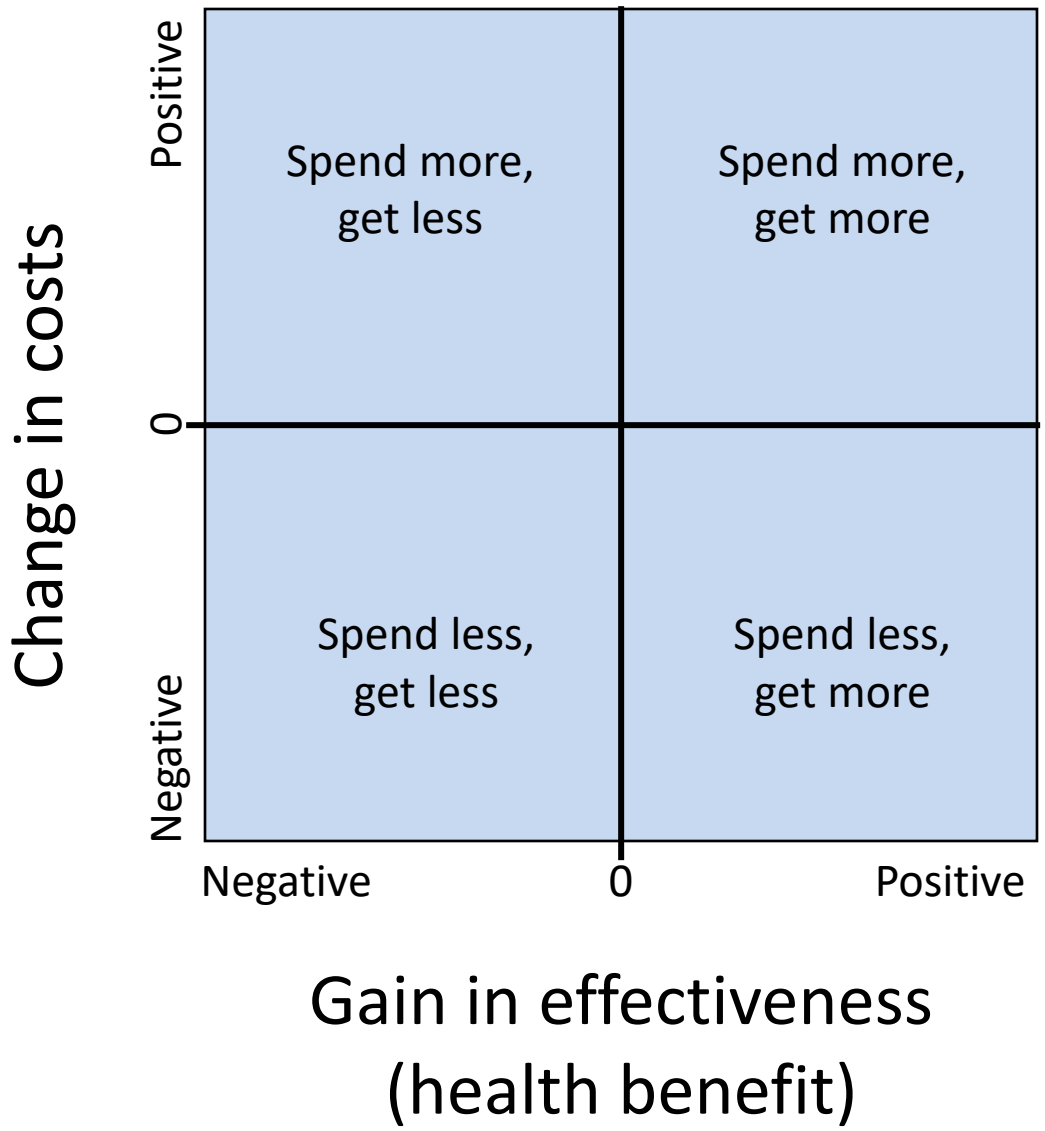
# Low Prices

**We assess Value, weighing both costs and effects, relative to available alternatives**

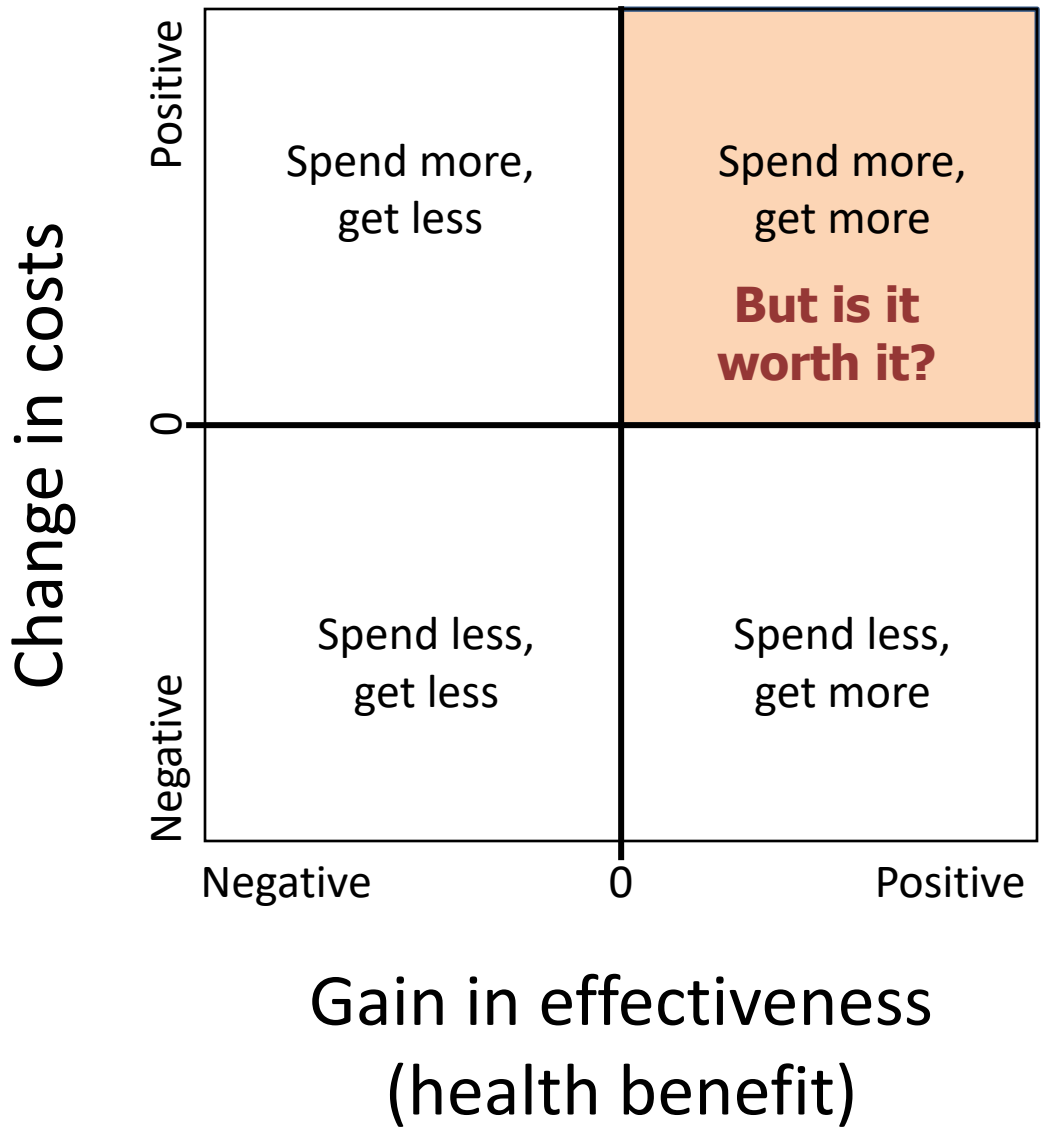
**HOW DO WE WEIGH THE COSTS AND EFFECTS OF EACH INTERVENTION? AND KNOW WHEN THEY PROVIDE SUFFICIENT VALUE?**

# COST-EFFECTIVENESS ANALYSIS: SIMPLE TECHNIQUE TO ACCOUNT FOR BOTH EFFECTIVENESS AND COSTS

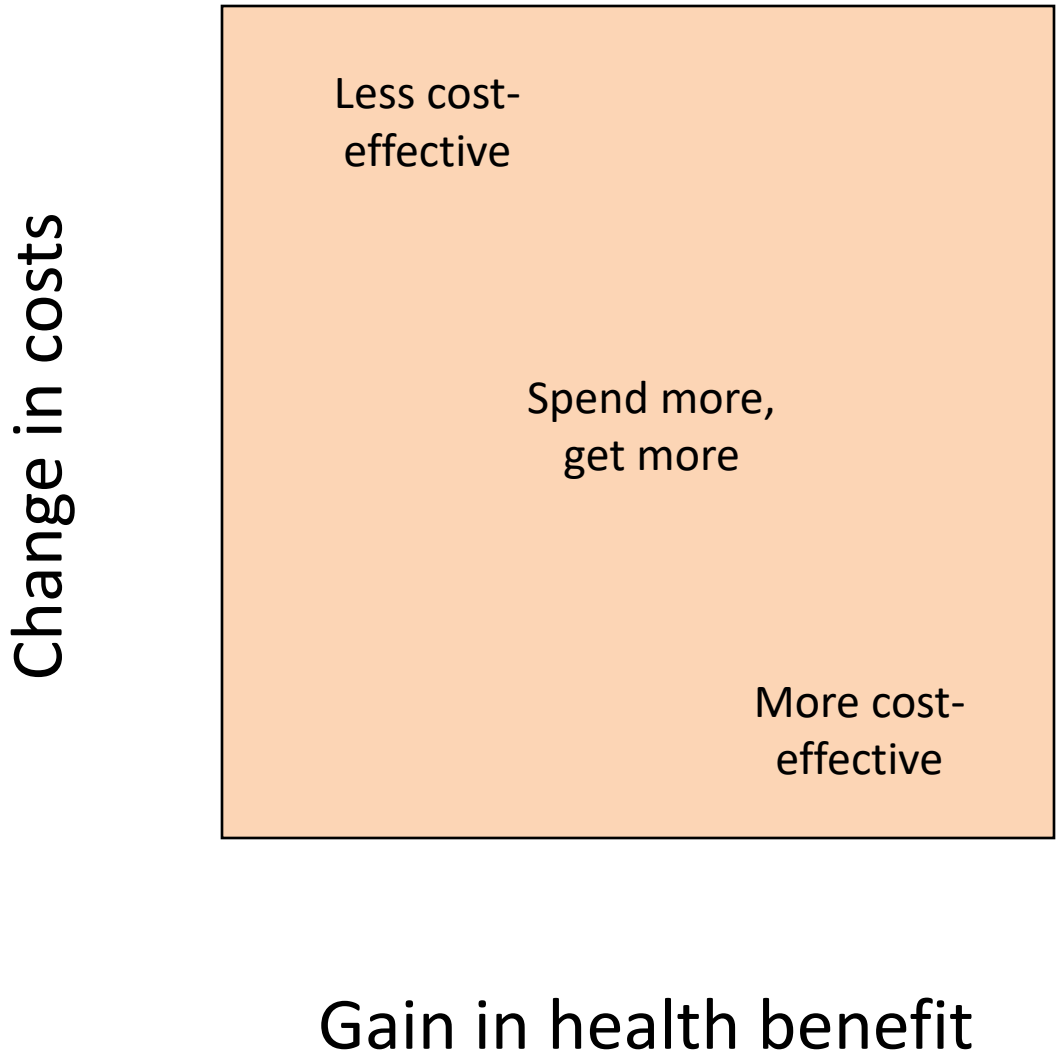
# Accounting for Value



# Accounting for Value

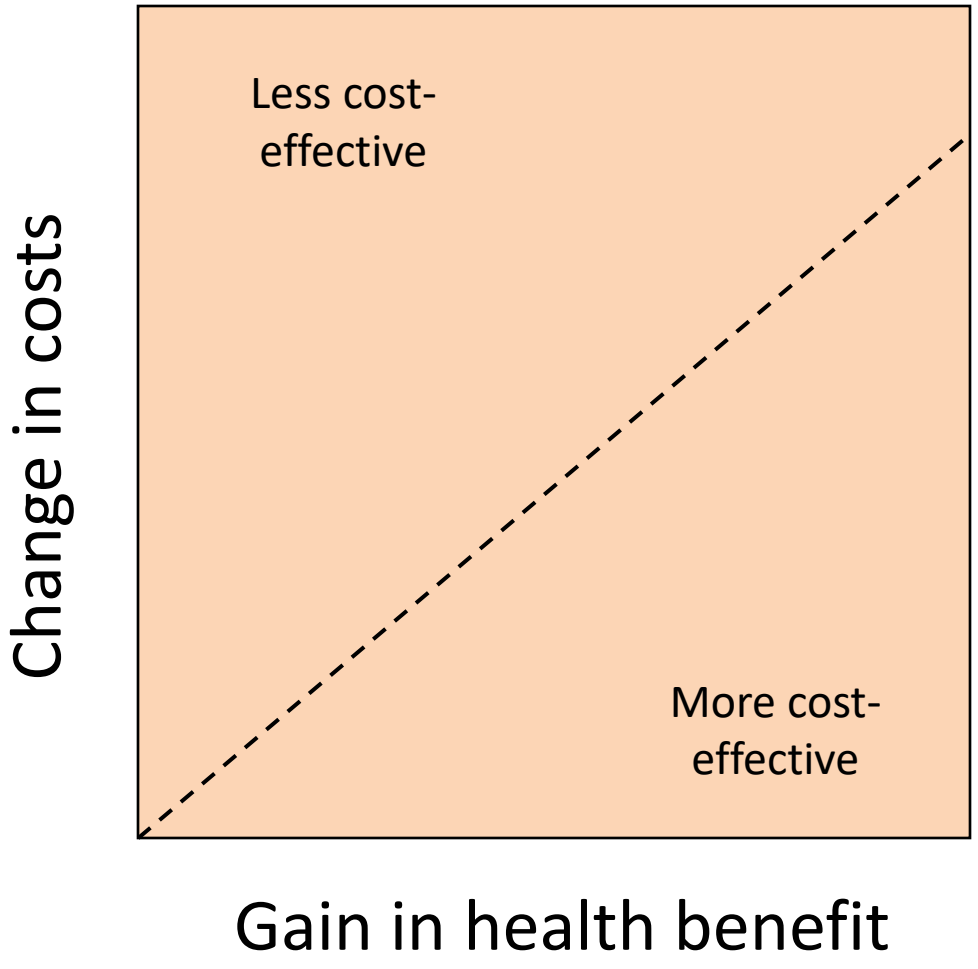


# Accounting for Value



# Accounting for Value

- **Health benefit measured in QALYs**
- **Value accounted by incremental cost-effectiveness ratio (ICER) (difference in costs divided by difference in benefits)**
- **Greater ICER means less cost-effective**
- **Dotted line represents our threshold willingness to pay**



# Incremental Cost-Effectiveness Ratio (ICER): How to compare two strategies in CEA

- **Numerator**: Difference between costs of the intervention (strategy) and costs of the
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  eness) o
  and healt comes of the a tive

**Incremental resources required by the intervention**

**Incremental health effects gained with the intervention**

$$ICER = \frac{C_i - C_{alt}}{E_i - E_{alt}}$$

## The Correct Cost-Effectiveness Ratio is NOT:

$$\frac{C_i}{E_i} \quad or \quad \frac{C_{alt}}{E_{alt}}$$

- These represent the AVERAGE cost-effectiveness ratio, not the INCREMENTAL cost-effectiveness ratio
- They should never be used

# Incremental Analysis: Overview

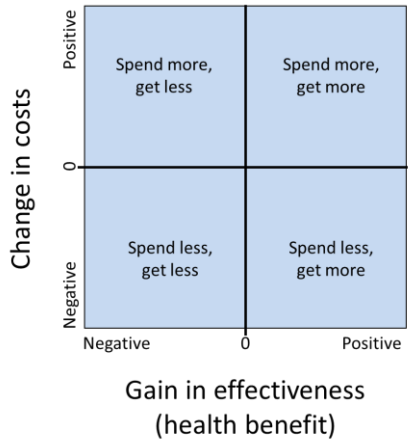
- Cost-effectiveness ratio always between two relevant alternatives
- When there are multiple alternatives, we
  - rank order by ascending costs
  - compute incremental effects, costs
  - remove dominated alternatives
  - compute ratios relative to the next best, non-dominated alternative
- The following slides detail this process

# Dominance and Extended Dominance:

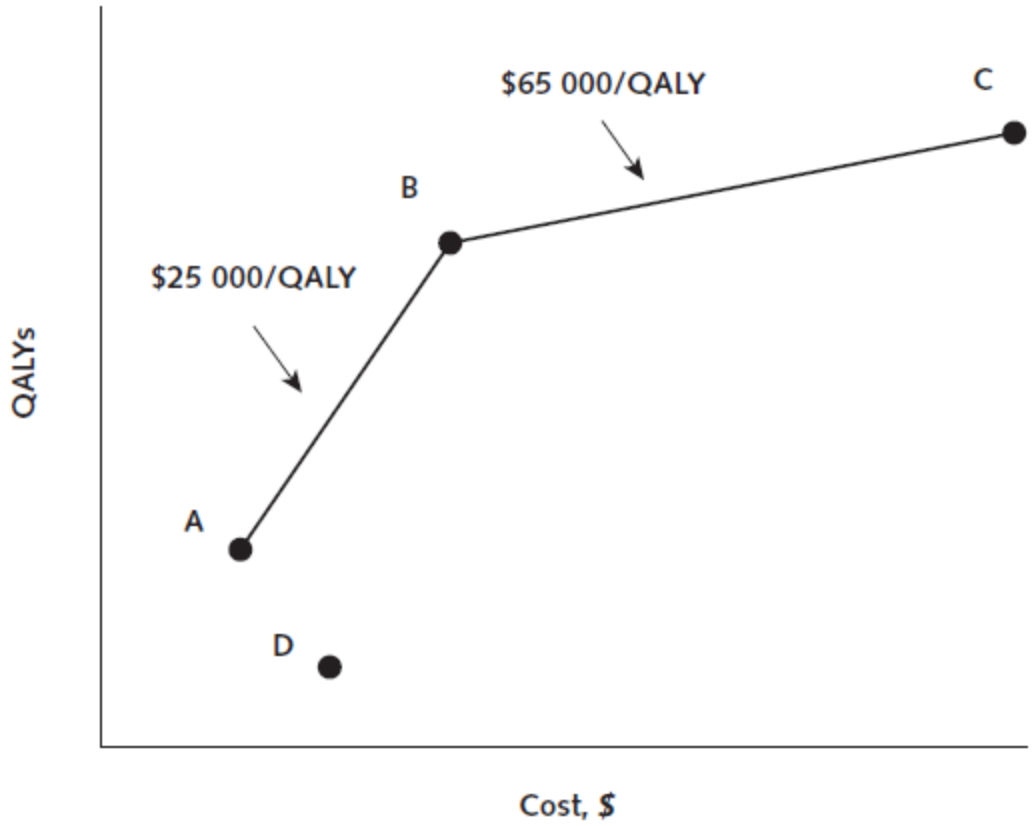
## *Eliminate Dominated Alternatives*

- **(Strict) dominance:** One intervention more effective and less costly than an alternative
- **Extended dominance:** More expensive intervention has a lower cost-effectiveness ratio than the lower-cost option. Alternatively, one intervention is strictly dominated by a linear combination of two other interventions.

*Rational decision maker will not choose an option that is dominated by another, whether under strict or extended dominance*

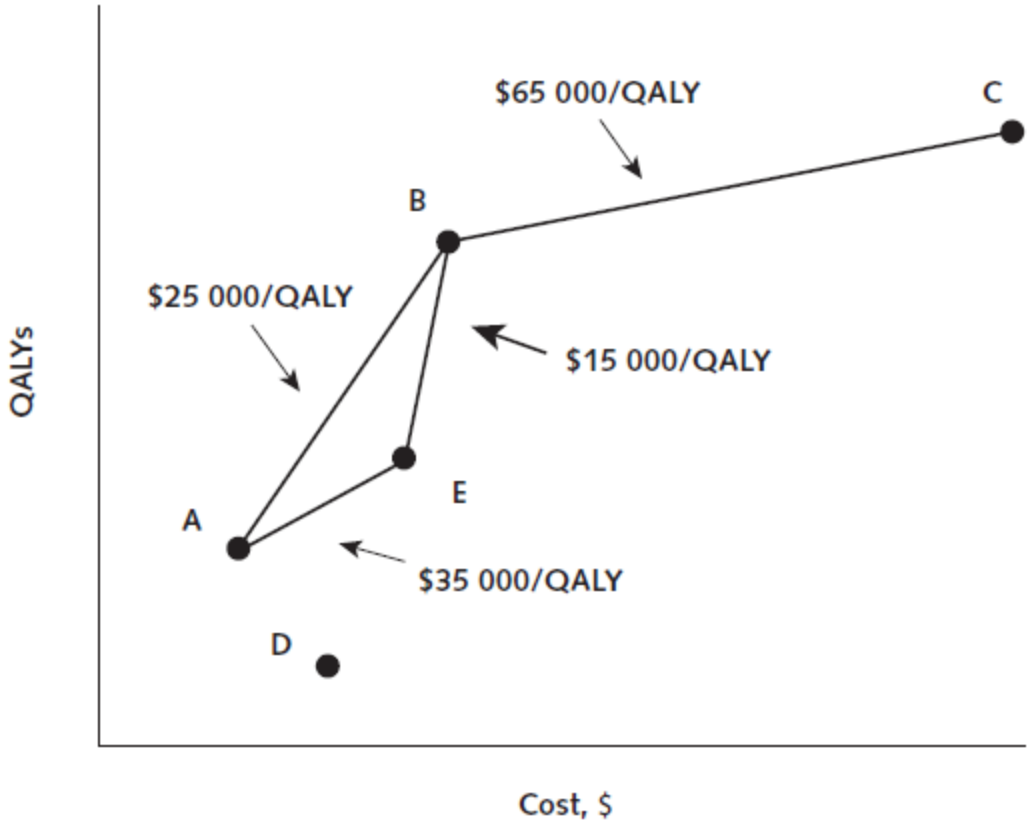


# Strict dominance




Owens DK et al Annals of Internal Medicine 2011; 154: 174-180

# Extended dominance




Owens DK et al Annals of Internal Medicine 2011; 154: 174-180

**Start with our strategies and their costs and effects in a table like this…**

| Strategy | Costs | QALYs | Incremental Costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|
| A | 10,000 | 1.00 | | | |
| B | 35,000 | 2.00 | | | |
| C | 51,250 | 2.25 | | | |
| D | 20,000 | 0.50 | | | |
| E | 27,500 | 1.50 | | | |

**First, sort strategies in ascending order of costs like this…**

| Strategy | Costs | QALYs | Incremental Costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|
| A | 10,000 | 1.00 | | | |
| D | 20,000 | 0.50 | | | |
| E | 27,500 | 1.50 | | | |
| B | 35,000 | 2.00 | | | |
| C | 51,250 | 2.25 | | | |

**Next, identify any strategies that cost more but are less effective (strictly dominated) …**

| Strategy | Costs | QALYs | Incremental Costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|
| A | 10,000 | 1.00 | | | |
| D | 20,000 | 0.50 | | | |
| E | 27,500 | 1.50 | | | |
| B | 35,000 | 2.00 | | | |
| C | 51,250 | 2.25 | | | |

**Remove the dominated strategies and then compute the incremental costs and QALYs like this …**

| Strategy | Costs | QALYs | Incremental Costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|
| A | 10,000 | 1.00 | | | |
| E | 27,500 | 1.50 | 17,500 | 0.50 | |
| B | 35,000 | 2.00 | 7,500 | 0.50 | |
| C | 51,250 | 2.25 | 16,250 | 0.25 | |

**Use the incremental costs and QALYs to compute incremental cost-effectiveness ratios …**

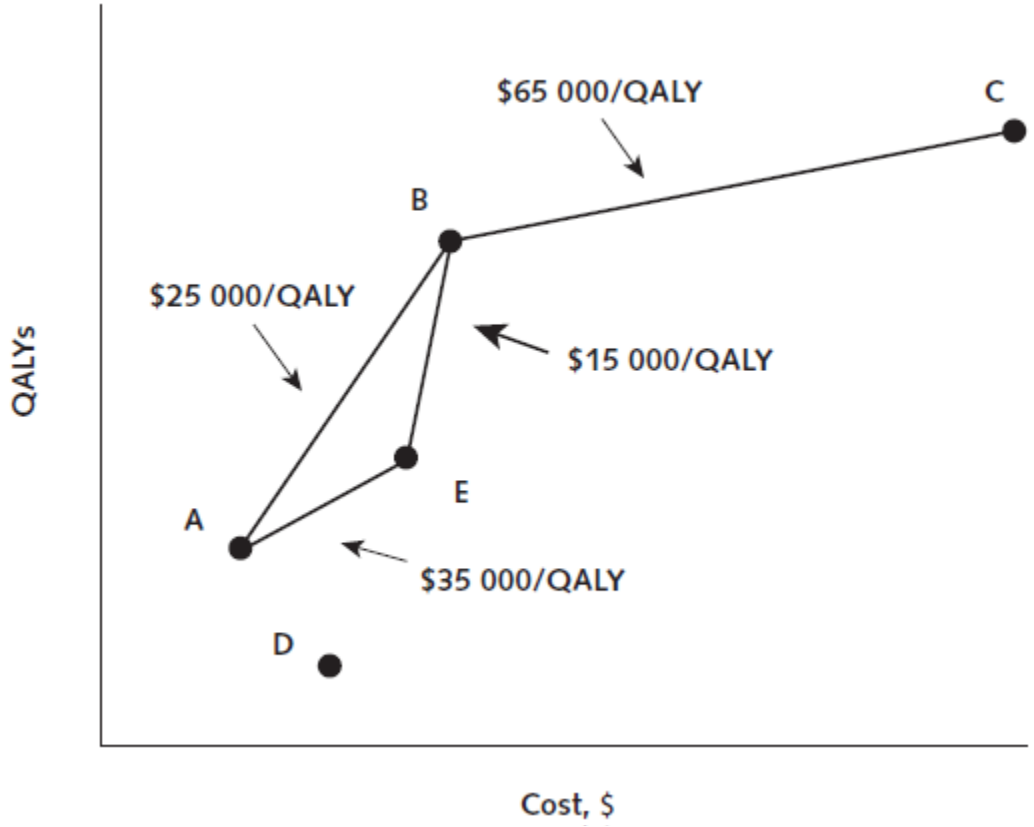
| Strategy | Costs | QALYs | Incremental Costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|
| A | 10,000 | 1.00 | | | |
| E | 27,500 | 1.50 | 17,500 | 0.50 | 35,000 |
| B | 35,000 | 2.00 | 7,500 | 0.50 | 15,000 |
| C | 51,250 | 2.25 | 16,250 | 0.25 | 65,000 |

**Search for patterns of extended dominance (rising and then falling incremental cost-effectiveness ratios), identifying strategies that are less costly but have a higher ICER as those dominated via extended dominance …**

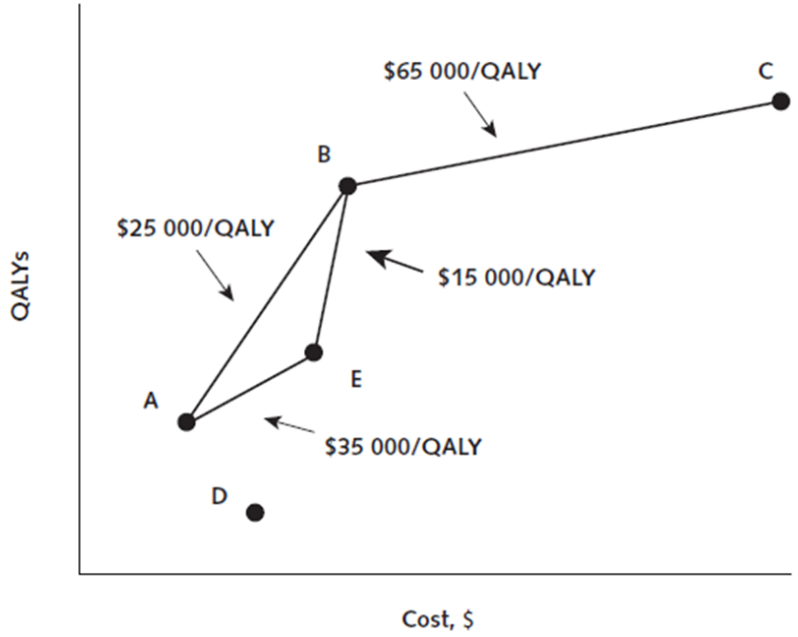
| Strategy | Costs | QALYs | Incremental Costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|
| A | 10,000 | 1.00 | | | |
| E | 27,500 | 1.50 | 17,500 | 0.50 | 35,000 |
| B | 35,000 | 2.00 | 7,500 | 0.50 | 15,000 |
| C | 51,250 | 2.25 | 16,250 | 0.25 | 65,000 |

**Finally, remove the extended dominated strategies and recompute the incremental costs, QALYs, and incremental cost-effectiveness ratios, checking that no new dominated strategies exist … if none, then the process is done.**

| Strategy | Costs | QALYs | Incremental Costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|
| A | 10,000 | 1.00 | | | |
| B | 35,000 | 2.00 | 25,000 | 1.00 | 25,000 |
| C | 51,250 | 2.25 | 16,250 | 0.25 | 65,000 |

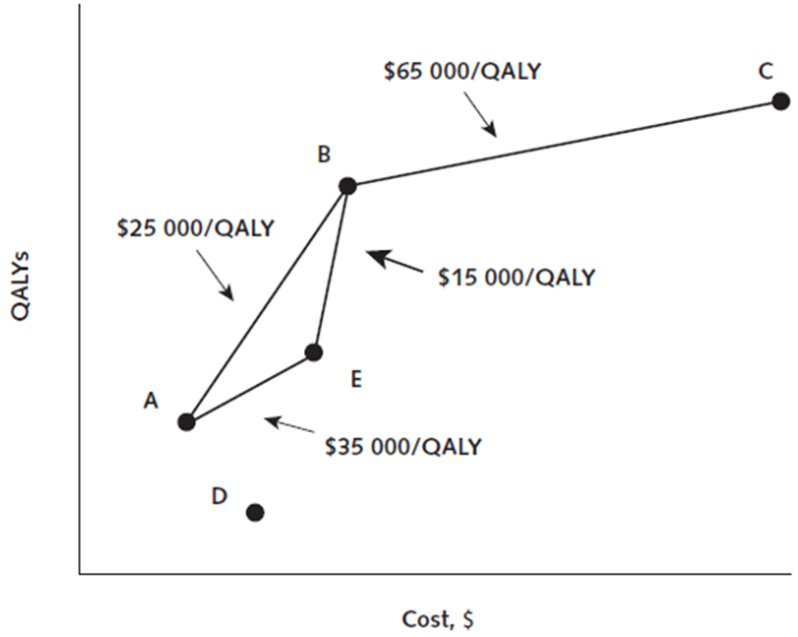


| Strategy | Costs | QALYs | Incremental Costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|
| A | 10,000 | 1.00 | | | |
| B | 35,000 | 2.00 | 25,000 | 1.00 | 25,000 |
| C | 51,250 | 2.25 | 16,250 | 0.25 | 65,000 |




**FOR THE NON-DOMINATED STRATEGY, WE NEED A WILLINGNESS-TO-PAY THRESHOLD TO IDENTIFY OUR PREFERRED STRATEGY**

| Strategy | Costs | QALYs | Incremental Costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|
| A | 10,000 | 1.00 | | | |
| B | 35,000 | 2.00 | 25,000 | 1.00 | 25,000 |
| C | 51,250 | 2.25 | 16,250 | 0.25 | 65,000 |

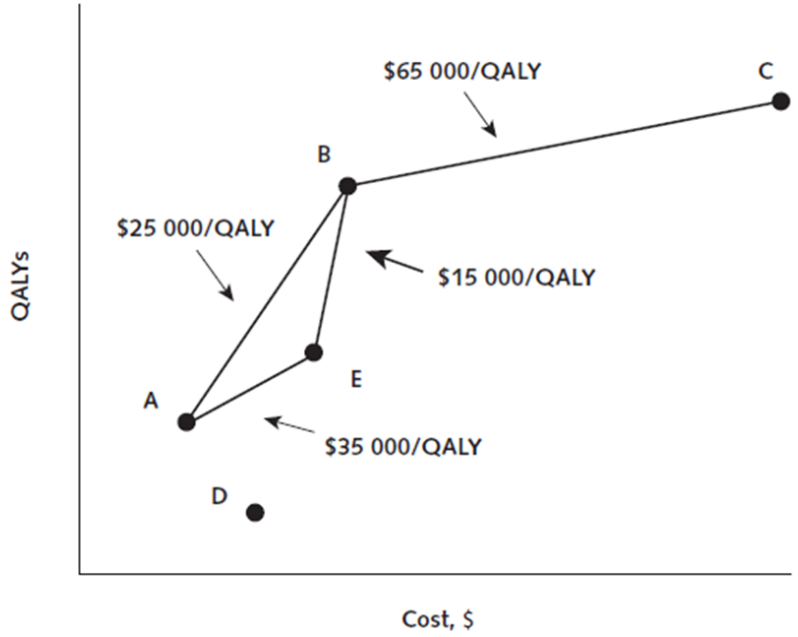



**IF WTP THRESHOLD <$25K/QALY GAINED, CHOOSE A**

**IF >= $25K BUT < $65K, CHOOSE B**

**OTHERWISE, CHOOSE C**

| Strategy | Costs | QALYs | Incremental Costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|
| A | 10,000 | 1.00 | | | |
| B | 35,000 | 2.00 | 25,000 | 1.00 | 25,000 |
| C | 51,250 | 2.25 | 16,250 | 0.25 | 65,000 |




# WHERE DO THE NUMBERS FOR THE COSTS AND EFFECTS FOR EACH STRATEGY/INTERVENTION COME FROM?

# MODEL-BASED COST-EFFECTIVENESS ANALYSES: BECAUSE WE ARE INTERESTED IN LONG TIME HORIZONS, MANY STRATEGIES, AND QUANTIFYING UNCERTAINTY

# Modeling Outcomes: Life Expectancy

Life expectancy is average amount of time a person can expect to live given their current age ($t_0$) (and any other relevant status)

It can be computed as the sum of the fraction ($\pi$) of an initial cohort of people aged ($t_0$) at all future times (i)

$$LE = \sum_{i=t_0}^{T} \pi_i$$

# Modeling Outcomes: Discounted Life Expectancy

Discounted life expectancy is analogous to life expectancy except that future years are given lower weight.

Applying discount rate of $0 \leq k \leq 1$ (think of $k$ as *1/[1+r] where 1+r might be 103% annually*), discounted life expectancy at age $t_0$ is

$$DLE = \sum_{i=t_0}^{T} k^{(i-t_0)} \pi_i$$

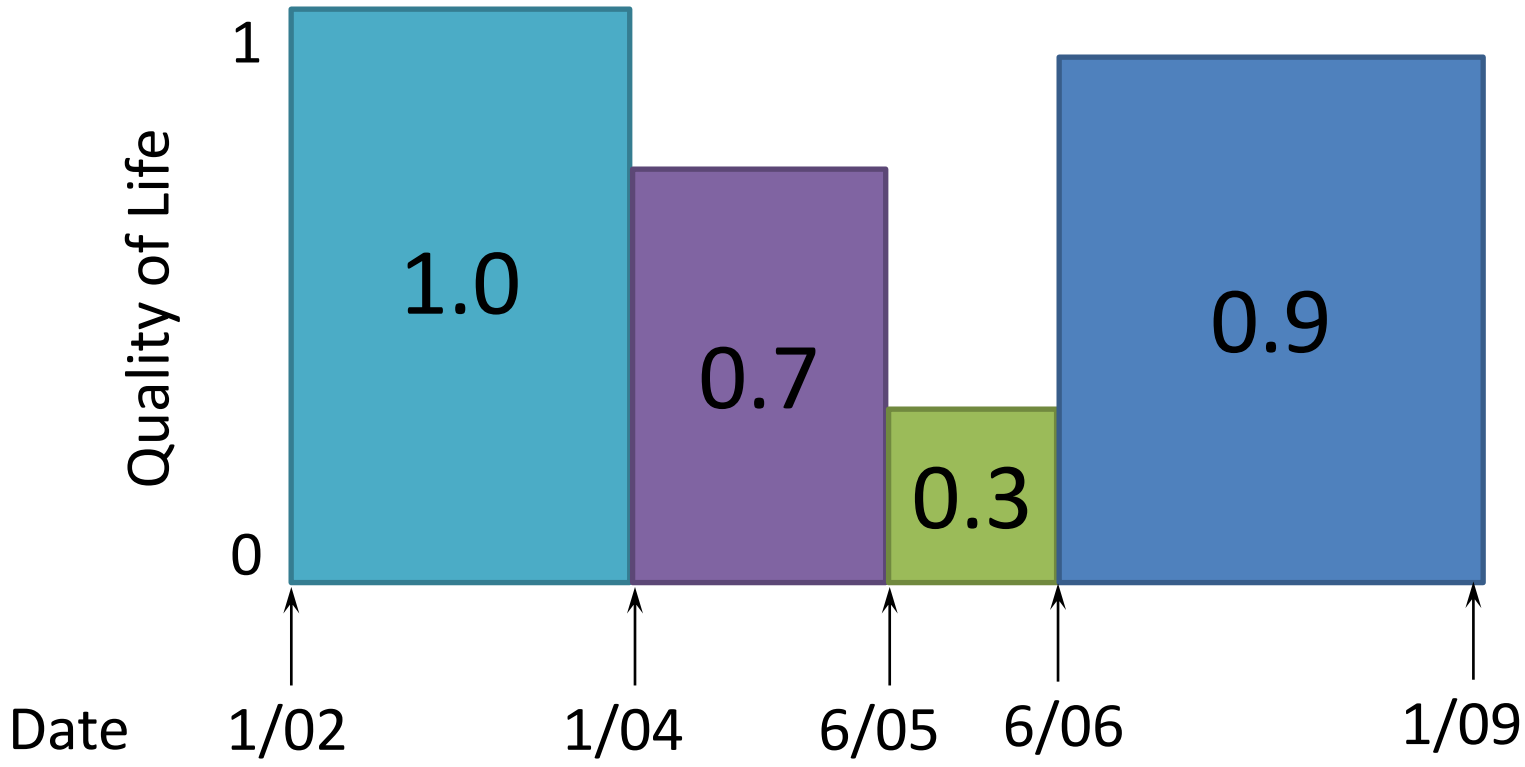
# Modeling Outcomes: Quality-Adjusted Life Years (QALYs)

QALYs analogous to life expectancy except that each year is given an average "quality weight" $q_i$, taking value between 0 and 1.

Value of 1 represents perfect health, 0 represents quality of life equivalent to death

$$QALE = \sum_{i=t_0}^{T} q_i k^{(i-t_0)} \pi_i$$

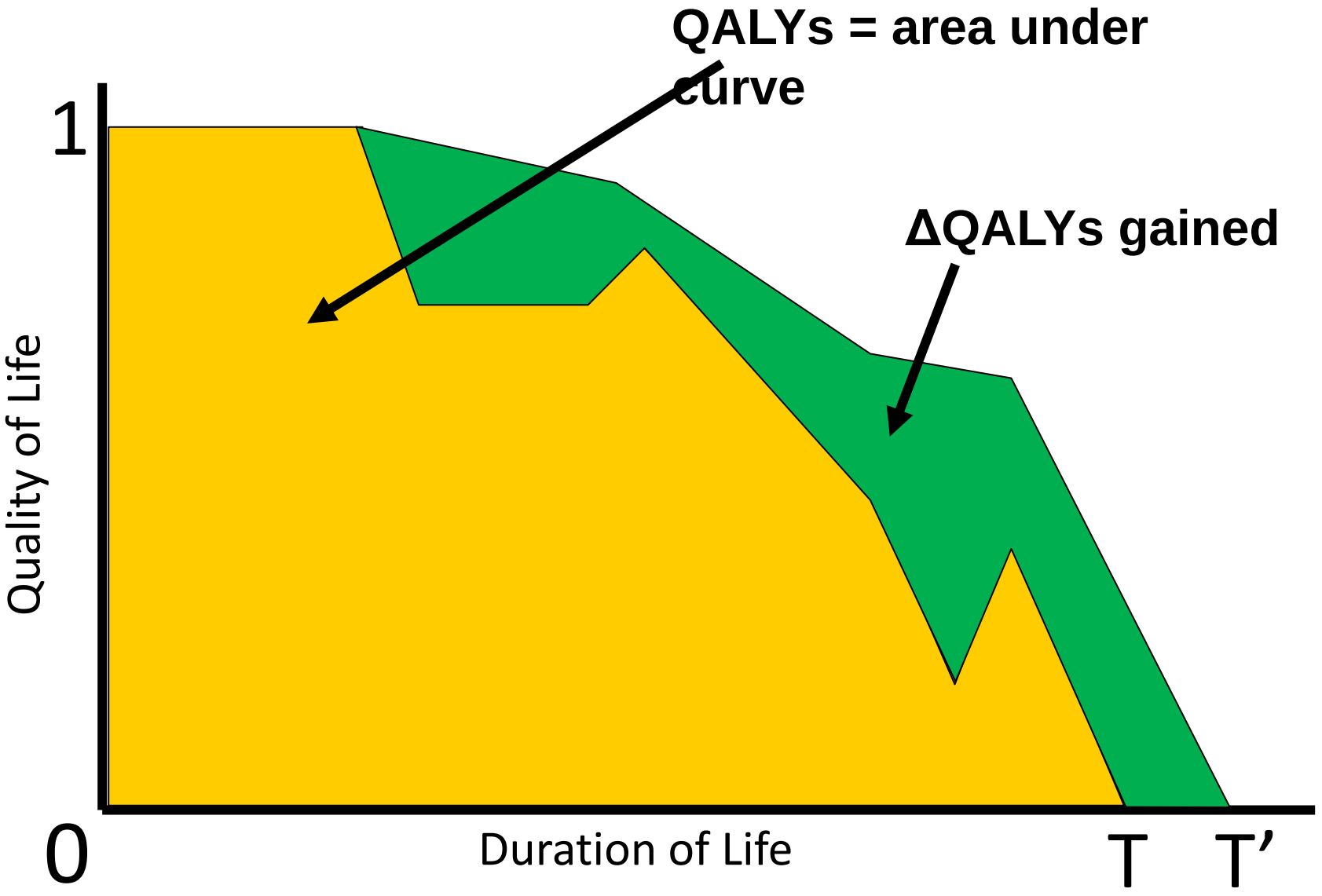
# Calculating QALYS (ignoring discounting, k=0)




**Life Years = 2.0 + 1.5 + 1.0 + 2.5 = 7.0 years**

**QALYs = (2.0)(1.0)+(1.5)(0.7)+(1.0)(0.3)+(2.5)(0.9) = 5.6 QALYs**

# A “Life Path” of health-related quality of life: Effect of intervention



# Model computations

- Our models produce the prevalence in each health state at each time under each strategy so we can easily compute total discounted QALYs for each strategy
- Similarly, if we know the costs of the interventions and the costs of living in each health state, we can compute total discounted costs for each strategy

# USING A DYNAMIC TRANSMISSION MODEL FOR COST-EFFECTIVENESS ANALYSES

OPEN ACCESS Freely available online

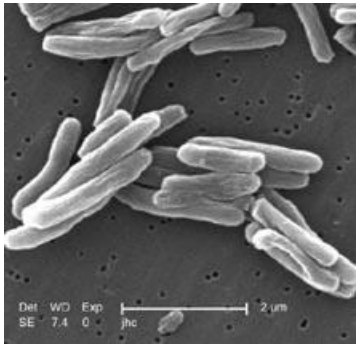
PLOS | MEDICINE

# Screening and Rapid Molecular Diagnosis of Tuberculosis in Prisons in Russia and Eastern Europe: A Cost-Effectiveness Analysis

Daniel E. Winetsky[1], Diana M. Negoescu[2], Emilia H. DeMarchis[1], Olga Almukhamedova[3], Aizhan Dooronbekova[3], Dilshod Pulatov[3], Natalia Vezhnina[3], Douglas K. Owens[4,5], Jeremy D. Goldhaber-Fiebert[5]*

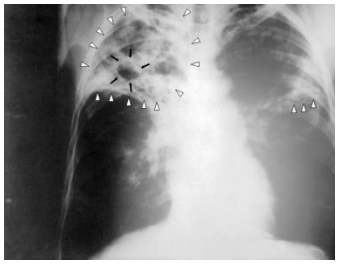
# Background on Tuberculosis

**Mycobacterium *tuberculosis***

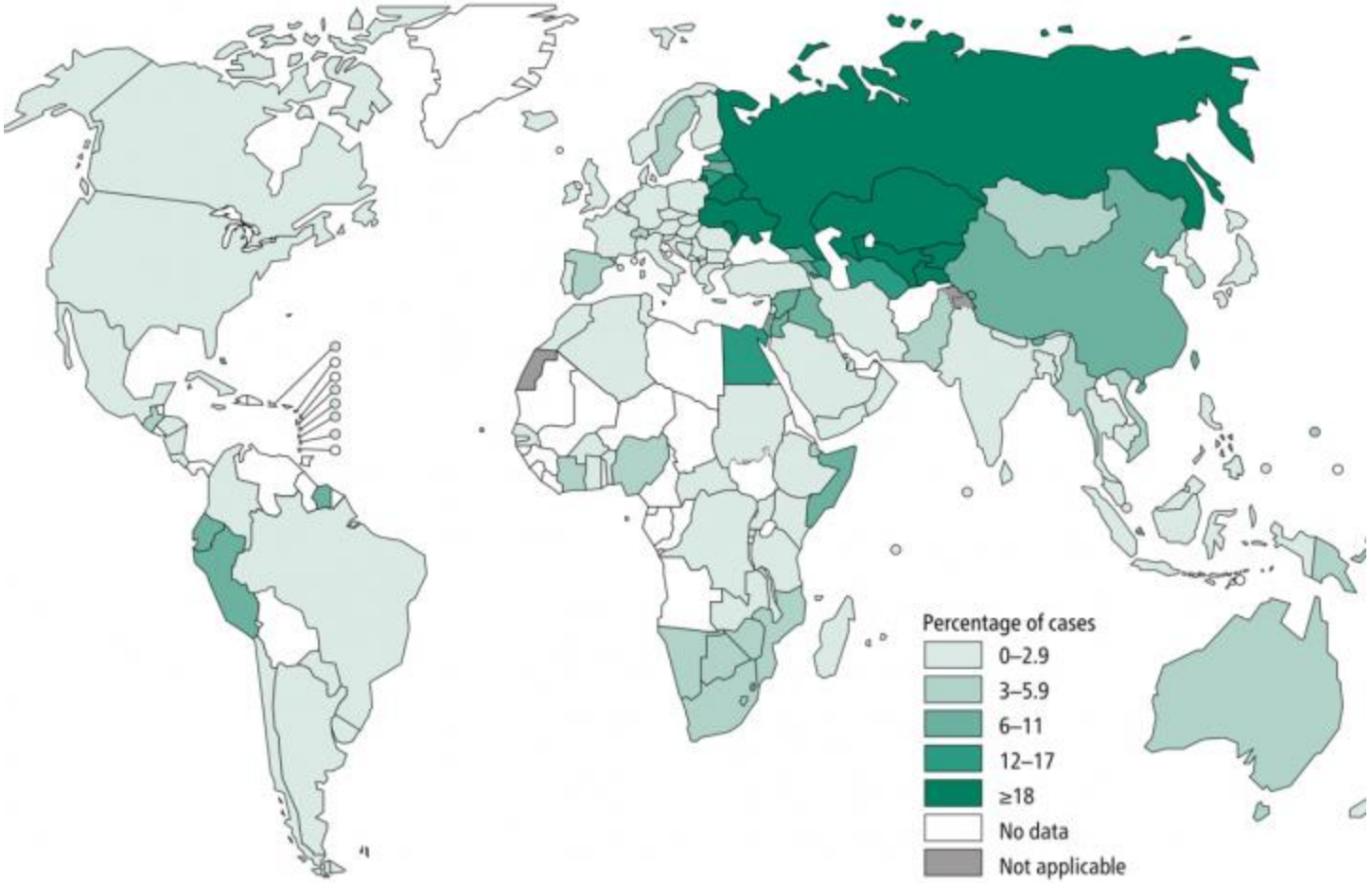



Pulmonary TB

| Drug-sensitive TB | Drug-resistant TB |
|---|---|
| 4 cheap drugs | 5-6 not-cheap drugs |
| Standard course | Individualized tx |
| 6 months | 2 years |
| $ | $$$$$$$$$$$ |

# Multi-drug resistant TB worldwide




Percentage of MDR-TB among new cases. WHO 2018

# TB in the former Soviet Union (FSU)

After the fall of the Soviet Union, TB incidence rose sharply in the newly formed countries taking its place.
The proportion of MDR-TB among new and retreatment cases has also seen a stark increase.

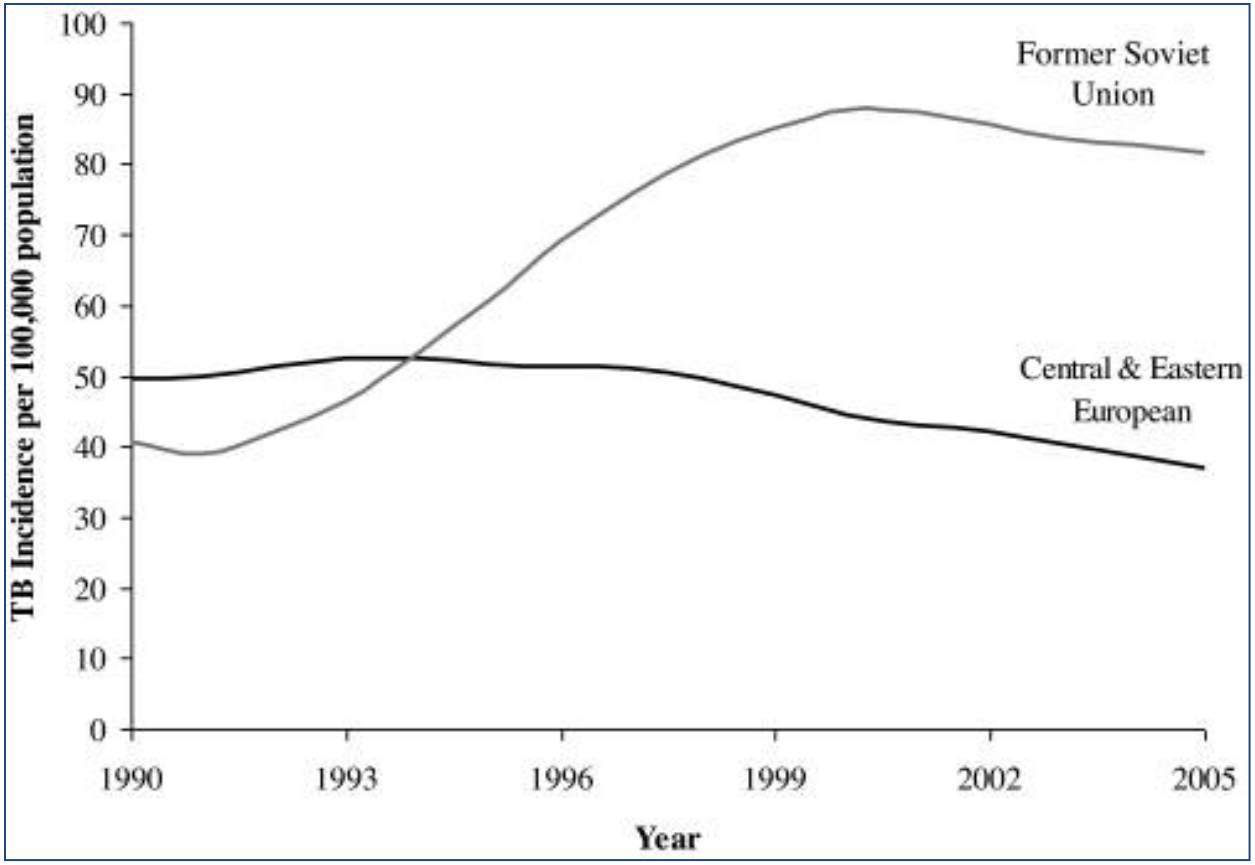



Figure from Stuckler et al. 2008

# TB and incarcerated populations

Prisons can concentrate TB, acting as an “epidemiologic pump”
In 1999-2002 there were an estimated 1.4 Million people in custody in the FSU (Walmsley 2003)

As TB incidence and the fraction coming from prisons increased in the 1990s so too did the fraction that was MDR

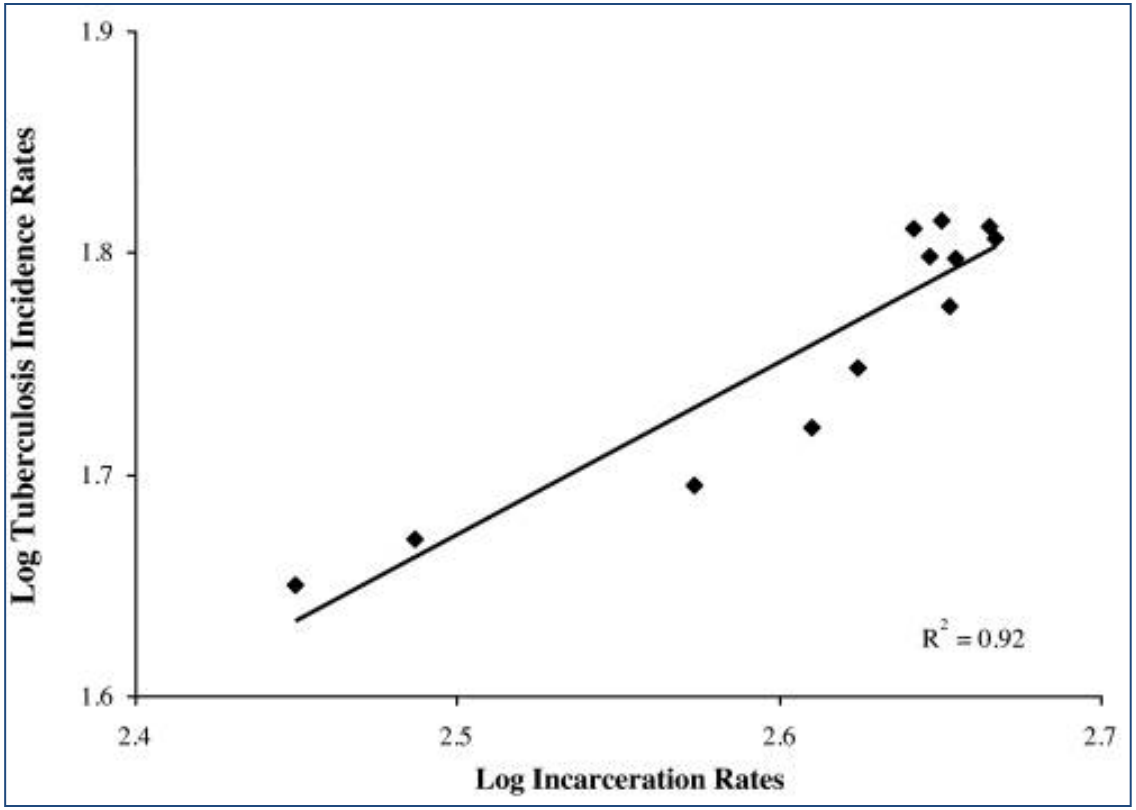



Figure from Stuckler et al. 2008

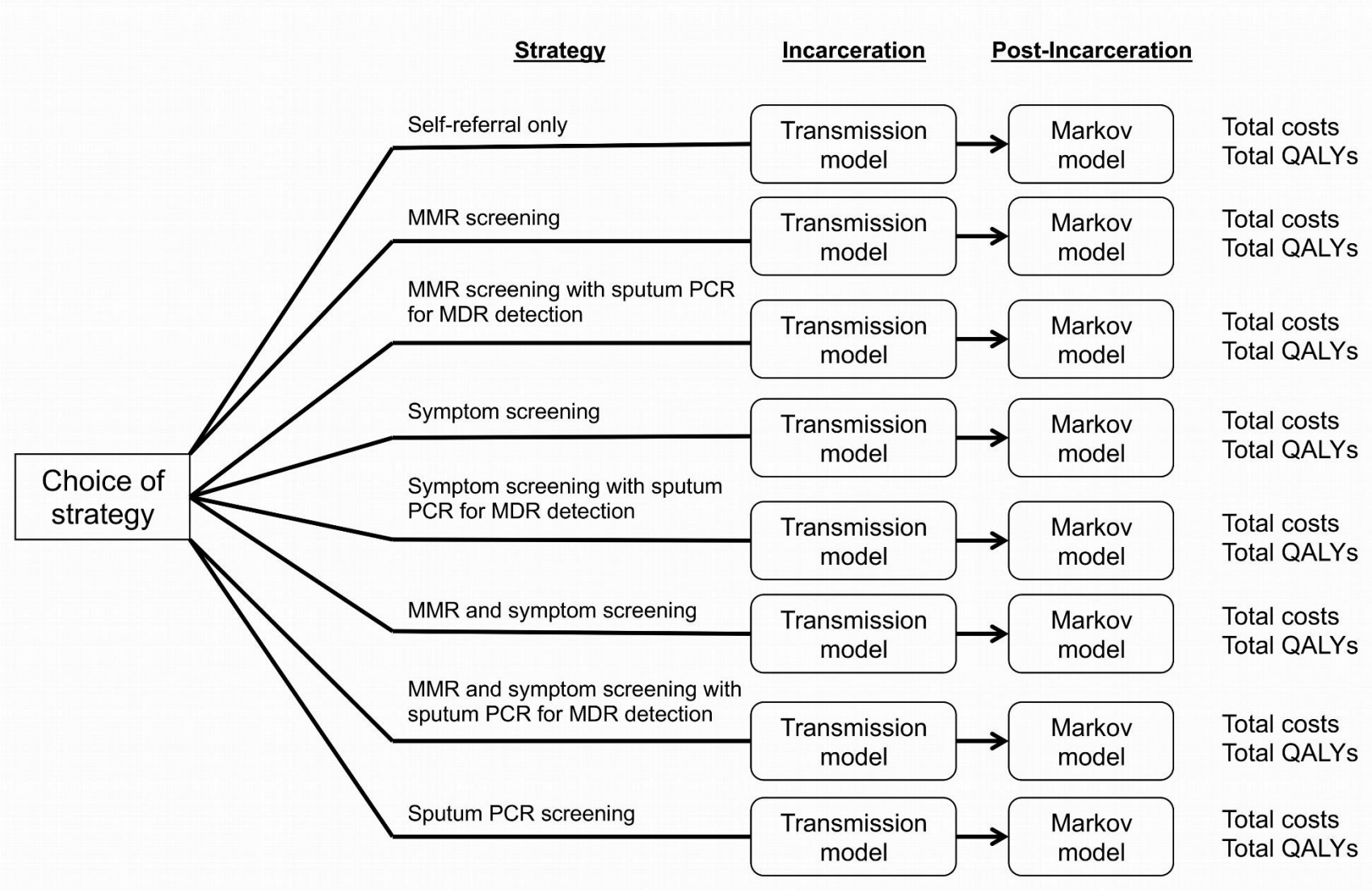
# TB diagnosis

- Symptoms
- Chest X-ray/Mass miniature radiography (MMR)
- Sputum analysis
  - Direct smear microscopy (Ziehl-Neelsen staining)
    → “smear-positive” vs. “smear-negative”
  - Polymerase chain reaction (PCR)
    - Newer and more expensive technology
    - Can be used for screening, to determine drug resistance, or both

# Research question

What is the relative effectiveness and cost-effectiveness of alternative strategies for screening and diagnosis of active TB available to prison health administrators in facilities where a substantial proportion of inmate TB cases are MDR-TB?

# Decision Model



| Diagnostic Tool | TB Form | Sensitivity | | Specificity | |
|---|---|---|---|---|---|
| | | Value | Range | Value | Range |
| **MMR** | Smear-negative | 0.80 | (0.79–0.82) | 0.98 | (0.980–0.982) |
| | Smear-positive | 0.64 | (0.59–0.69) | | |
| **Symptom screening** | Smear-negative | 0.30 | (0.28–0.32) | 0.89 | (0.888–0.892) |
| | Smear-positive | 0.58 | (0.54–0.63) | | |
| **Sputum PCR** | Smear-negative | 0.68 | (0.61–0.74) | 0.99 | (0.98–1.00) |
| | Smear-positive | 0.98 | (0.97–0.99) | | |
| **Sputum PCR for rapid MDR-TB detection** | MDR | 0.98 | (0.95–1.00) | 0.98 | (0.97–0.99) |

- **Symptom screening has the lowest sensitivity**
- **MMR (x-ray) and PCR are 1 and 2 for detecting smear+ and smear- TB**
- **Specificity is high except for symptom screening**

- **How will this matter for the effectiveness of each strategy?**

| | |
|---|---|
| **Screening/Diagnostic Method** | |
| MMR | $4.85 (3.64–6.06) |
| Symptom screening | $2.19 (1.64–2.74) |
| Sputum smear | $2.16 (1.62–2.70) |
| Sputum PCR | $24.08 (18.06–30.09) |
| **Treatment** | |
| Drug sensitive TB (smear-negative) | $364.45 (273.39–455.65) |
| Drug sensitive TB (smear-positive) | $441.42 (331.11–551.85) |
| Multi-drug resistant TB | $7,961.02 (5,970.90–9,951.50) |

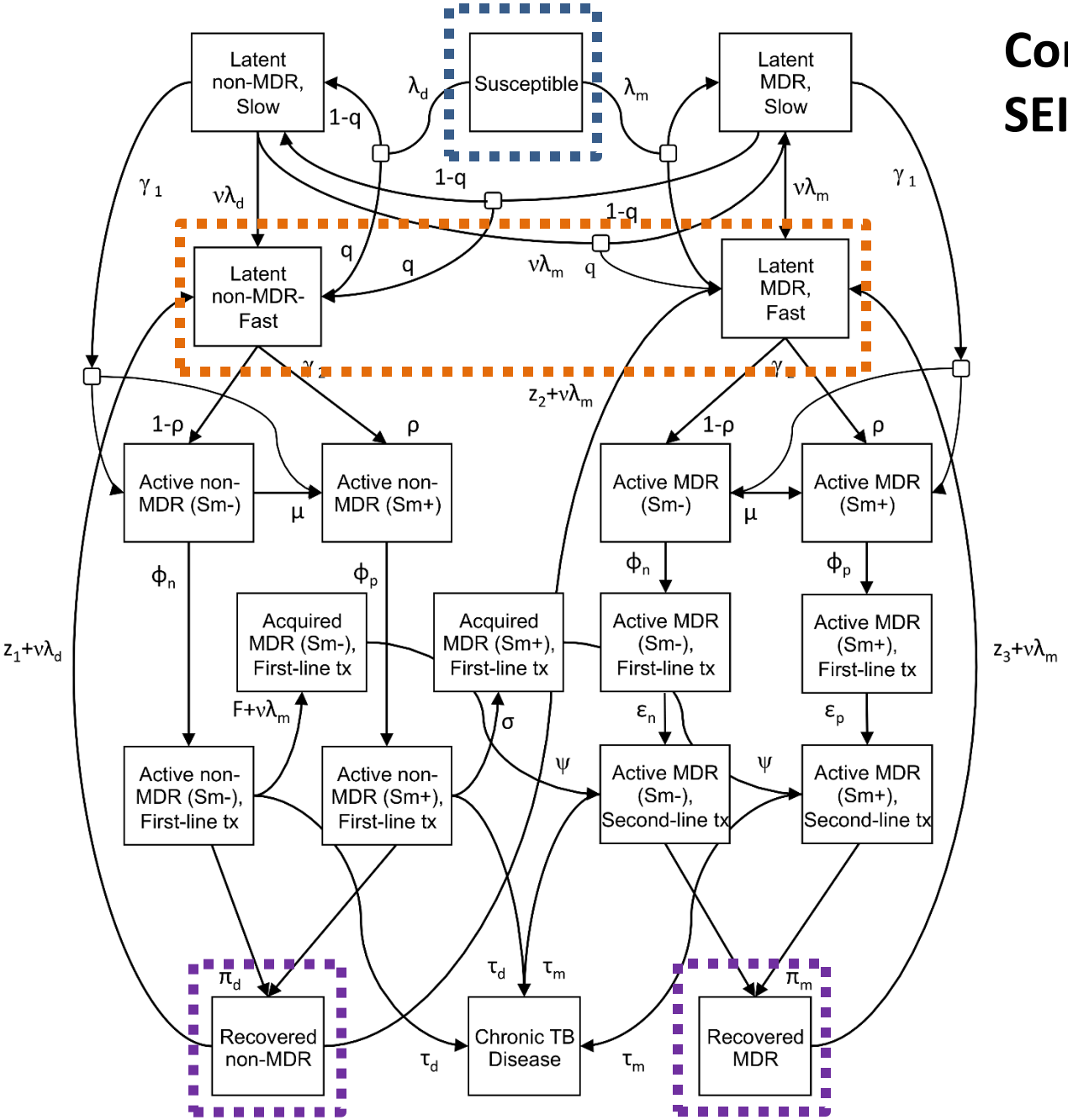
- **Symptom screening is cheapest**
- **PCR is the most expensive**
- **DS treatment is 1/20 the cost of MDR treatment**

- **How will more sensitive strategies' costs depend on this? How about more specific strategies?**
- **What will happen for the costs of strategies that can differentiate MDR-TB?**

# Modeling framework and overview

- A prison in the FSU (3 specific countries used in paper)
- Stable prison population of 1,000 with density-dependent homogenous mixing.
- 1/3 of population leaves every year with equal probability from all health states; replaced by the same # of new inmates
- Those entering the prison each year reflect the epidemiology of general population in FSU and sensitivity of initial MMR screen

**Figure S2.** Transmission model for natural history, diagnosis and treatment of tuberculosis




**Complicated SEIR model**

**Figure S2.** Transmission model for natural history, diagnosis and treatment of tuberculosis

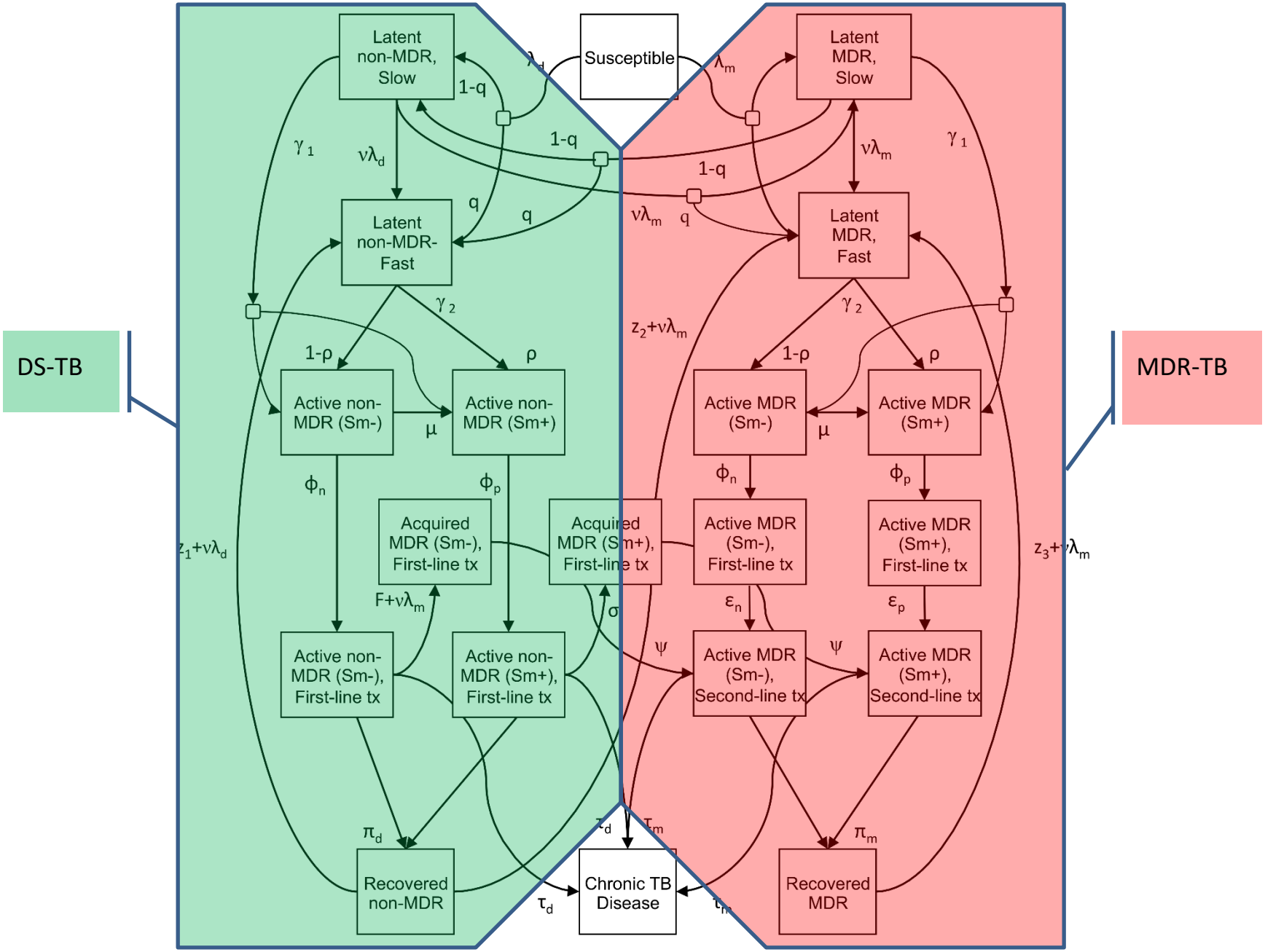
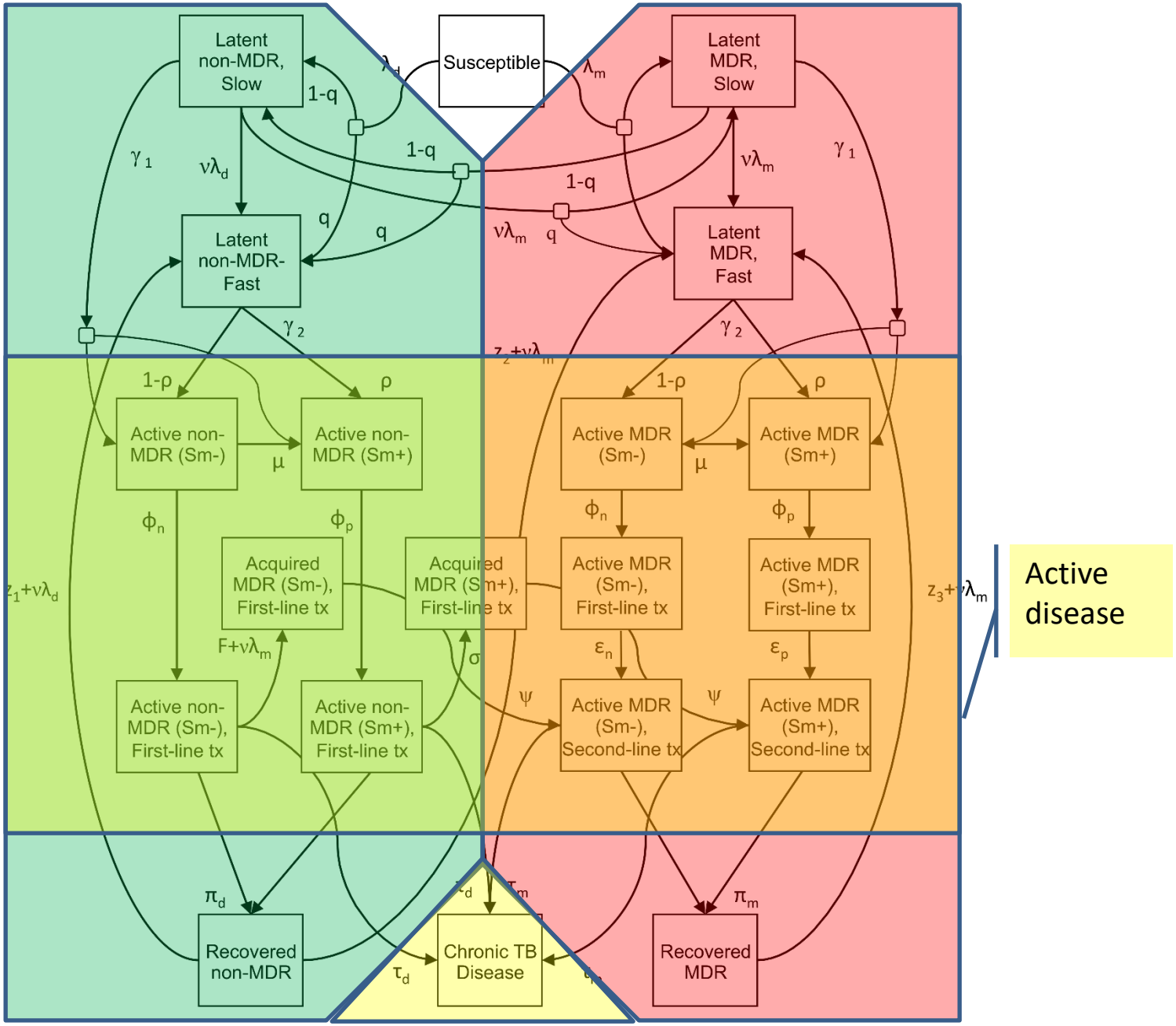


**Figure S2.** Transmission model for natural history, diagnosis and treatment of tuberculosis



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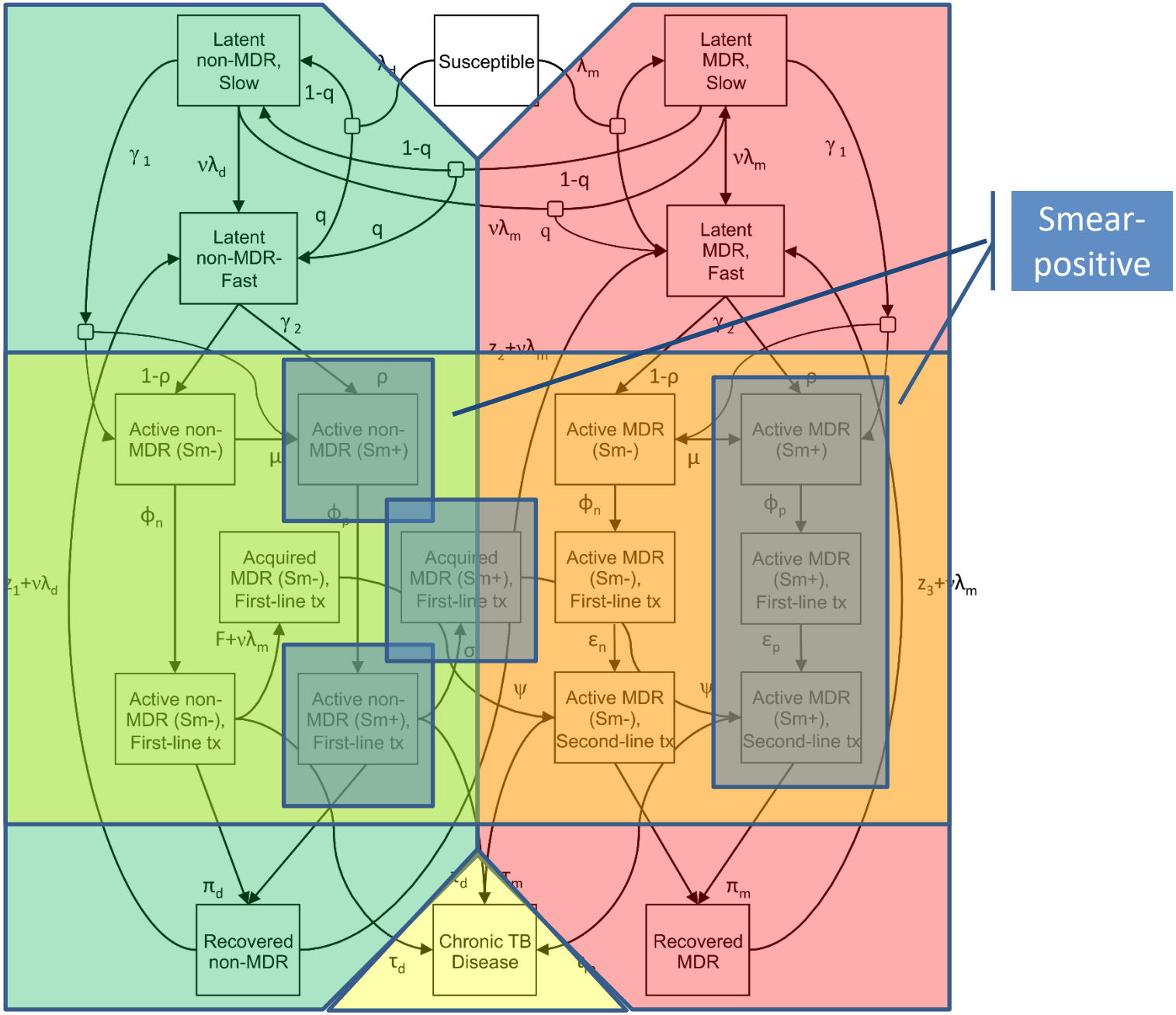

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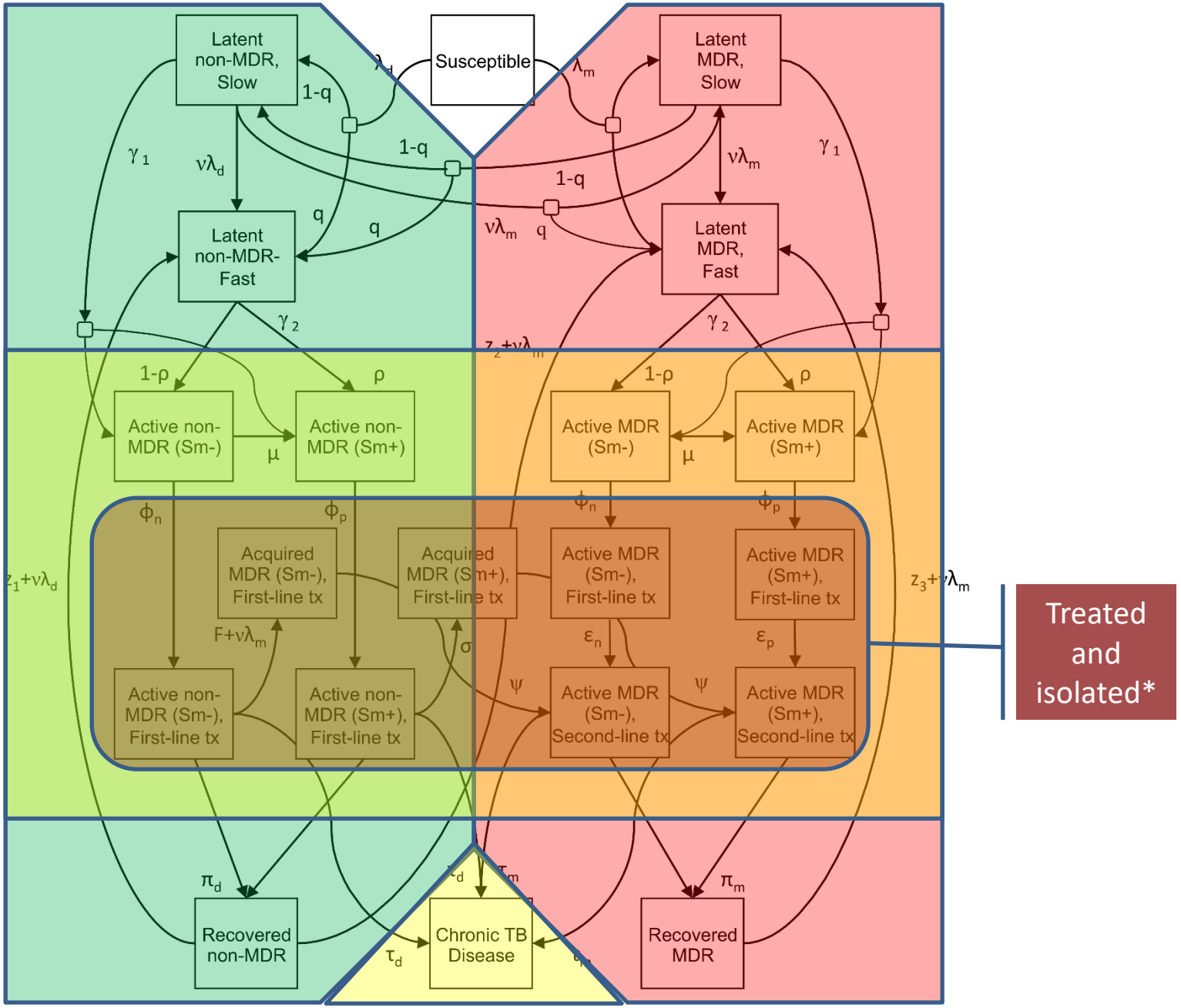

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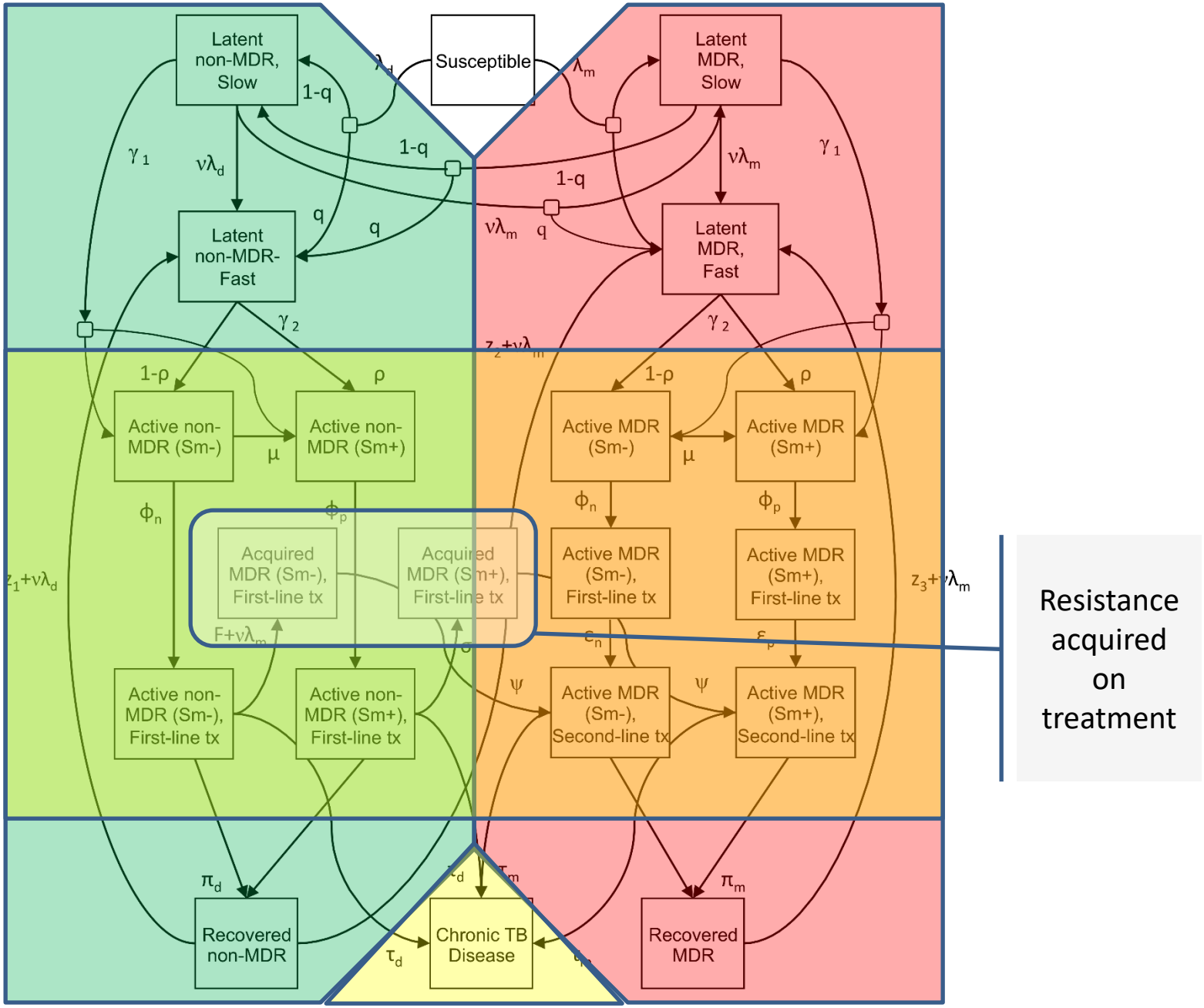

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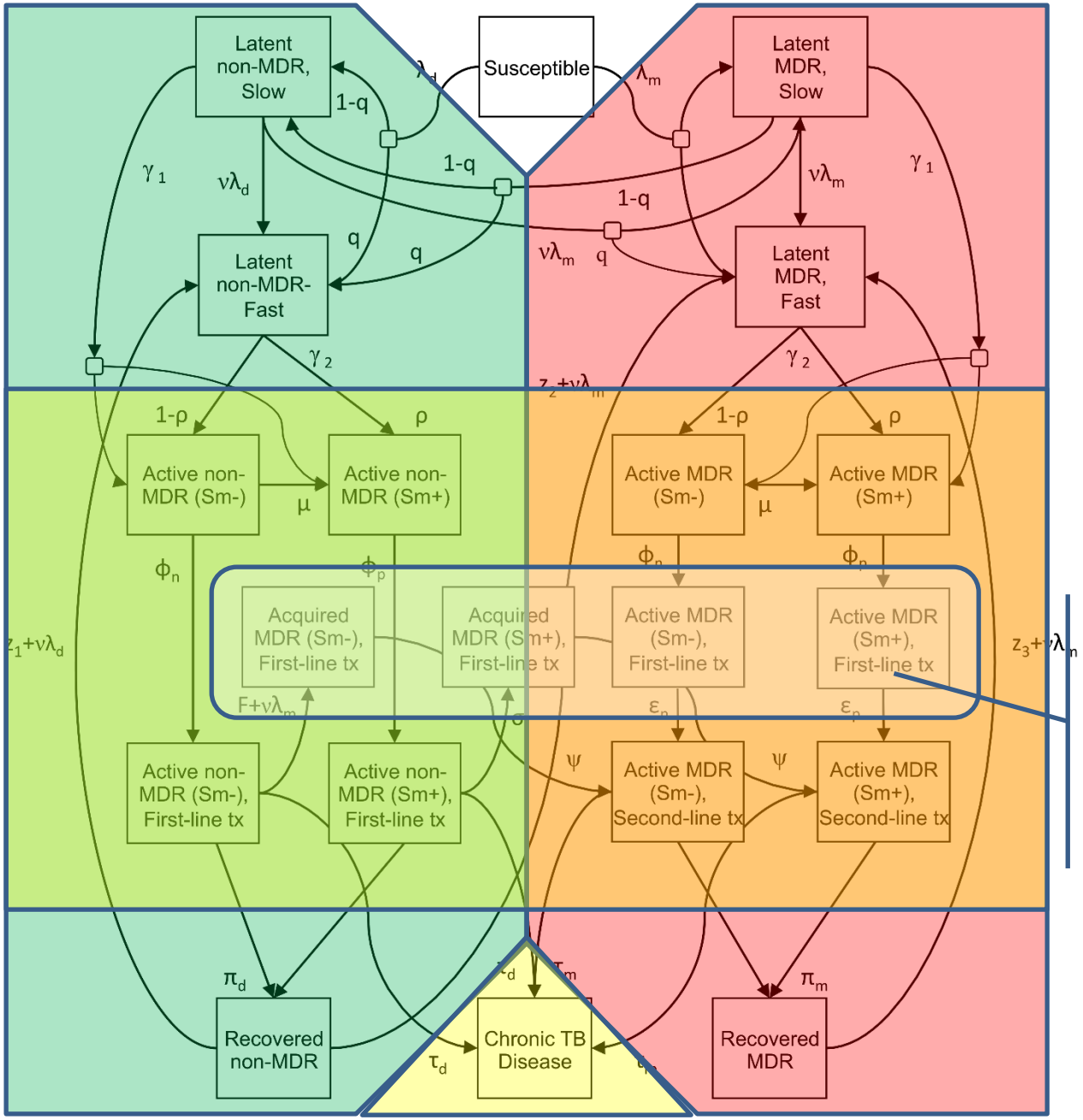

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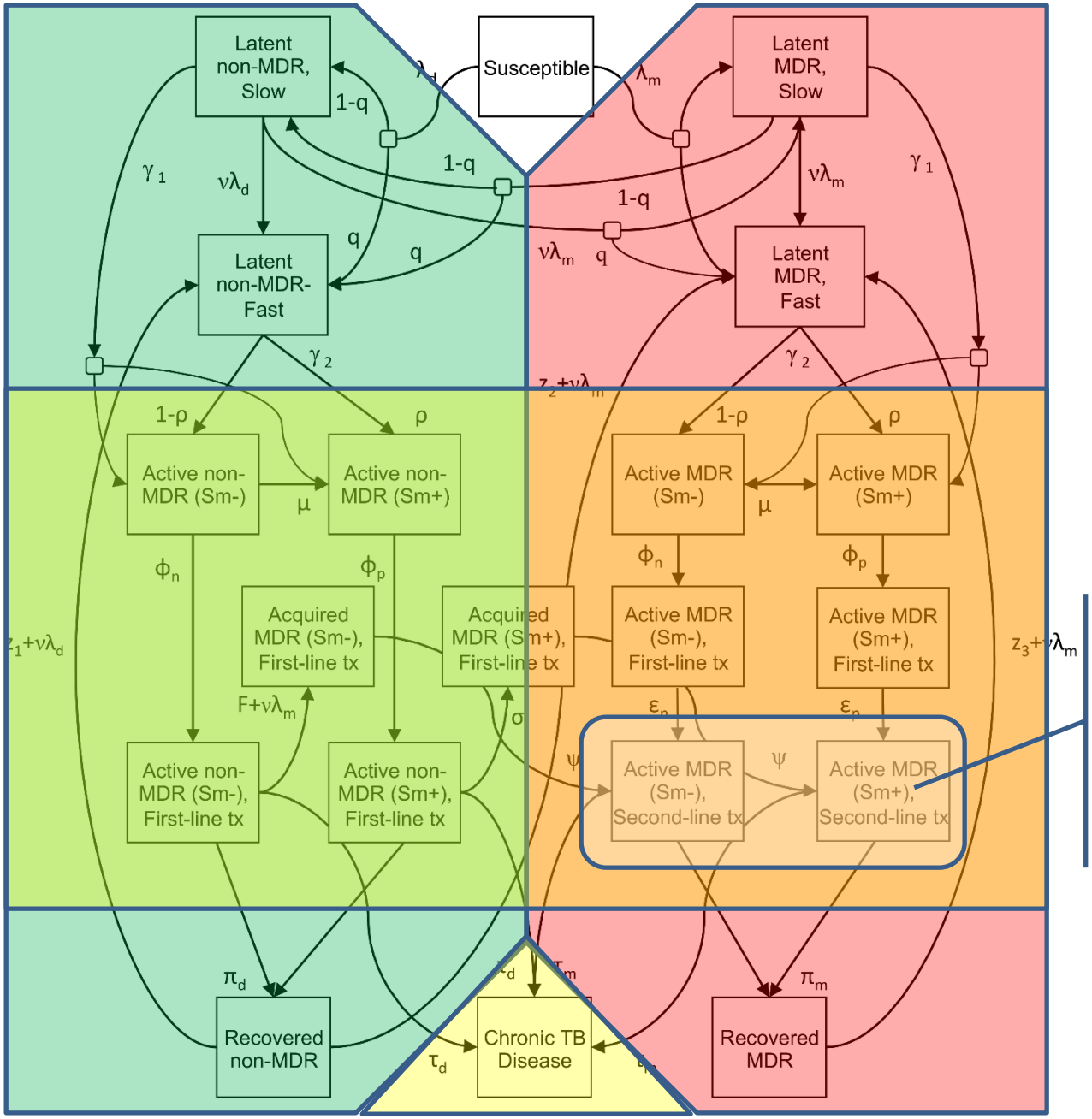
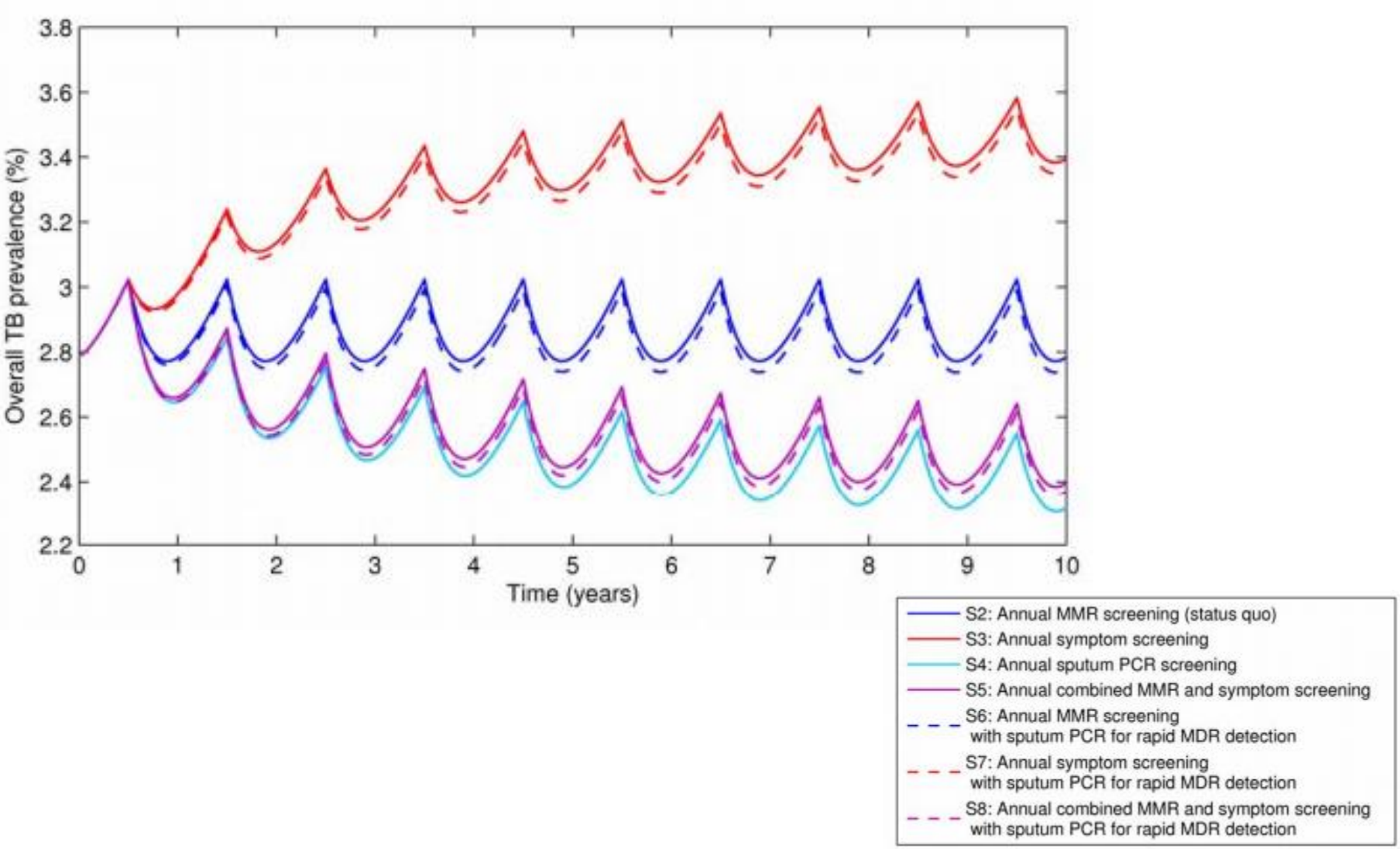
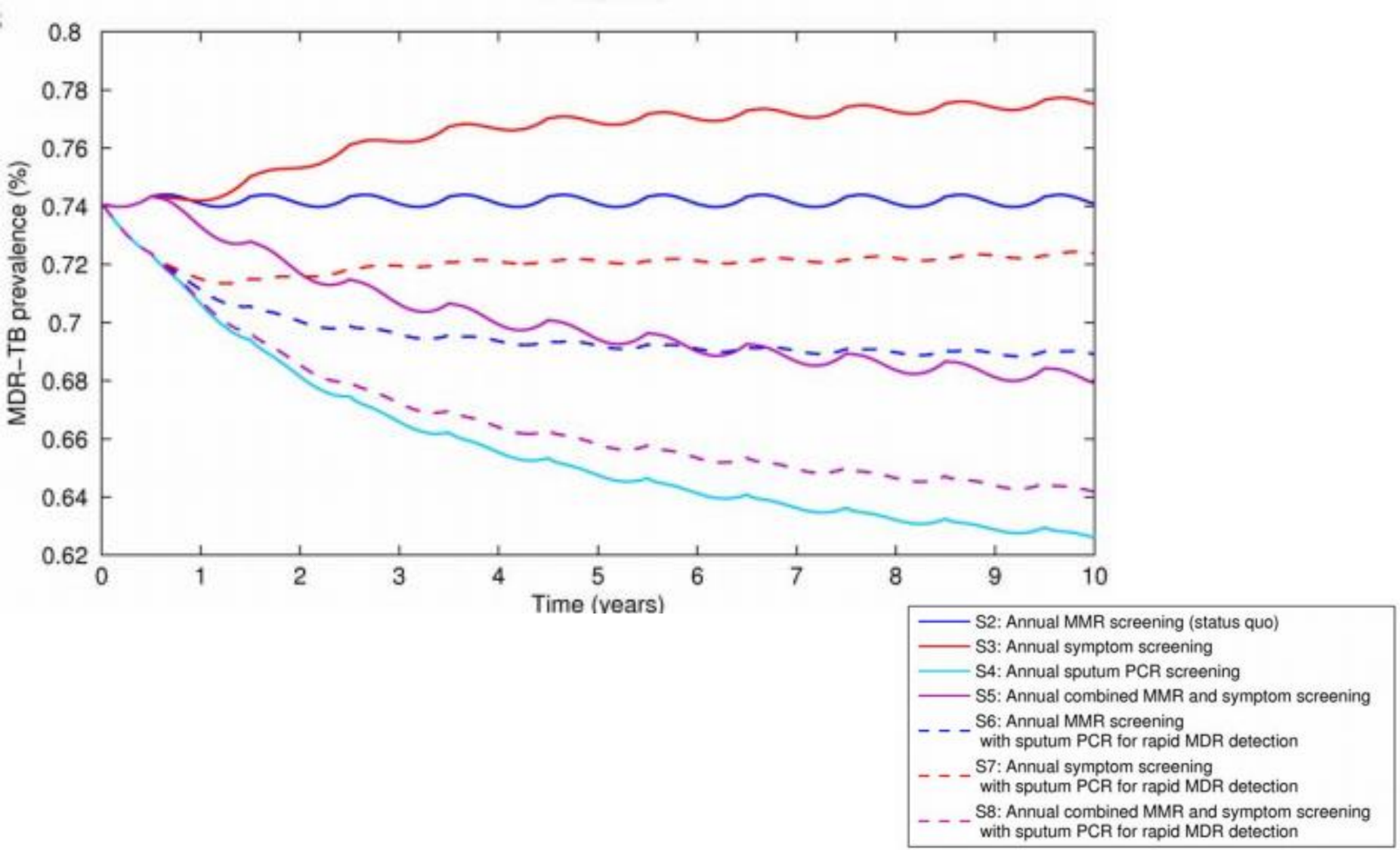


**Symptom screening is less effective on TB prevalence than status quo; PCR or combo symptom screening/MMR more effective; Adding PCR for MDR testing only has little effect on TB prevalence**

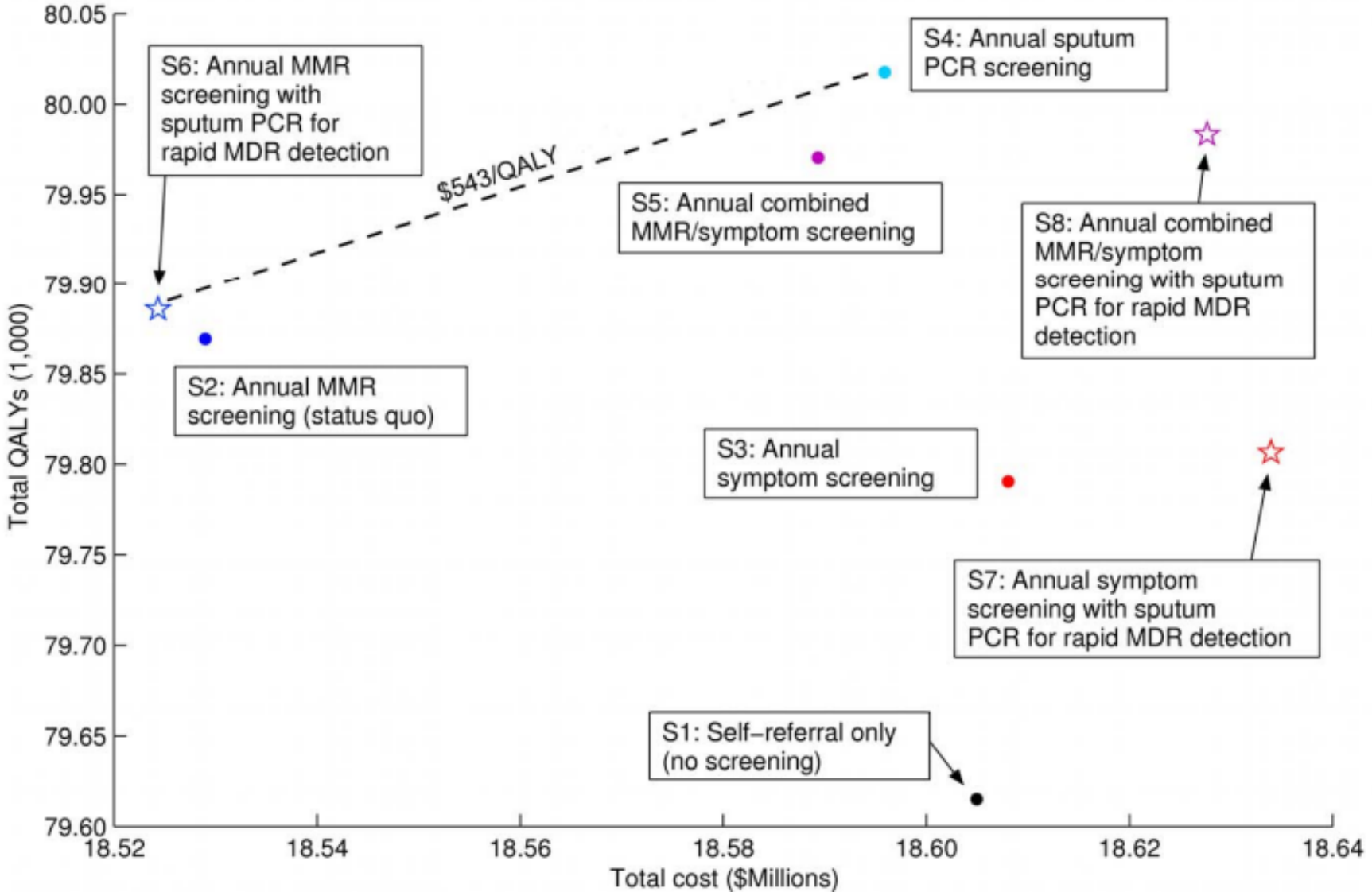


# For MDR prevalence (~30% of overall cases in status quo), effectiveness story is very different

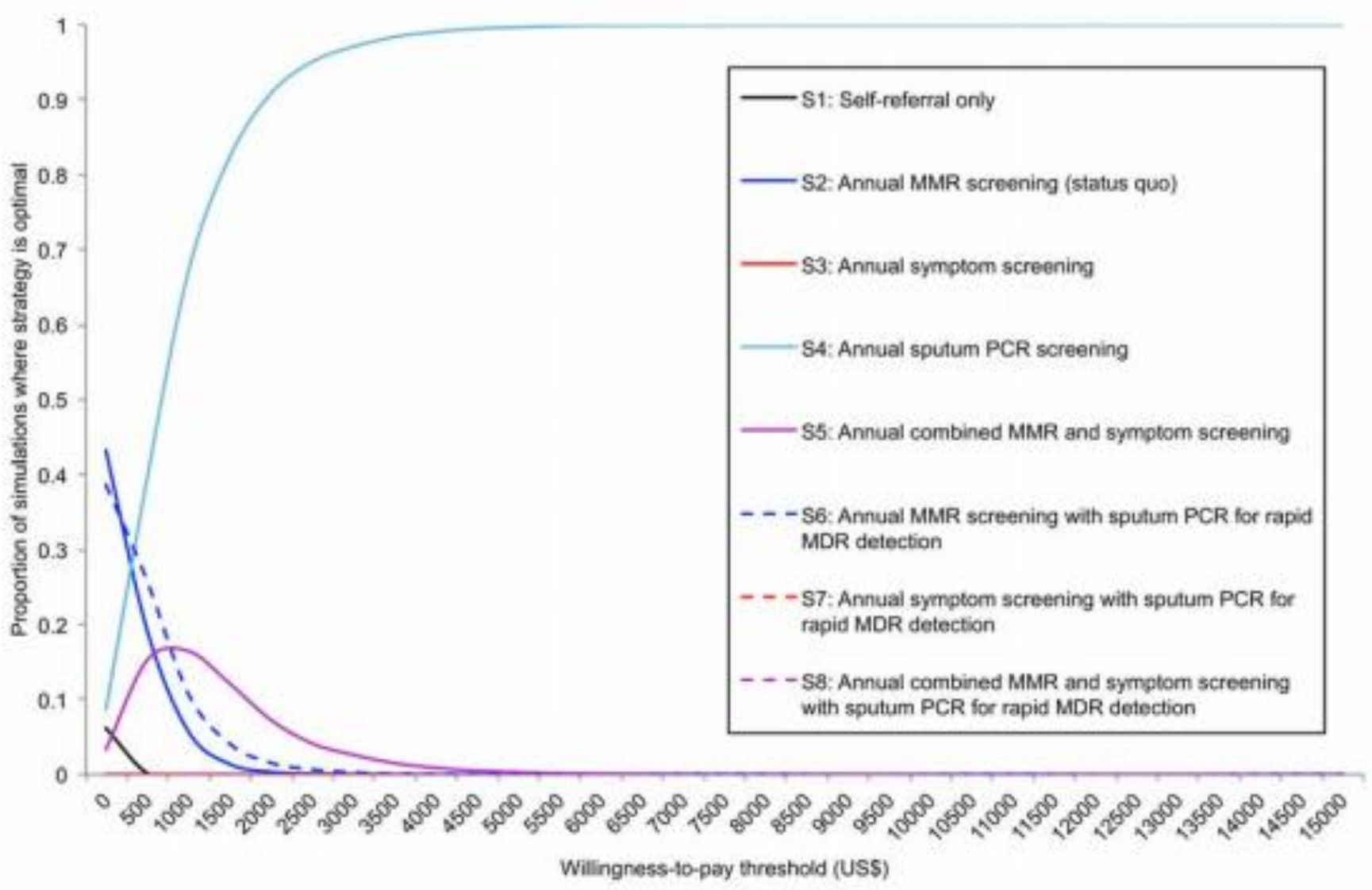


# Cost-effectiveness plane and frontier.

# What strategy should we choose?



# Advanced topic: Which strategy is most likely to be the cost-effective strategy?

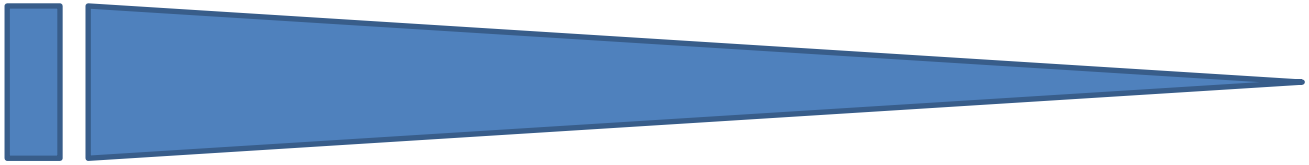


# ADVANCED TOPIC: SPECIAL CONSIDERATIONS WHEN USING A DYNAMIC TRANSMISSION MODEL FOR COST-EFFECTIVENESS ANALYSES (COHORTS VS. POPULATION MODELS)

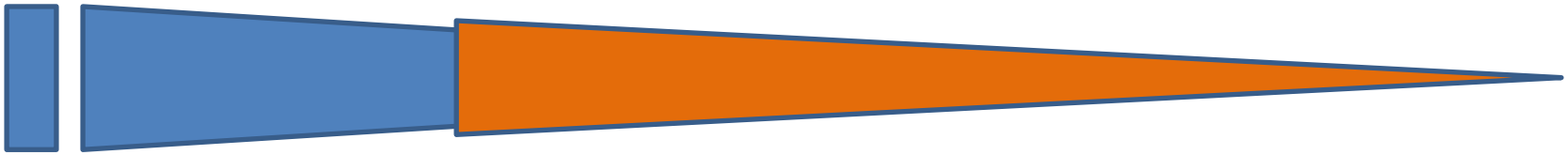
# For comparison: CEA with Cohort (Closed) Models with no Transmission

**Starting time t=0: Cohort (often a birth cohort) so everyone the same age**

**Without intervention, follow cohort over its remaining lifetime counting discounted QALYs and costs**



**With intervention: Count discounted lifetime QALYs and costs; starting intervention at time ($t=t_i$) has chance to alter these quantities**

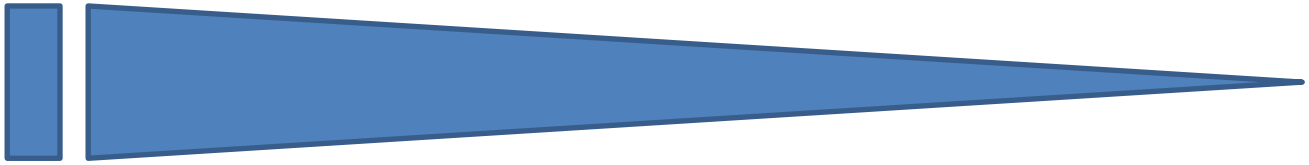


**<u>Only 1 relevant time horizon: cohort's lifetime horizon</u>**

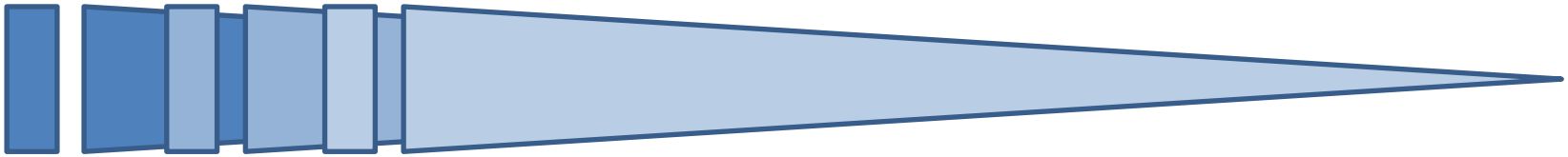
# For comparison: CEA with Open Models (especially with Transmission)

**Starting time t=0: Cohort (often a birth cohort) so everyone the same age**

**Without intervention, follow cohort over its remaining lifetime counting discounted QALYs and costs**



**However, with open population models, new cohorts enter at times after t=0. There is no single "lifetime" horizon for the population**



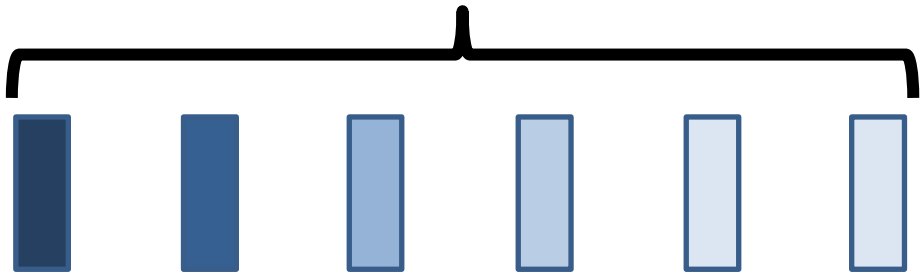
**<u>So what are the appropriate horizon(s)?</u>**

# Time Horizons for CEA with Open Models (especially with Transmission)

**We introduce the notion of an "analytic horizon" in addition to a "lifetime horizon"**

- **The analytic horizon (in general) is defined by the time over which the intervention(s) is directly relevant**
- **Benefits for any person/cohort alive during the analytic horizon should be counted over their lifetime**

**Analytic Horizon (e.g., 20 years)**



***t=0*** ***t=AH***

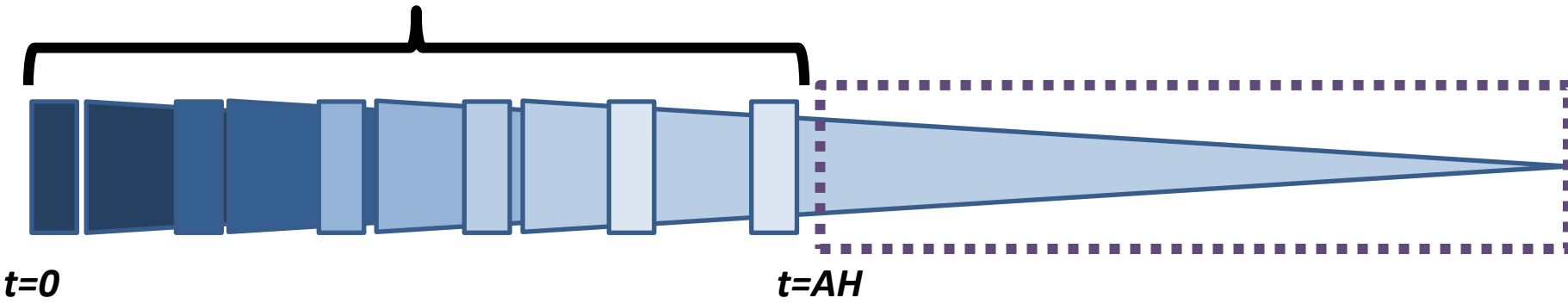
**During the analytic time horizon, QALYs and/or costs of those alive can change due to intervention(s) which means that the numbers of people surviving to the AH may be different and in different health states than w/o the intervention (e.g., more uninfected people alive because transmission was reduced). <u>What should we do about these survivors in terms of taking a "lifetime horizon" for them?</u>**

# Time Horizons for CEA with Open Models (especially with Transmission)

**After "analytic horizon", goal: count up the remaining QALYs & costs (discounted)**

- **Ignore additional births (cohorts) entering the model for t>AH**
- **Ignore additional transmission effects after t>AH**
- **Need to ensure we not only discount back to from t>AH to t=AH but actually back to t=0**

**Analytic Horizon (e.g., 20 years)**




**How would you implement this post-AH counting of QALYs and costs?**
**How would you assess whether the length of the AH matters for your ICER estimates?**
**If it matters, how would you address this (generally)?**

# Time Horizons for CEA with Open Models (especially with Transmission)

**How would you implement this post-AH counting of QALYs and costs?**
**How would you assess whether the length of the AH matters for your ICER estimates?**
**If it matters, how would you address this (generally)?**

**How would you implement this post-AH counting of QALYs and costs?**

1. **Could run the model with births and transmission turned off**
2. **Could flow anyone alive at the end of the AH into simple Markov models**

**How would you assess whether the length of the AH matters for your ICER estimates?**

1. **Run analysis with different AH durations and see**
2. **Could probably theorize about it more, but I think harder to know for sure**

**If it matters, how would you address this (generally)?**

1. **This means that transmission even far in the future is having an effect. Probably implies that the relevance of the decision is actually longer. In any case, report the results for a range of AH durations.**

# Important Announcements