Bayesian Modeling Assessing the **E**ffectiveness of a Vaccination **St**rategy to Prevent HPV-related Diseases: the BEST Study

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Outline of presentation

1. **Health economic evaluations**
2. Markov models
3. HPV and its clinical management
4. Statistical modelling
   - Distributional assumptions
5. Cost-effectiveness analysis
6. Conclusions

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Health economic evaluations

- **Objective**: Combine costs & benefits of a given intervention into a rational scheme for allocating resources
  - Recently, models have been built upon more advanced statistical foundations
  - This problem can be formalised within a statistical decision-theoretic approach. Rational decision-making is effected through the comparison of expected utilities

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- Increasingly under a Bayesian framework
  - David Spiegelhalter (2006). *Bayesian methods, health technology assessment, and performance monitoring*. Report on progress 2001-2006 for MRC Unit's Quinquennial Review
    - Specific focus on Bayesian decision-theoretic development of cost-effectiveness analysis
  - Contributions by several scholars and research groups
    - Tony O'Hagan (University of Sheffield — Centre for Bayesian Statistics in Health Economics)
    - Karl Claxton, Mike Sculpher (University of York)

Markov models

- Assume a set of "clinically relevant" states
  - Exhaustive and mutually exclusive
- The structure (links among nodes) describes the dynamics of disease history
  - Arrows connecting two states encode the assumption that a transition from the one where the arrow originates to the one reached by it is possible
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  - Absence of an arrow between two states implies that the transition from one to the other is not allowed by our model
- From one period to the next, subjects can move among the states according to the rules specified by the arrows
- Movements occur according to suitable *transition probabilities*

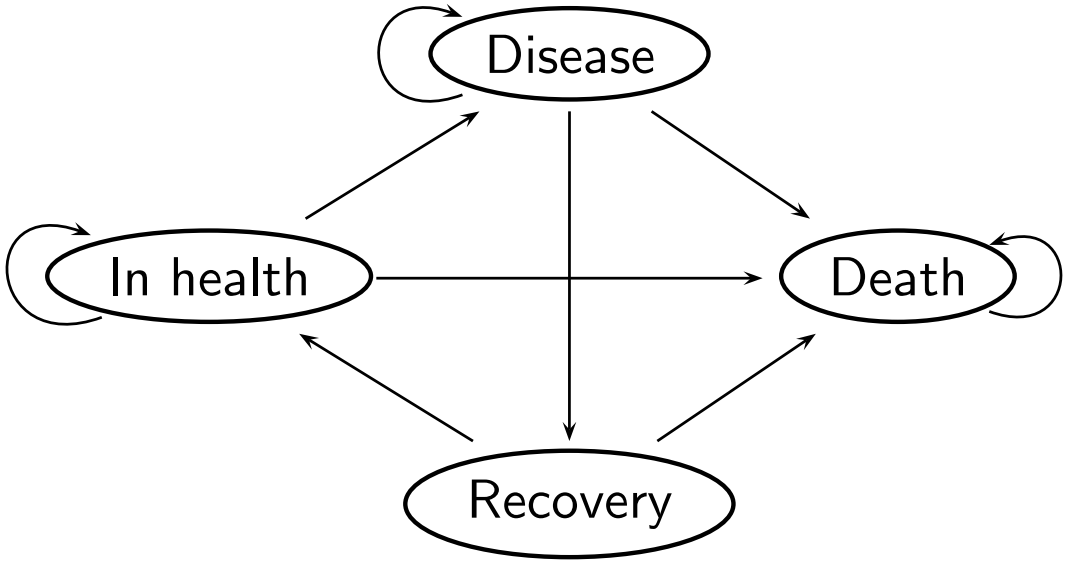
$$\mathbf{p}_t = \mathbf{p}_{t-1}\mathbf{\Lambda}_t$$

where

- $\mathbf{p}_t$ is the vector of probabilities for each state at time t
- $\mathbf{\Lambda}_t = [\Lambda_{t;j,h}]$ is a transition matrix describing the probability of moving from state j to state h at time t

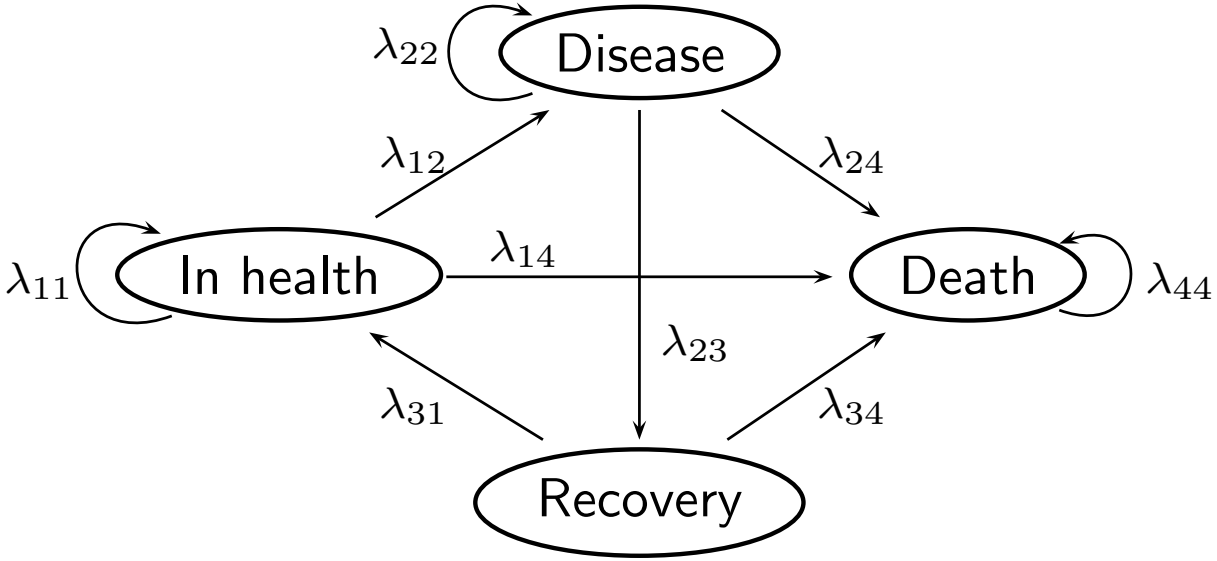
Markov models

1. Define a structure

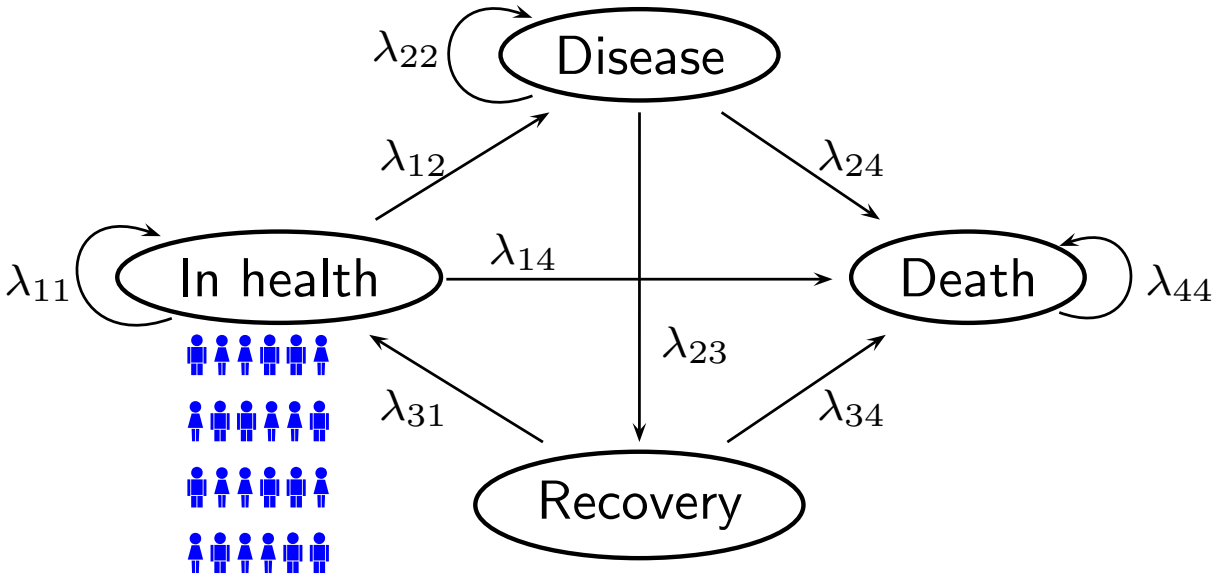


Markov models

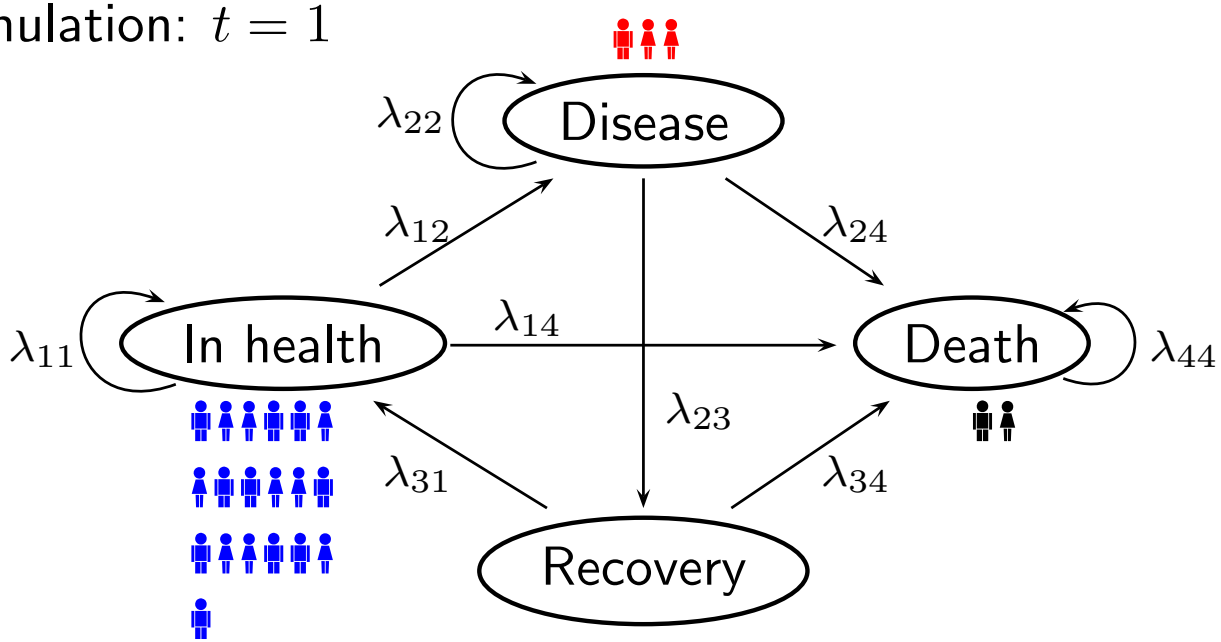
2. Estimate the transition probabilities



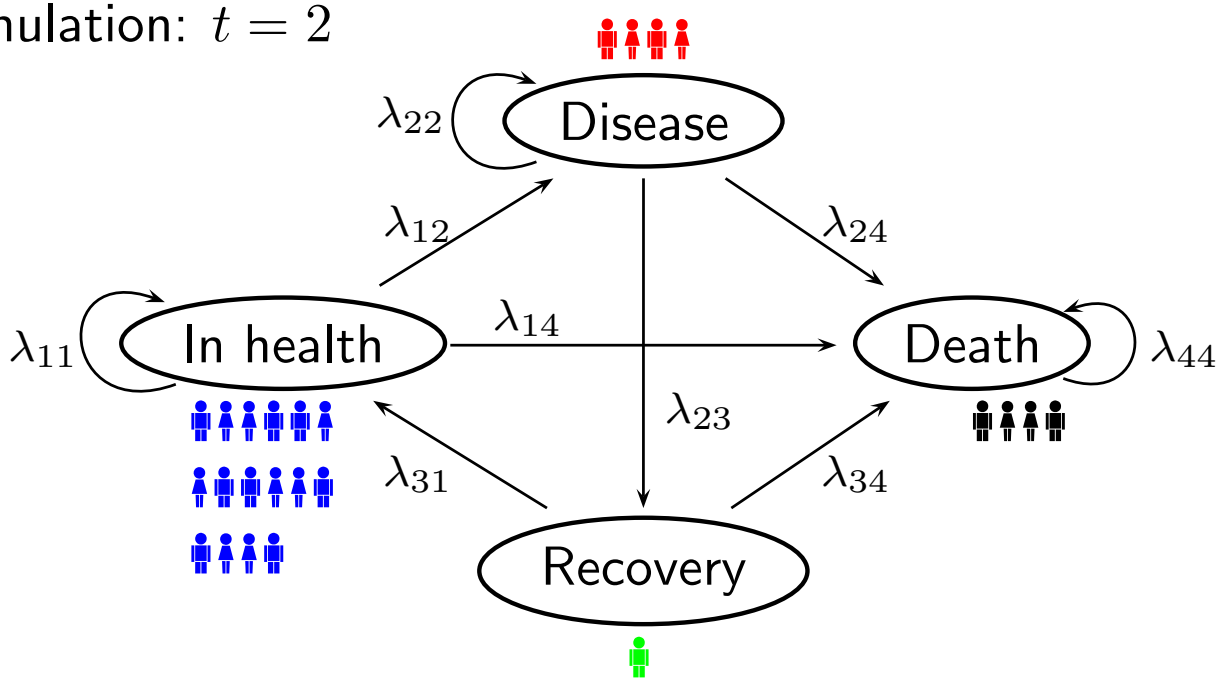
3. Run the simulation: $t = 0$



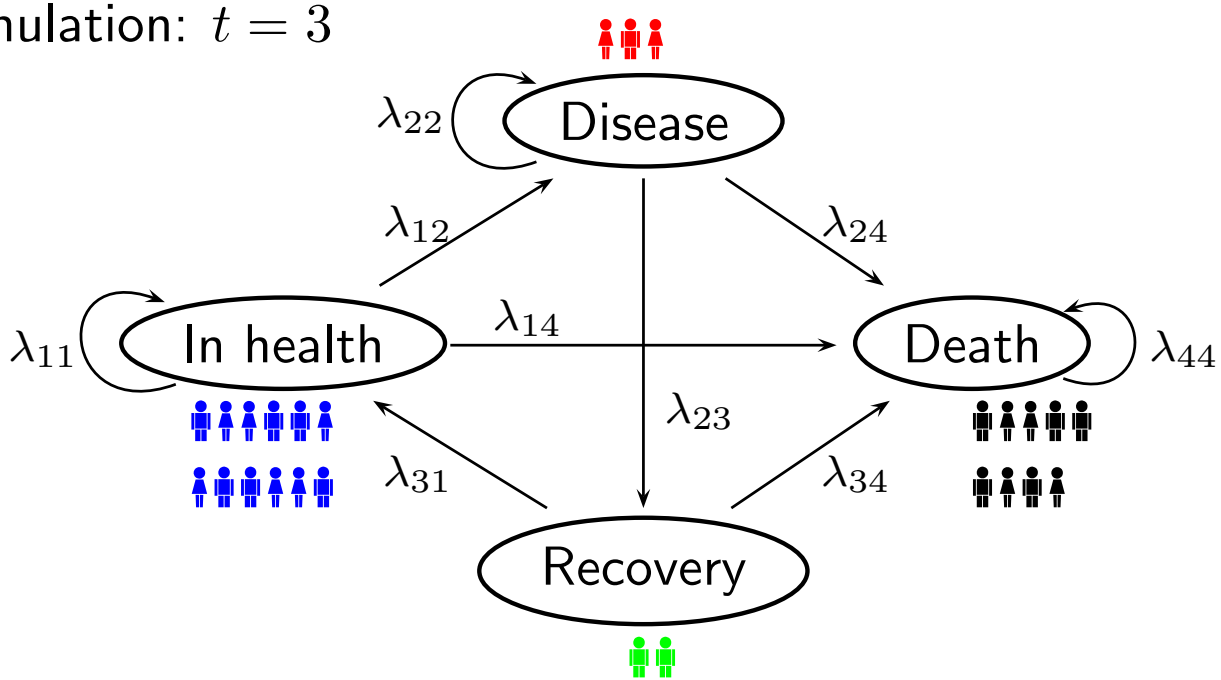
3. Run the simulation: $t = 1$



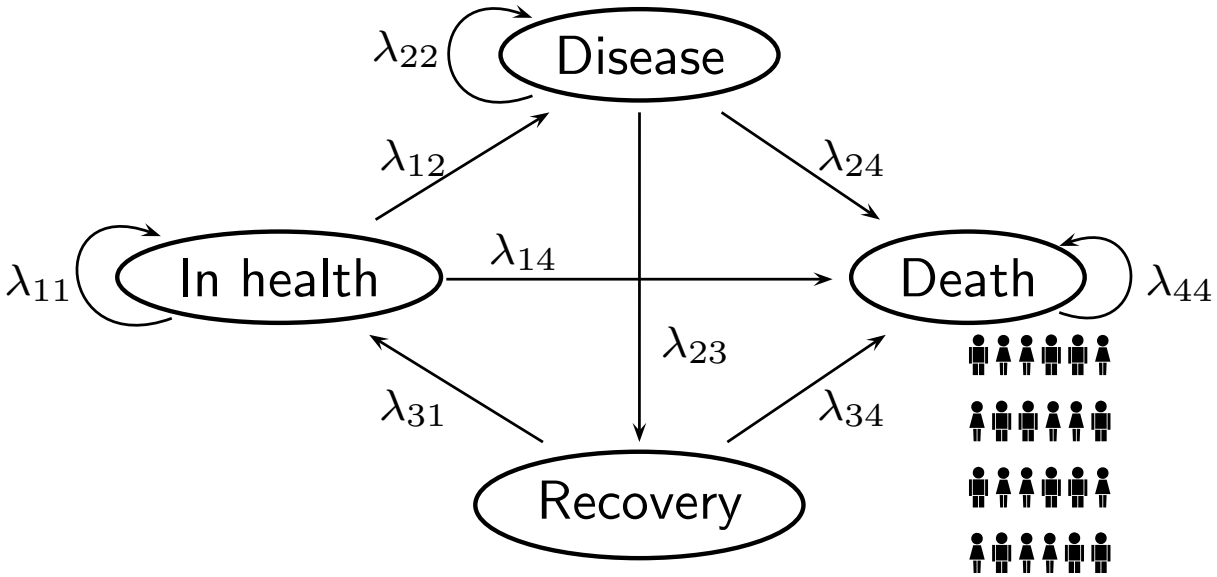
3. Run the simulation: $t = 2$



3. Run the simulation: $t = 3$



3. Run the simulation: $t = T$



HPV and its management

- Human Papillomavirus (HPV) is the *primum movens* both in the etiopathogenesis of invasive cervical cancer and in other malignant and benign neoplastic lesions
- In most western countries, screening programmes have been established to detect and treat early instances of infection-related diseases
- Vaccination programmes have been suggested as an effective alternative, but the disease process is complicated so there is uncertainty over the cost-effectiveness

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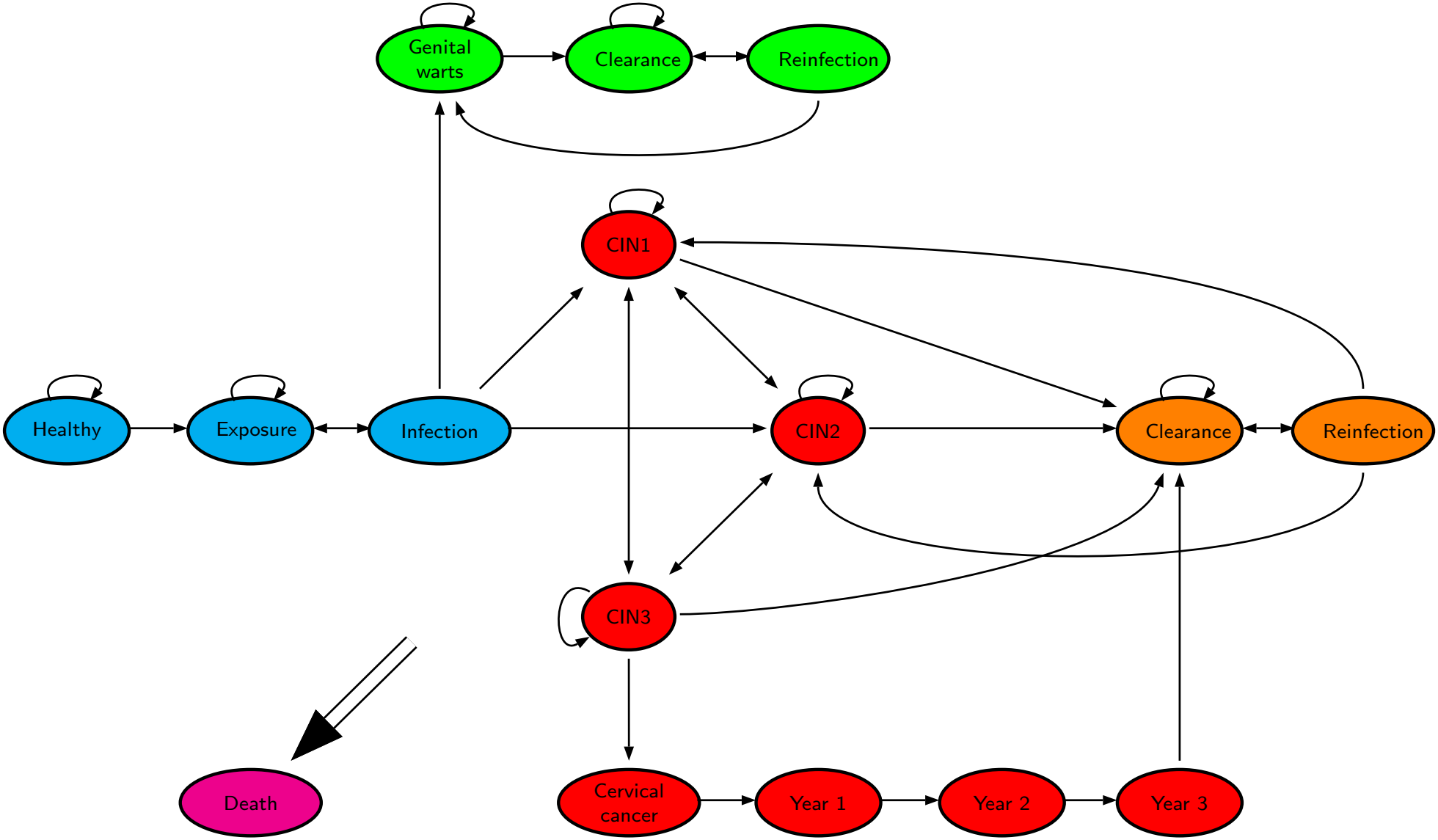
- Our objective is compare the two interventions
  - $i = 0$: screening only (current standard)
  - $i = 1$: screening + multi-cohort quadrivalent vaccination

What's the story?



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- In case hard data were not directly available, we encoded the information provided by literature review or expert opinion elicitation in suitable informative prior distributions
- Moreover, we used official data from registry or population databases to get information on the age-specific mortality rates, incidence of genital warts and probability of sexual activity

Model parameters assumptions (example)

Vaccine-related parameters

Variable	Description	Distributional assumption	Mean	95% Cred Int	
γ	Vaccine effectiveness	Informative LogNorm	0.7830	0.6830	0.8960
μ	Vaccine compliance	Flat Beta	1.0000	0.9990	1.0000
α	Vaccine coverage rate	Flat Beta	0.8470	0.8340	0.8600
ω_1	Probability 1 shot	Flat Dirichlet	0.0000	0.0000	0.0010
ω_2	Probability 2 shots	Flat Dirichlet	0.0000	0.0000	0.0010
ω_3	Probability 3 shots	Flat Dirichlet	1.0000	0.9999	1.0000
ξ	Reduction in risk due to cross protection	Informative LogNorm	0.0740	0.0410	0.1290
χ	Decrease in effectiveness due to non compliance	Informative Beta	0.5040	0.3110	0.7020

Screening-related parameters

Variable	Description	Distributional assumption	Mean	95% Cred Int	
	Screening rate				
σ_a	12-24 yo	Informative Beta	0.0500	0.0500	0.0500
σ_a	25-29 yo	Informative Beta	0.1530	0.1480	0.1590
σ_a	30-34 yo	Informative Beta	0.2150	0.2100	0.2190
σ_a	35-44 yo	Informative Beta	0.2460	0.2440	0.2470
σ_a	45-54 yo	Informative Beta	0.2600	0.2540	0.2660
σ_a	55-64 yo	Informative Beta	0.2420	0.2320	0.2520
σ_a	65-74 yo	Informative Beta	0.1840	0.1640	0.2020
σ_a	75- yo	Informative Beta	0.1080	0.0920	0.1250

Economic measures

Costs

- For each relevant state in the model, costs are defined as the product between the unit cost (specified as parameters) and the total number of subjects who are in that state at any given time
- For example, for each intervention and time of the simulation, the cost associated with cervical cancer is

$$C_{i,t}^{\text{can}} = \sum_{r=1}^{4} \beta_r \, Ca_{i,t} \left(c_r^{\text{can}} + 2c^{\text{pap}} + 2c^{\text{col}} + c^{\text{dna}} \right)$$

where $Ca_{i,t}$ is the number of people who are in the state "cancer" at time t under strategy i

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where $Ca_{i,t}$ is the number of people who are in the state "cancer" at time t under strategy i

- The **present value of cost** is then

$$PVC_i = \sum_{t=1}^{T} \frac{C_{i,t}}{(1+v_c)^{(t-1)}}$$

where v_c is the *costs discount rate* and $C_{i,t}$ is the sum of all costs

Utilities

- Similarly, we can estimate the overall utility for each relevant state in the model as the product between the unit utilities (specified as parameters) and the total number of subjects who are in that state at any given time
- The **present value of utility** is then

$$PVU_i = \sum_{t=1}^{T} \frac{U_{i,t}}{(1+v_u)^{(t-1)}}$$

where v_u is the *benefit discount rate* and $U_{i,t}$ is the sum of all utilities

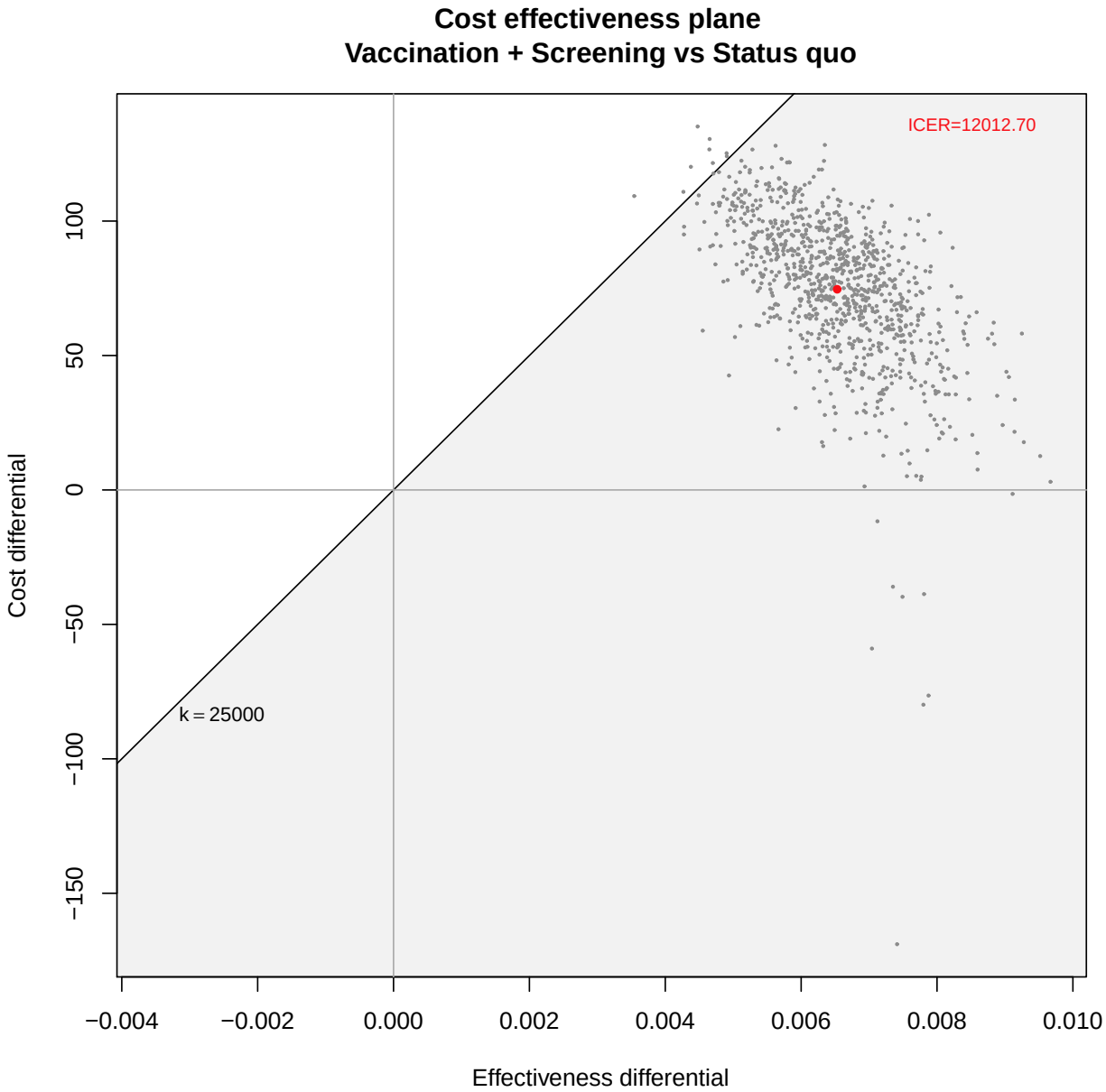
Economic analysis

Assume that all the parameters are included in a vector $\boldsymbol{\theta} = (\boldsymbol{\theta}^1, \boldsymbol{\theta}^0)$. Then the relevant quantities for the economic analysis are

- The increment in the average clinical benefits:
$$\Delta_e = \mathsf{E}[PVU \mid \boldsymbol{\theta}^1] - \mathsf{E}[PVU \mid \boldsymbol{\theta}^0]$$
- The increment in the average costs:
$$\Delta_c = \mathsf{E}[PVC \mid \boldsymbol{\theta}^1] - \mathsf{E}[PVC \mid \boldsymbol{\theta}^0]$$
- The expected incremental benefit:
$$\mathsf{EIB} = k\mathsf{E}[\Delta_e] - \mathsf{E}[\Delta_c] = \mathcal{U}^1 - \mathcal{U}^0$$

The distributions of these quantities can be estimated using the simulated values for the parameters in $\boldsymbol{\theta}$

Cost-effectiveness plane



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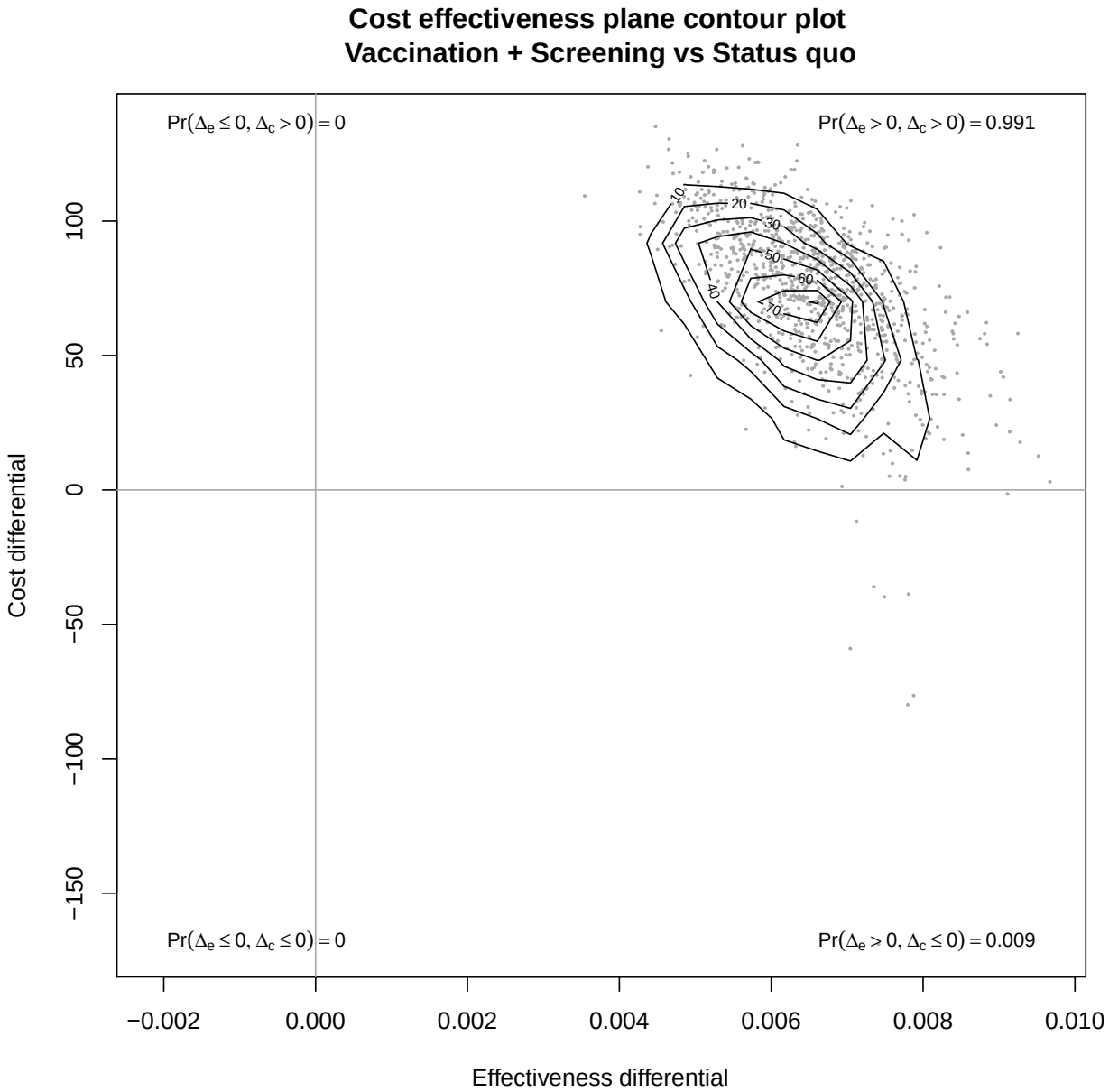
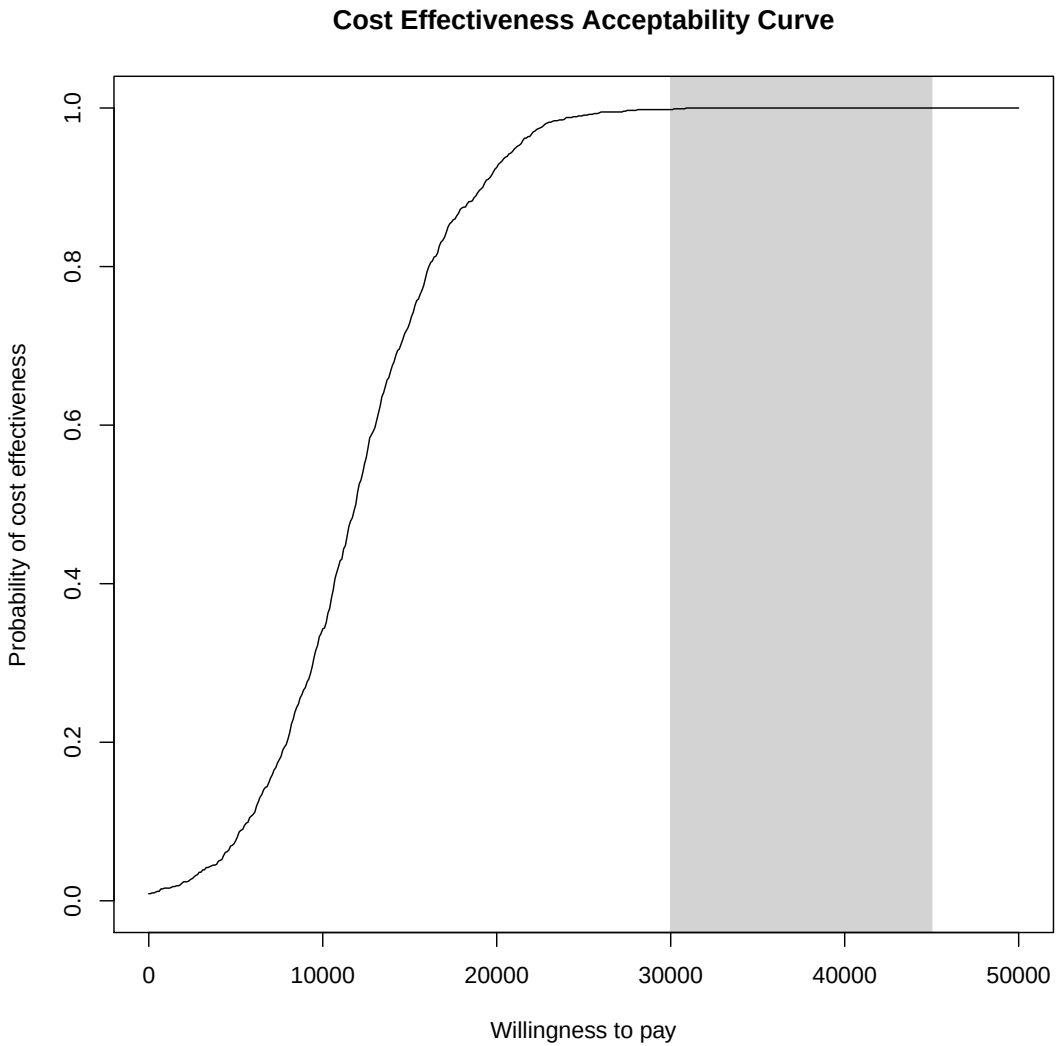


Cost Effectiveness Acceptability Curve



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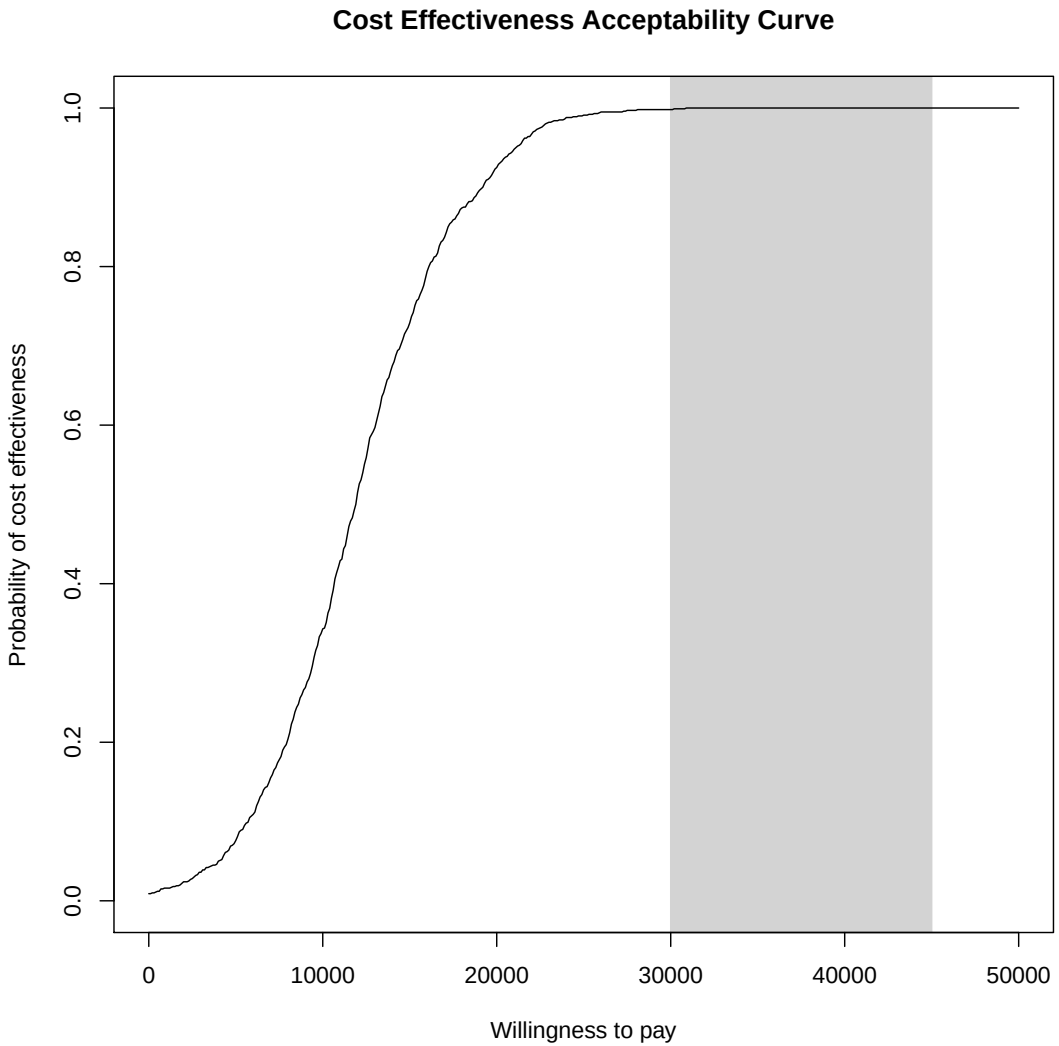

- Use net benefit utility $u(e, c, i) = ke_i - c_i$, but consider varying k
- CEAC represents $\Pr(k\Delta_e - \Delta_c > 0 \mid \text{Data})$ as a function of k
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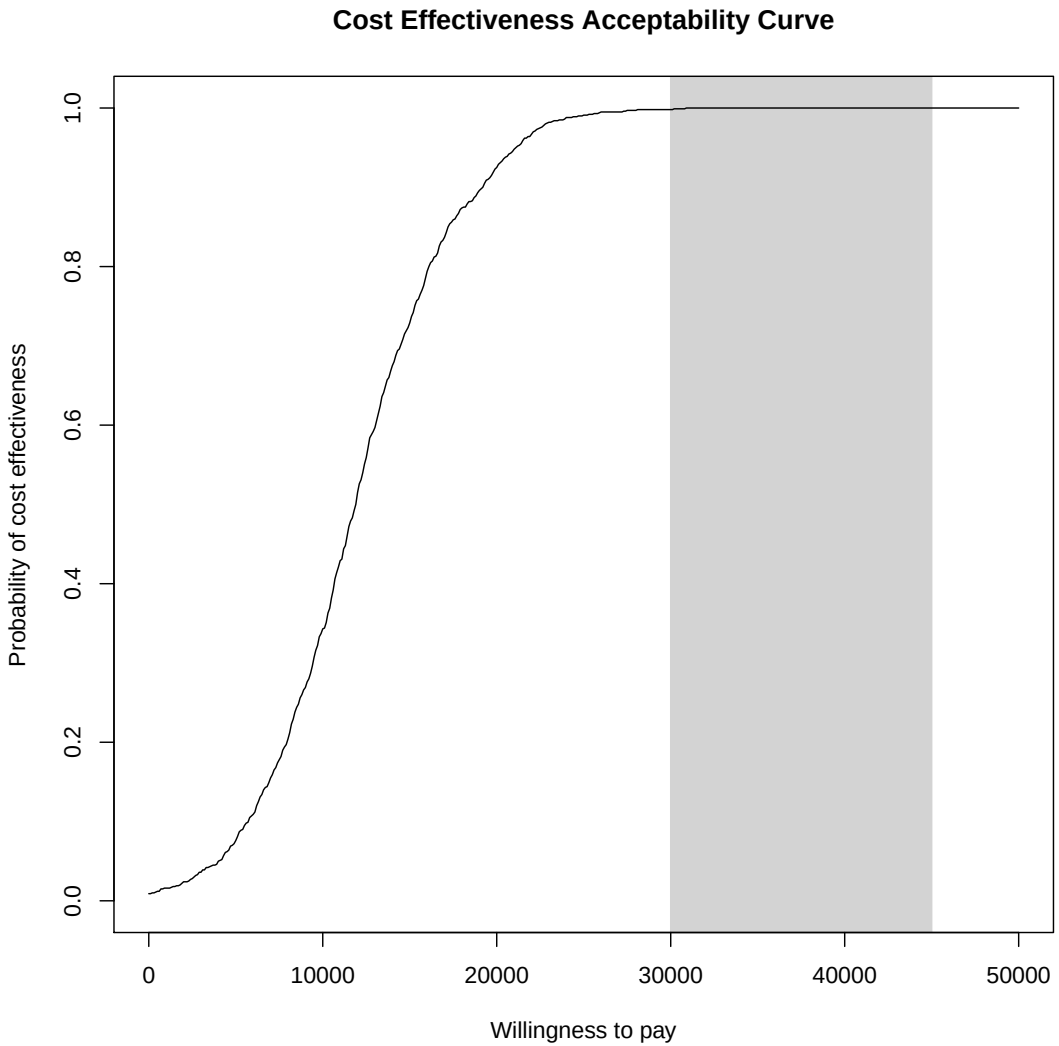

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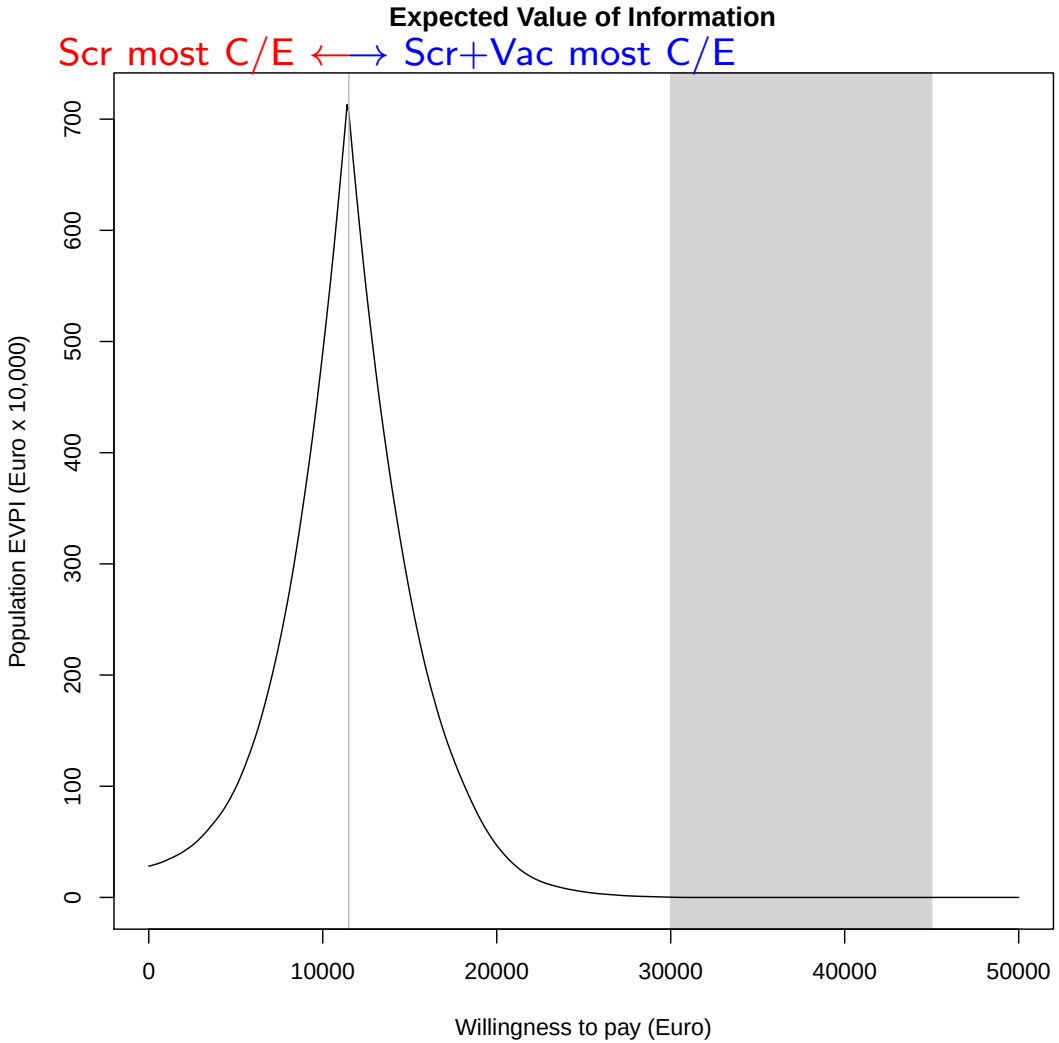
- CEAC represents $\Pr(k\Delta_e - \Delta_c > 0 \mid \text{Data})$ as a function of k
- Suggested as the standard tool for PSA by NICE
- Summarises the probability of cost effectiveness, as it depends on the willingness to pay parameter k
- Meaningful only if the parameters are considered random, i.e. within the Bayesian framework

Expected value of information



(EVPI per patient: € 12.8)

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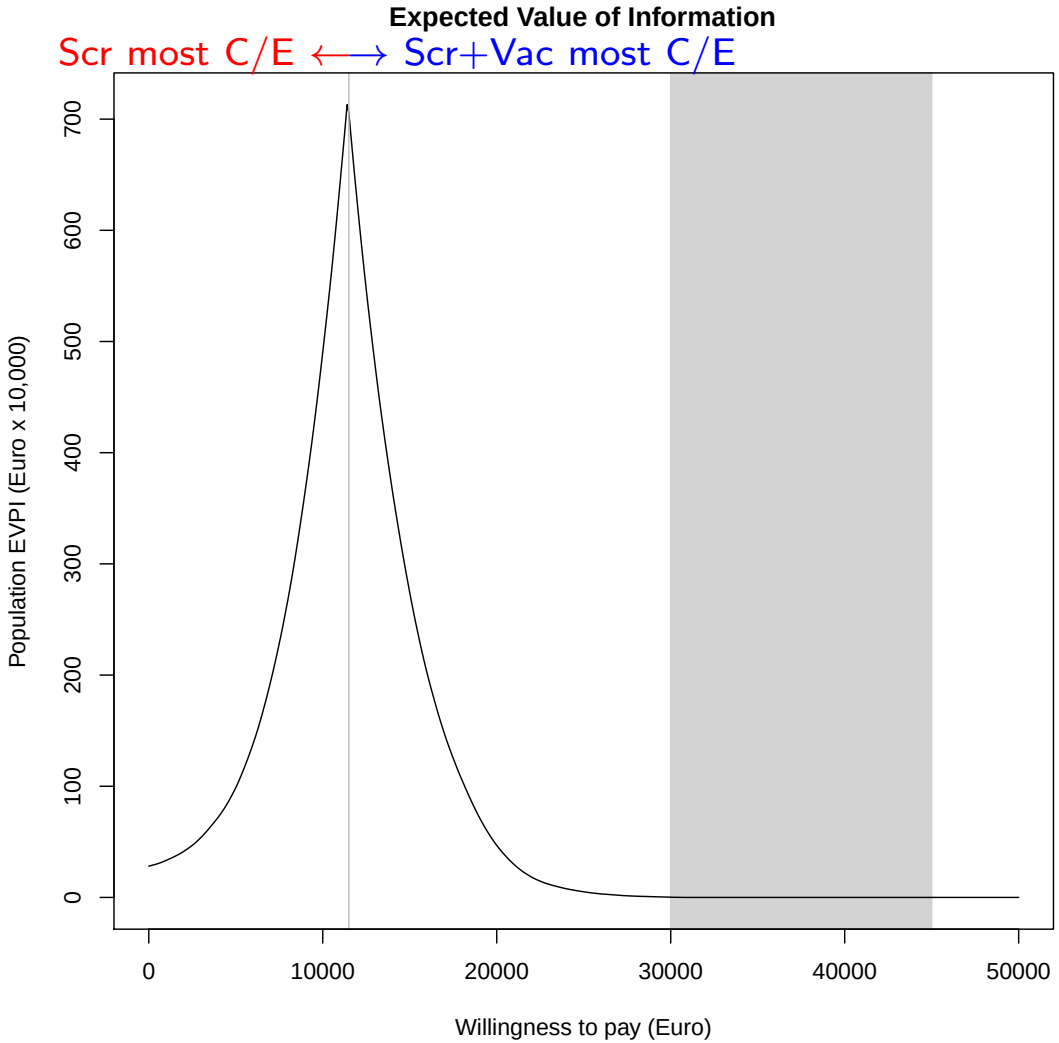

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$$\mathrm{E}[\max_i u(e, c, i) \mid \boldsymbol{\theta}] - \mathcal{U}^*$$

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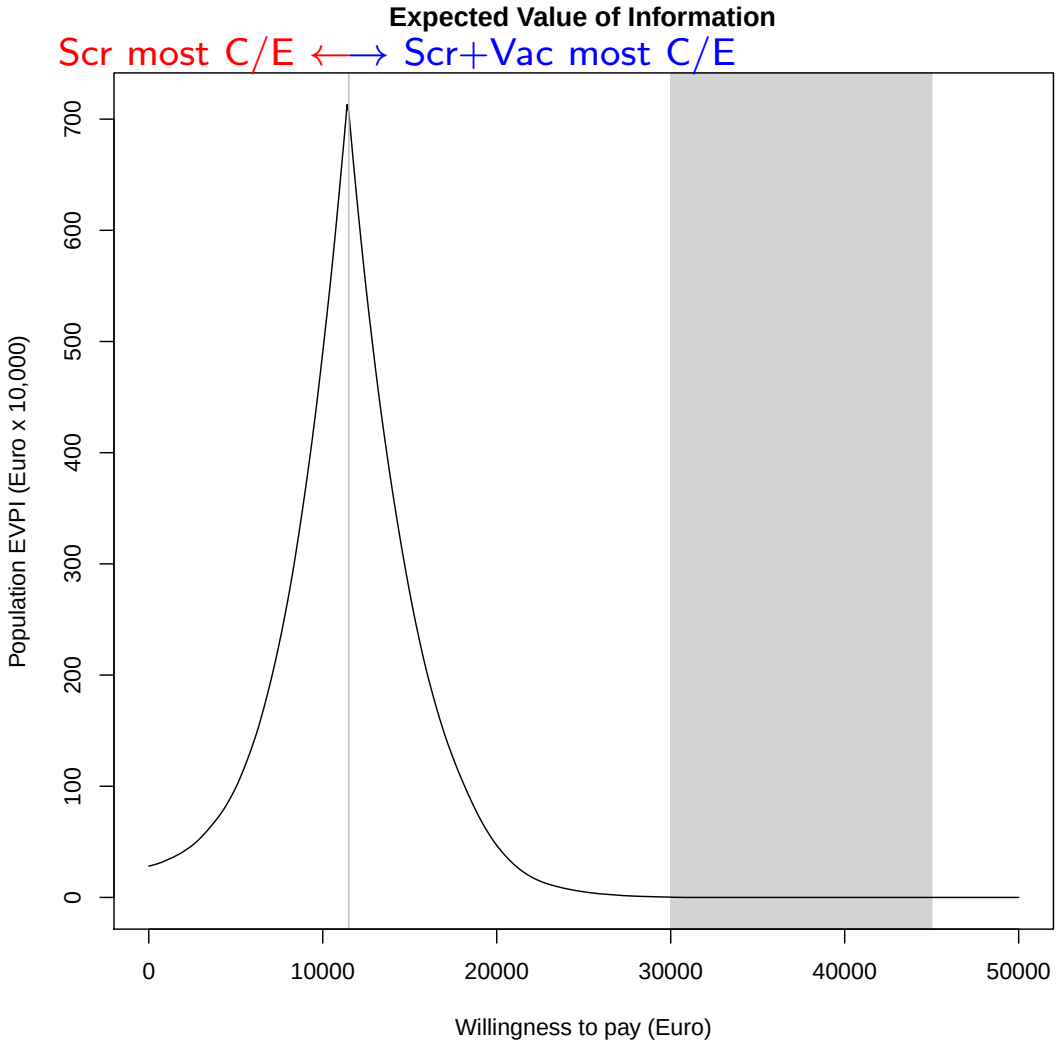

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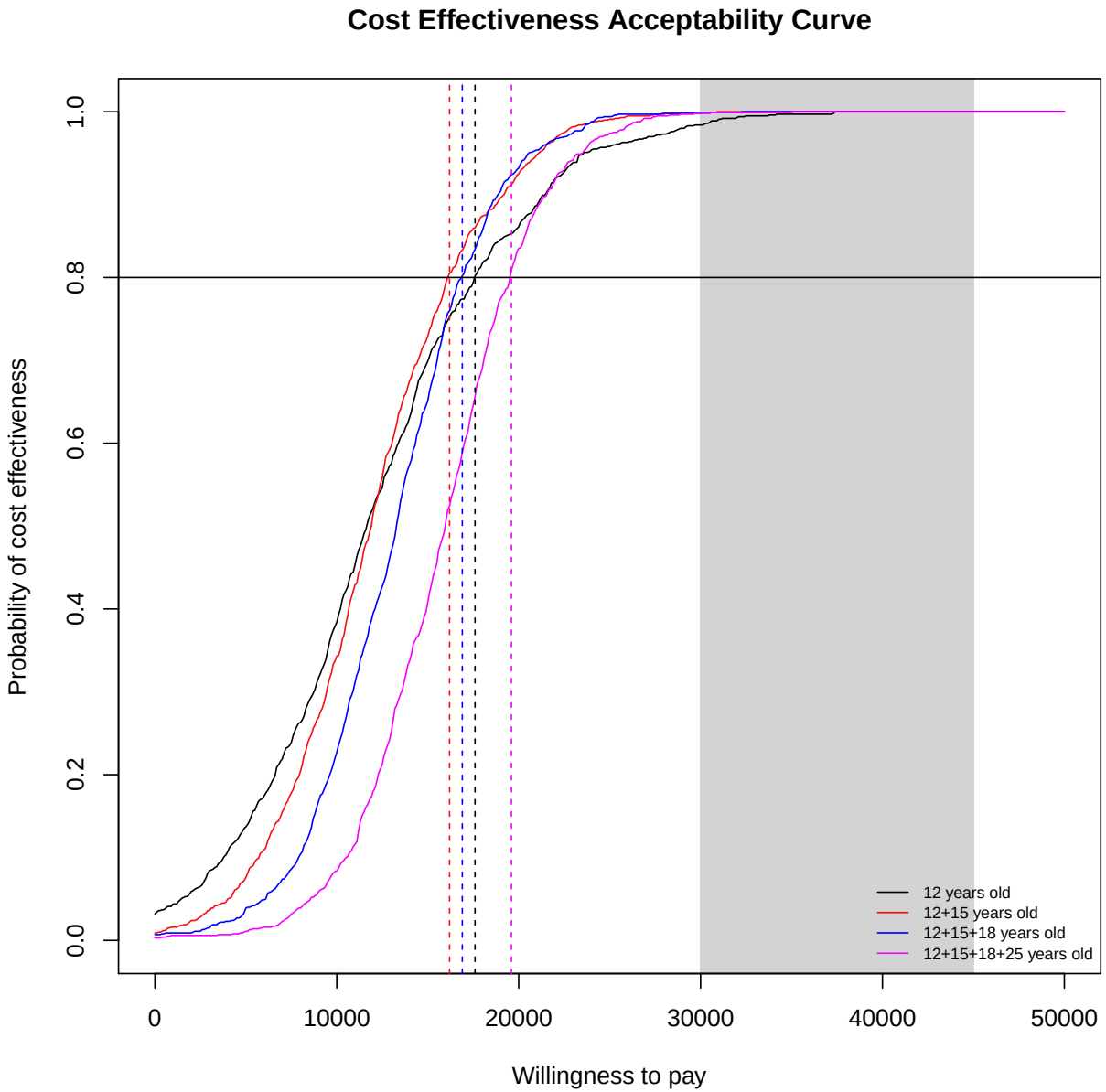
- Describes the **average opportunity loss**
- Equivalently, it is the maximum amount the decision maker should be willing to pay to *resolve the uncertainty* in the parameters
- By construction, combines
  - *a)* *how much* we are likely to lose if we take the "wrong" decision
  - *b)* *how likely* it is that we take it
- Drives the process of gathering additional evidence

Multicohort analysis: 12-15-18-25 yo



Conclusions

- The strategy that combines a multi-cohort quadrivalent-based vaccination and screening seems to be cost-effective as compared to screening only
- Uncertainty in the model parameter is first integrated out (i.e. computing the expected utilities) and then accounted for separately (PSA)
- The optimal decision does not seem to be affected by this uncertainty

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- The model can be modified to include more complex situations
  - "Herd" immunity: vaccinating girls will protect boys, which in turn will protect more girls
  - Different scenarios in terms of provision of health care: limited vaccine effectiveness (booster), specific economic conditions (partial vs complete reimbursement)
  - Vaccination of males

Thank you!