Bayesian Markov models for the cost-effectiveness analysis of HPV vaccination

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Outline of presentation

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Identifying the most cost-effective vaccination strategy against human papillomavirus (HPV)

1. Incorporating the effects of herd immunity into the Bayesian Markov model
2. Including boys in a quadrivalent HPV vaccination scheme
3. Considering a great variety of HPV-induced diseases

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Human papillomavirus (HPV)

- Mainly sexually transmitted virus
- Infects both mucous membrane and skin
- In rare cases transmission through:
  - Shared towels
  - Public saunas
  - Digital-genital contact
- Around 40 identified genotypes, including 13 high-risk types
  - HPV 16 and 18: 79.1% of all cervical cancers
  - HPV 6 and 11: anogenital warts and recurrent respiratory papillomatosis (RRP)
  - HPV 1 and 2: benign skin warts
- Contributory cause of anal, vaginal, vulvar, penile and head/neck cancers

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HPV-induced disease burden in the UK

HPV prevalence

- 20.7% in females
- 17.4% in males

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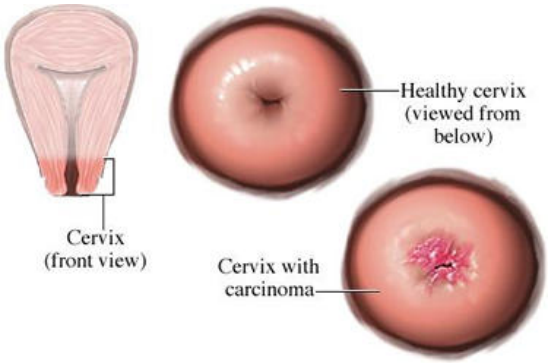

Cervical cancer

- Yearly 2,890 new cervical cancer diagnoses
- Cervical cancer 11th most frequent cancer in females

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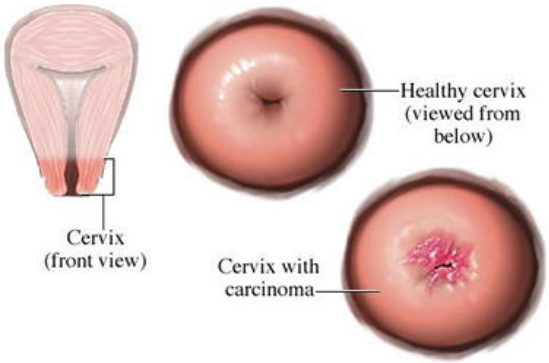

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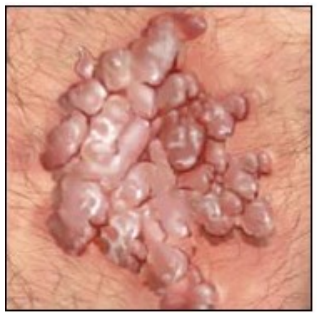
Genital warts prevalence

- 4.7% in females
- 2.2% in males



Economic impact

Yearly costs borne by the NHS

- £17 million for genital warts treatment
- £157 million for cervical cancer treatment

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European public health insurance systems

- National Health Service (NHS) in the UK
- Servizio Sanitario Nazionale (SSN) in Italy
- Couverture Maladie Universelle (CMU) in France

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Country-specific information

- Data on costs and utilities specific for Italy
- Cost-effectiveness analysis in an Italian context

Literature review

- 5 databases searched with variety of search word combinations
- Altogether 116 publications reviewed and summarized
- Hybrid models for HPV vaccination
  1. Simulate the process of sexual mixing
  2. Calculate age-and gender-specific HPV prevalence by means of
     - Difference equations
     - ODEs
  3. Integrate those probabilities into natural disease history models afterwards

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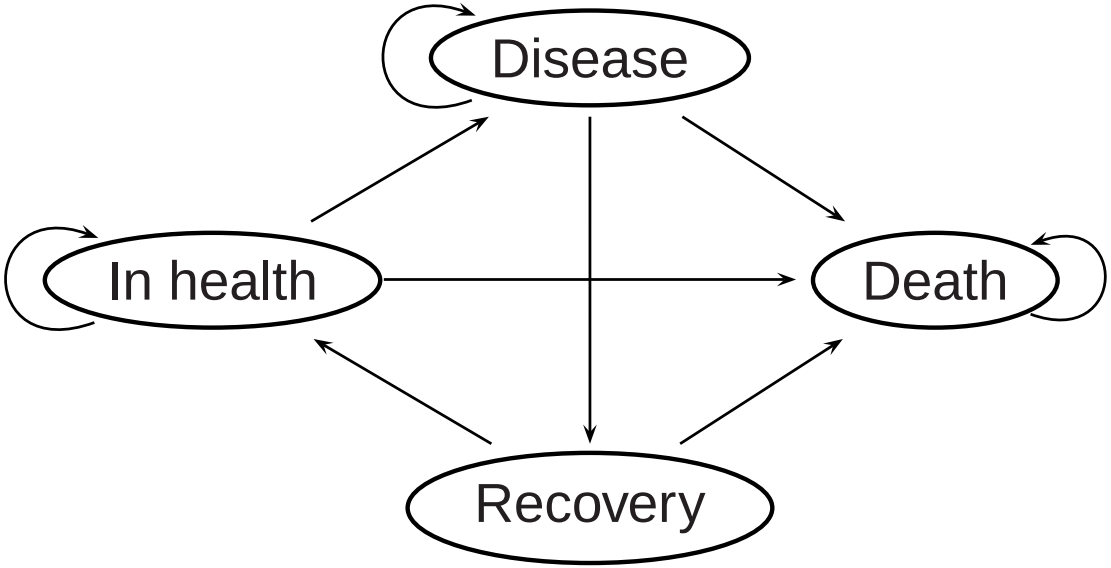
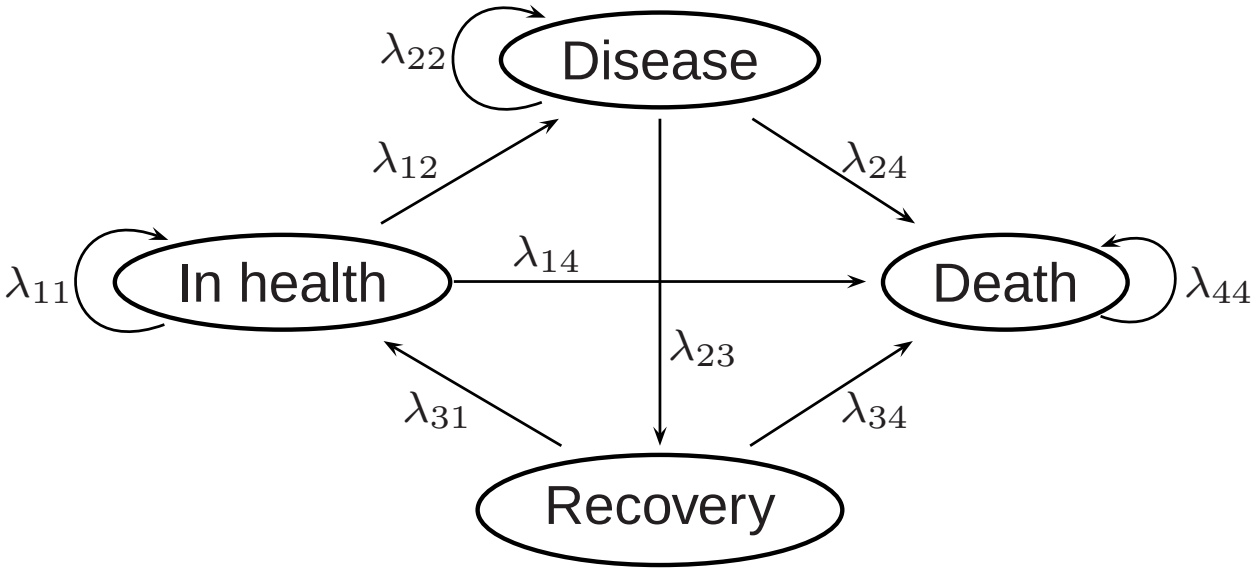
To the best of our knowledge, our methodology of including dynamic interactions between individuals directly into a static Bayesian Markov model is unique in the field of HPV transmission and disease progression modelling.

1. Define a structure



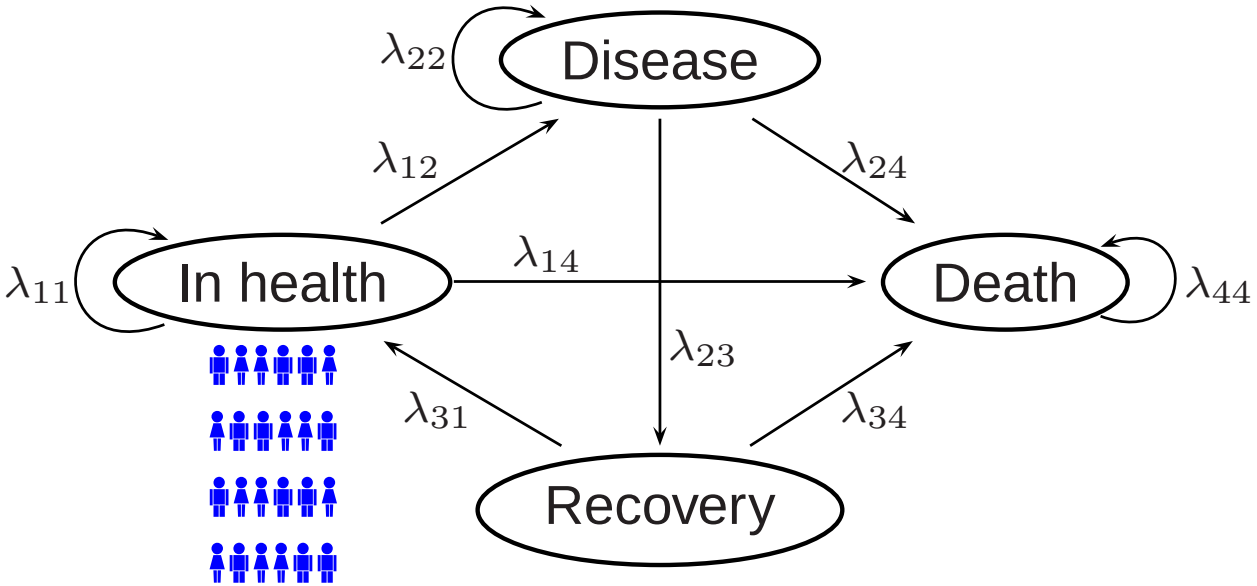
- Exhaustive and mutually exclusive health states

2. Estimate the transition probabilities



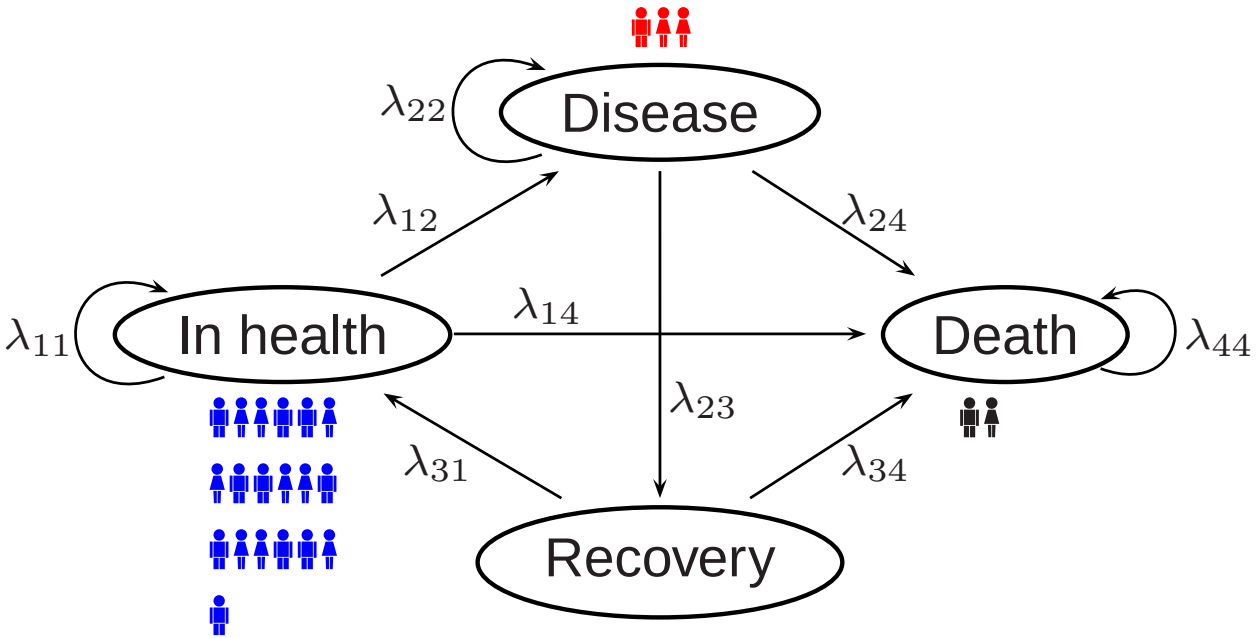
- Transition probabilities λ are functions of θ
- Assigning flat and informative distributions to parameters θ

3. Run the simulation: $t = 0$



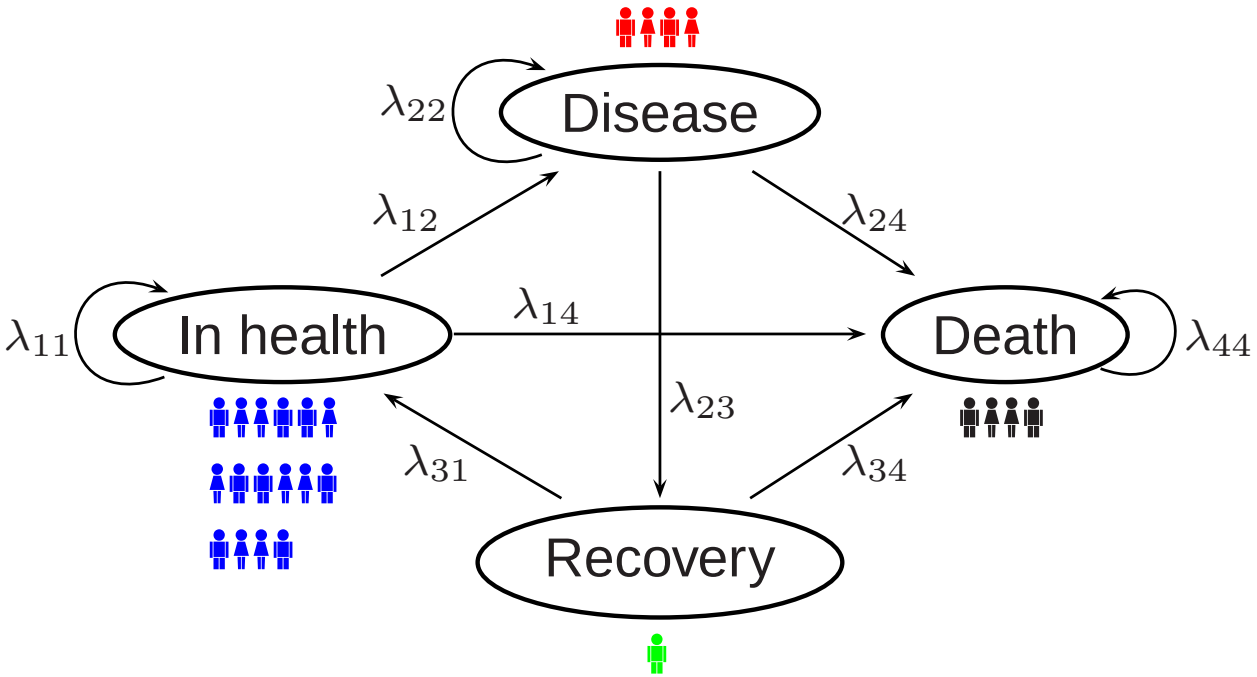
- Each health state is assigned a value of utility
- Ranging between 0 (death) and 1 (perfect health)

3. Run the simulation: $t = 1$



- Markov cycle length of 1 year

3. Run the simulation: $t = 2$



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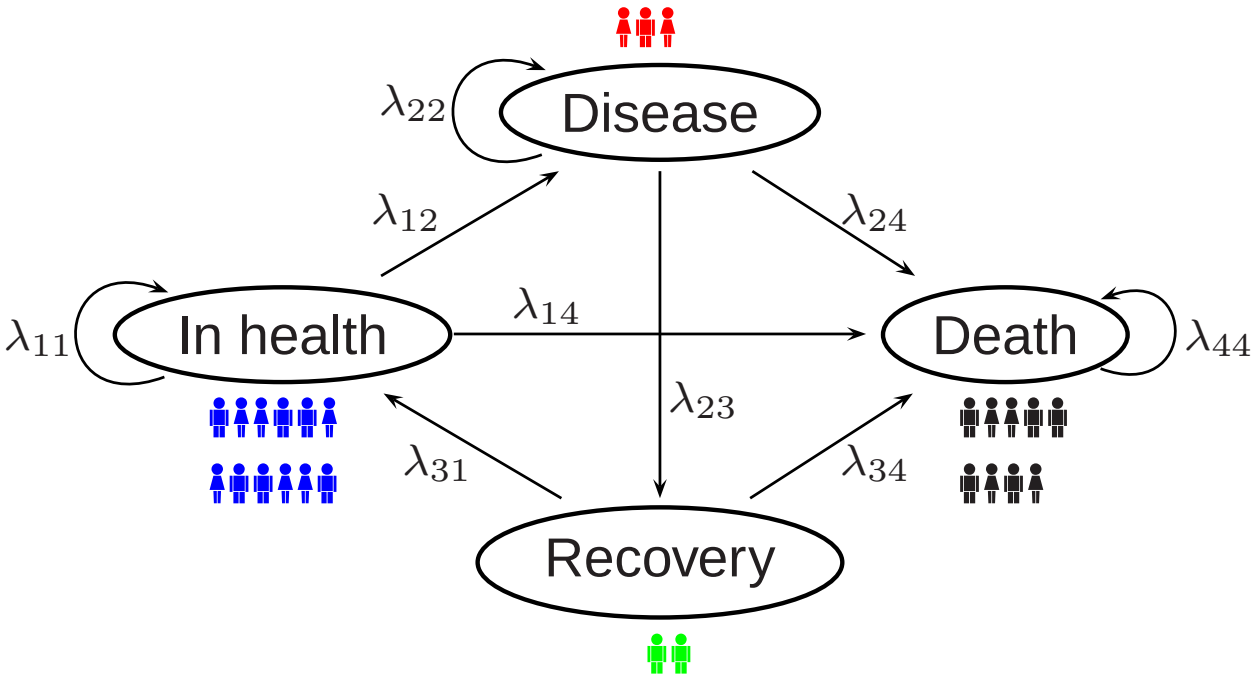
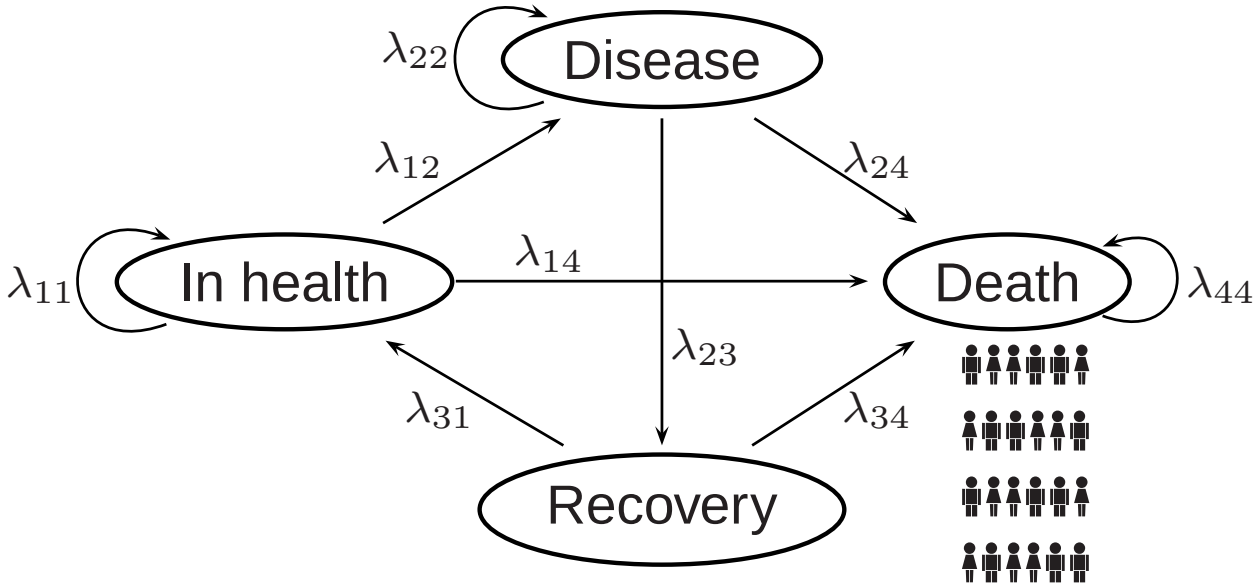


3. Run the simulation: $t = T$



- Health economic analysis of multi cohort vaccination strategy

Reference population and follow-up

- 24 cohorts of females and males aged 12-35 years
- Follow-up period of 55 years
- Population dynamics: Entering of healthy 12 year old individuals during first 10 years of observation

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Model assumptions

Interventions i

1. *Screening-only*: Screening in females, no intervention in males
2. *Female-only vaccination*: Screening and vaccination in 12 year old females, no intervention in males
3. *Universal vaccination*: Screening and vaccination in 12 year old females, vaccination in 12 year old males
   - Sensitivity analyses to male vaccination age
4. *Catch-up vaccination*: Screening and vaccination in 12 year old females with a catch-up at 15 years and no intervention for males
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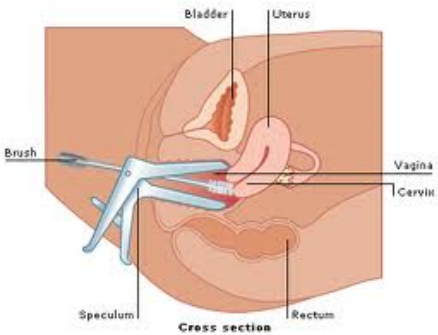

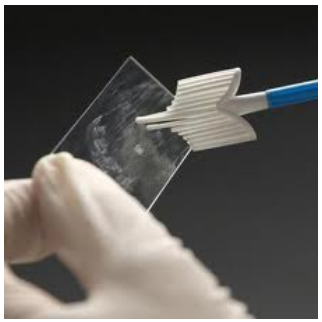

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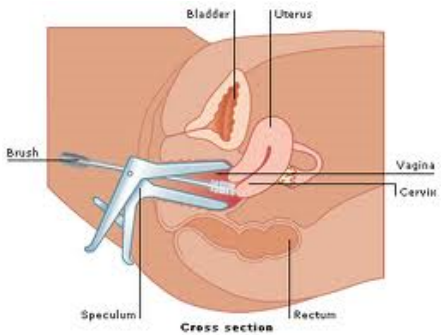

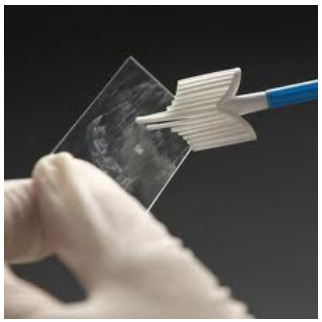

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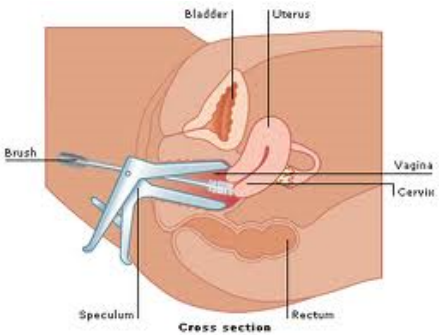

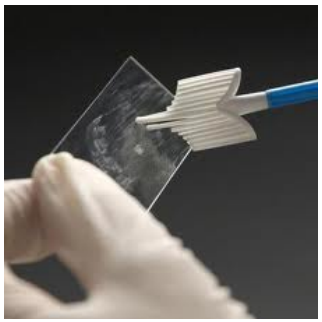

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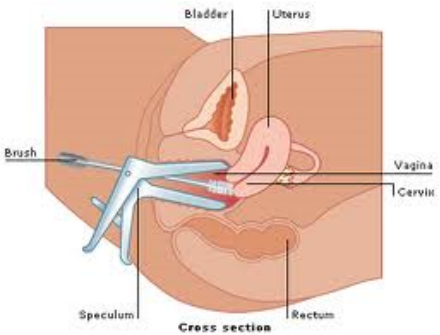

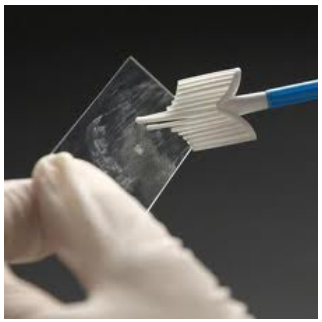

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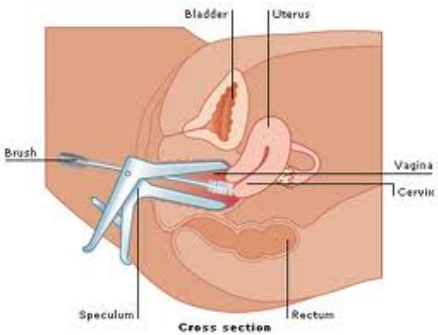
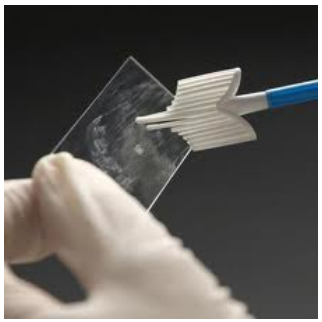
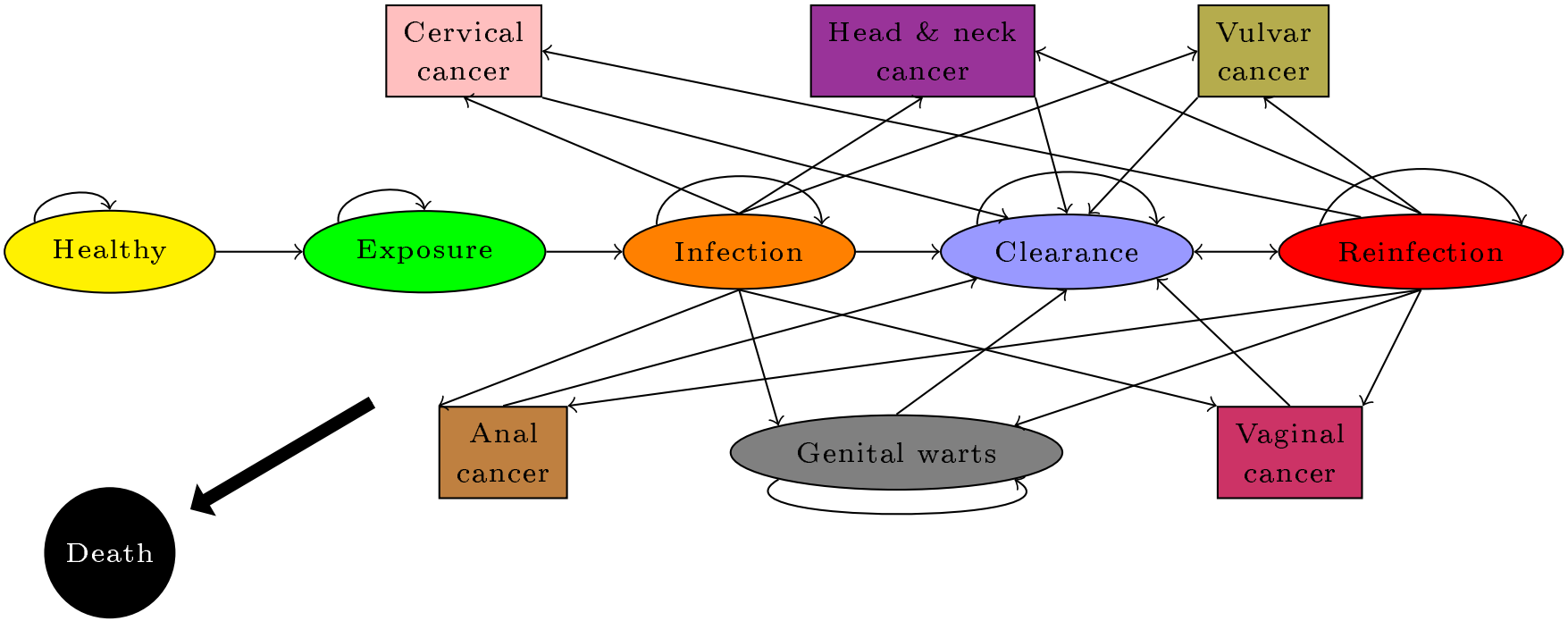


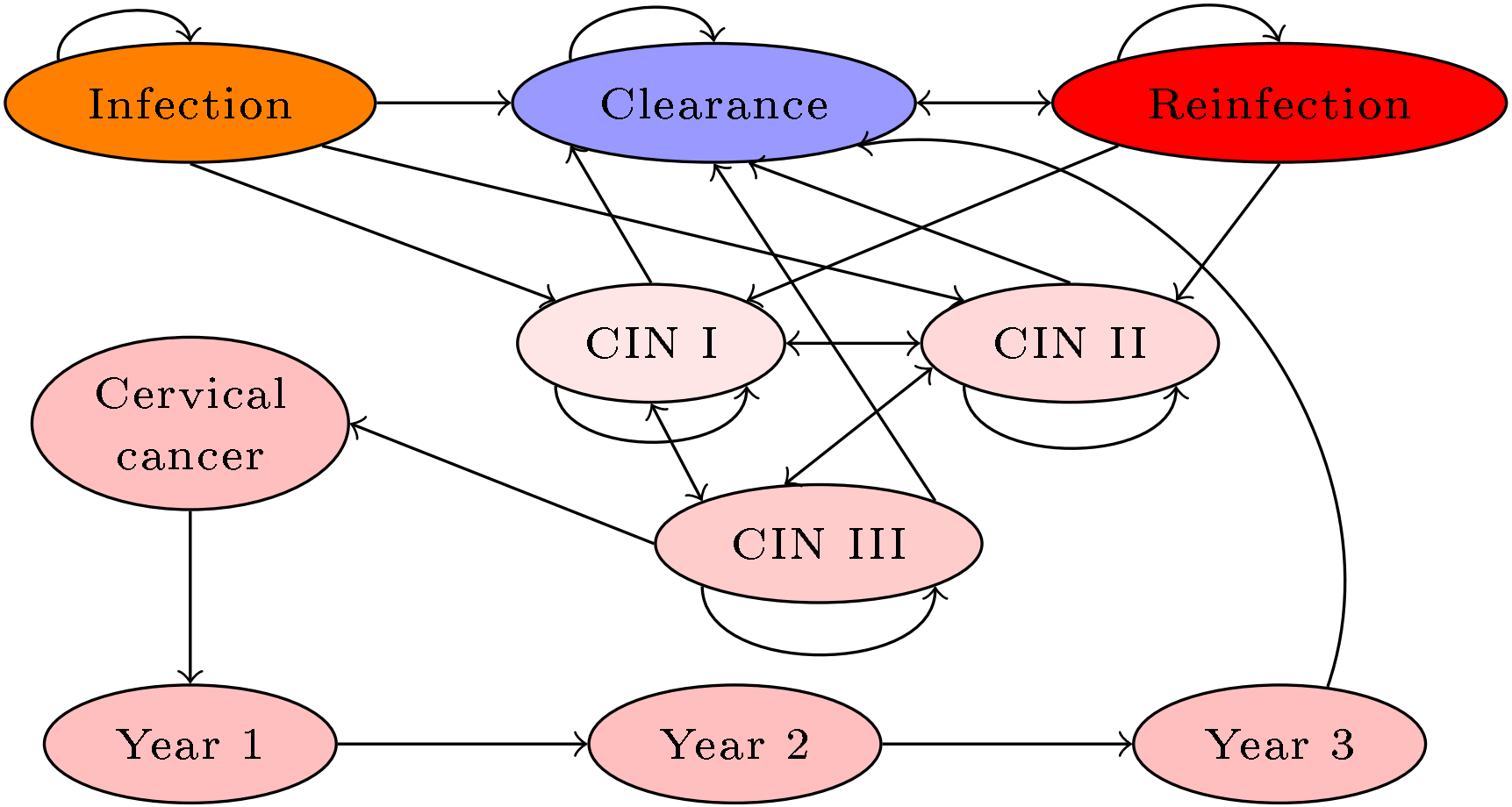


Female model compartment

$S_f = 36$ health states



Cervical cancer



The process of sexual mixing

- Most important aspect of our research
- Transforms the Bayesian MM into a hybrid model
- Accounting for herd immunity
  - unvaccinated individuals are indirectly protected
  - females and males benefit from male HPV vaccination by
    1. decrease in prevalence of HPV and induced diseases
    2. reduction of HPV transmission between the sexes
  - vaccine benefits are no longer underestimated in CE-analyses

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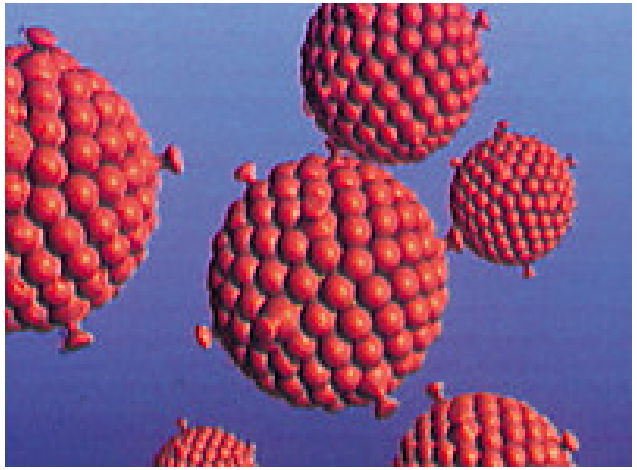
HPV transmission probabilities ϵ

Average-risk sexual activity

- 80% of the population
- 2-10 lifetime sex partners



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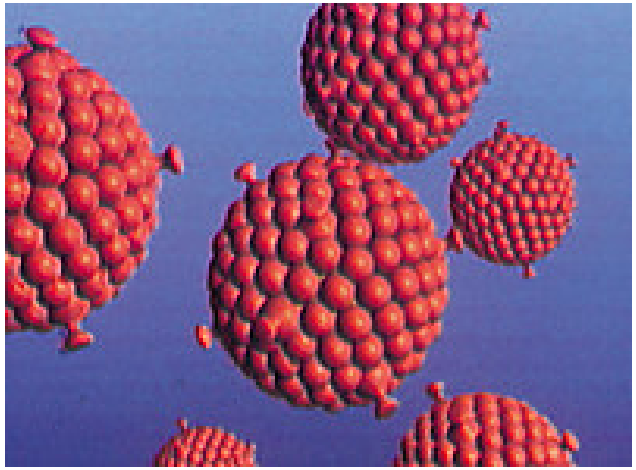


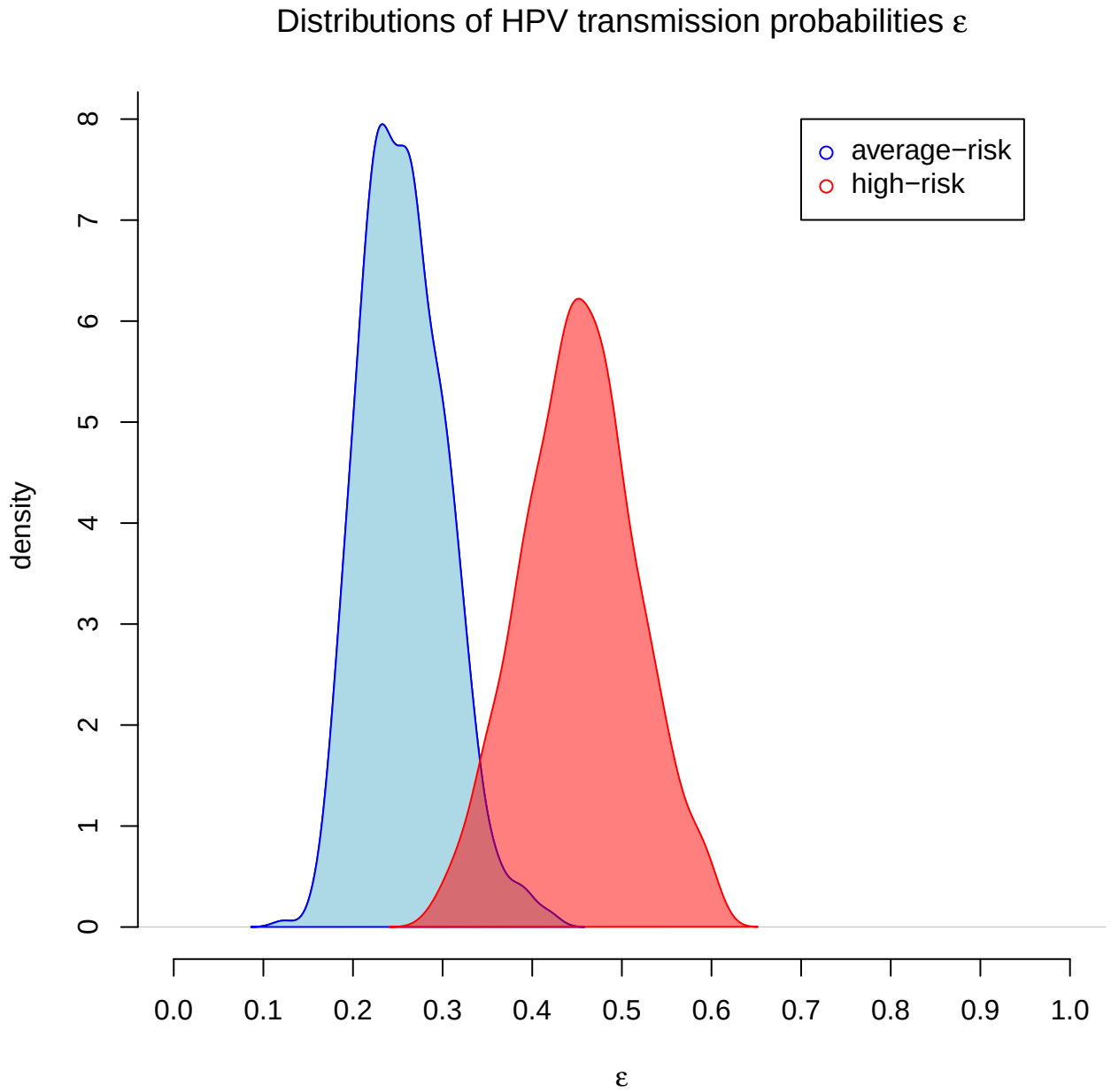
Average-risk sexual activity

- 80% of the population
- 2-10 lifetime sex partners

High-risk sexual activity

- 20% of the population
- 11 or more lifetime sex partners
- Promiscuity correlates with
  - smoking
  - a low education level
  - early first sexual intercourse before the age of 18

Distributions of transmission probabilities



Sexual mixing matrix

Sexual partnership matrix for female (average-risk group)

Age	**12 -14**	**15 -19**	**20 -24**	**25 -29**	**30 -34**	**35 -39**	**40 -44**	**45 -49**	**50 -54**	**55 -59**	**60 -64**	**65 -80**
12-19	1%	26%	58%	15%	1%	0%	0%	0%	0%	0%	0%	0%
20-24	0%	0%	36%	49%	12%	2%	0%	0%	0%	0%	0%	0%
...	...	...	...	...	...	...	...	...	...	...	...	...
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Annual max, average and mean partner acquisition rate for females

	Females			Males		
Age	**Min**	**Mean**	**Max**	**Min**	**Mean**	**Max**
12-19	0.74	1.26	1.78	0.90	1.92	2.94
20-24	0.54	0.96	1.38	0.68	1.38	2.09
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- Consider a 20 year old female in the average-risk group and assume the maximum partner acquisition rate

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60-	0.05	0.10	0.15	0.04	0.11	0.18

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Sexual mixing matrix

Sexual partnership matrix for female (average-risk group)

Age	12 -14	15 -19	20 -24	25 -29	30 -34	35 -39	40 -44	45 -49	50 -54	55 -59	60 -64	65 -80
12-19	1%	26%	58%	15%	1%	0%	0%	0%	0%	0%	0%	0%
20-24	0%	0%	36%	49%	12%	2%	0%	0%	0%	0%	0%	0%
...	...	...	...	...	...	...	...	...	...	...	...	...
65-80	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	14%	86%

Annual max, average and mean partner acquisition rate for females

	Females			Males		
Age	Min	Mean	Max	Min	Mean	Max
12-19	0.74	1.26	1.78	0.90	1.92	2.94
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Sexual mixing equation

Equation introduced by Korostil et al.

$$\kappa_{g,s,a} = \epsilon \sum_{s',a'} m_{g,s,s',a,a'} \left(\frac{I_{g',s',a'}}{N_{g',s',a'}} \right)$$

- ϵ represents the HPV transmission probability per partnership
- $m_{g,s,s',a,a'}$ represents the sexual mixing matrix
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Equation introduced by Cooper et al.

$$\lambda_{g,s,a} = 1 - \exp^{-\kappa_{g,s,a}}$$

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5. Calculating overall costs and utilities, resulting in the cost-effectiveness analysis

Running the model

- **J**ust **A**nother **G**ibbs **S**ampler (JAGS)
- Integrated into `R` by means of package `R2jags`
- 2 parallel chains ($n_{chains} = 2$)
- $n_{iter} = 40,000$ simulations
- burn-in of $n_{burn} = 4,000$
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$$n_{sims} = n_{chains} \frac{(n_{iter} - n_{burn})}{n_{thin}} = 2 \frac{(40{,}000 - 4{,}000)}{360} = 200$$

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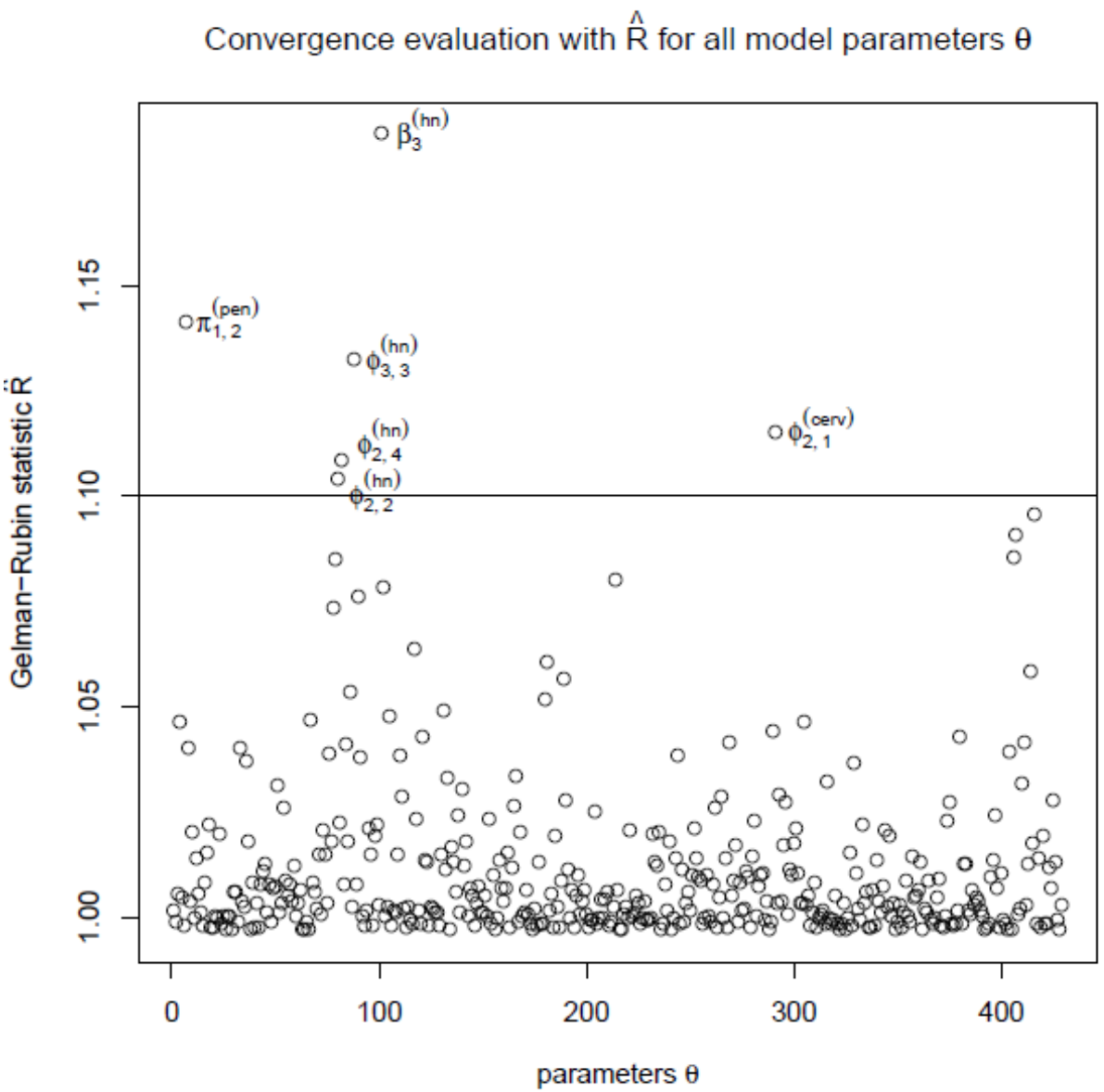
Gelman-Rubin statistics $\hat{R}$ for θ



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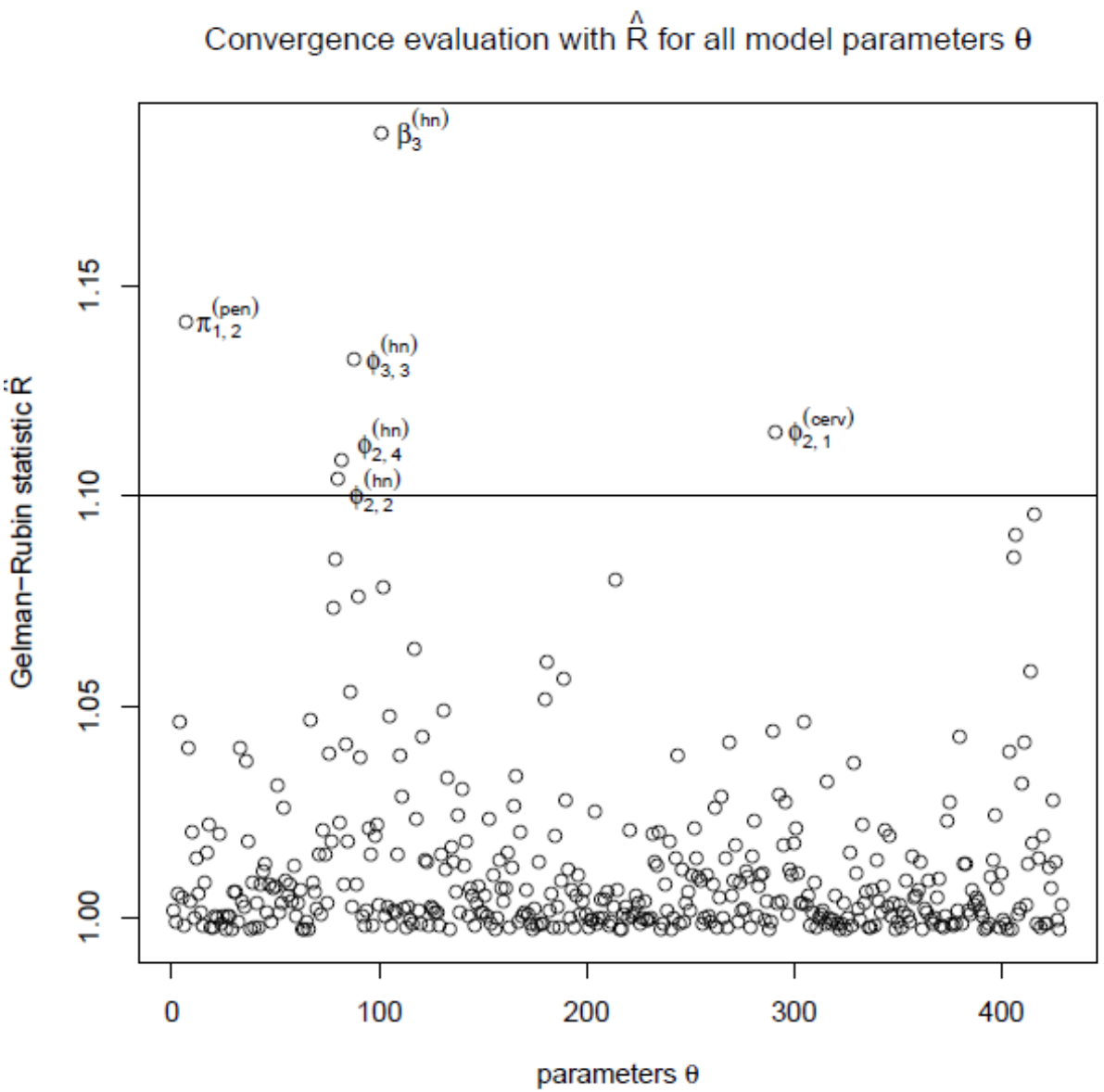

$$\hat{R} = \sqrt{\frac{\widehat{Var}(\theta_k|y)}{W(\theta_k)}}$$

Present values of cost (PVC) and utility (PVU)

The PVC

- Sum of overall costs in intervention i for time $t = 1$ to $t = 55$
- Commonly discounted by $\nu_c = 0.03$

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Comparison of universal to female-only vaccination

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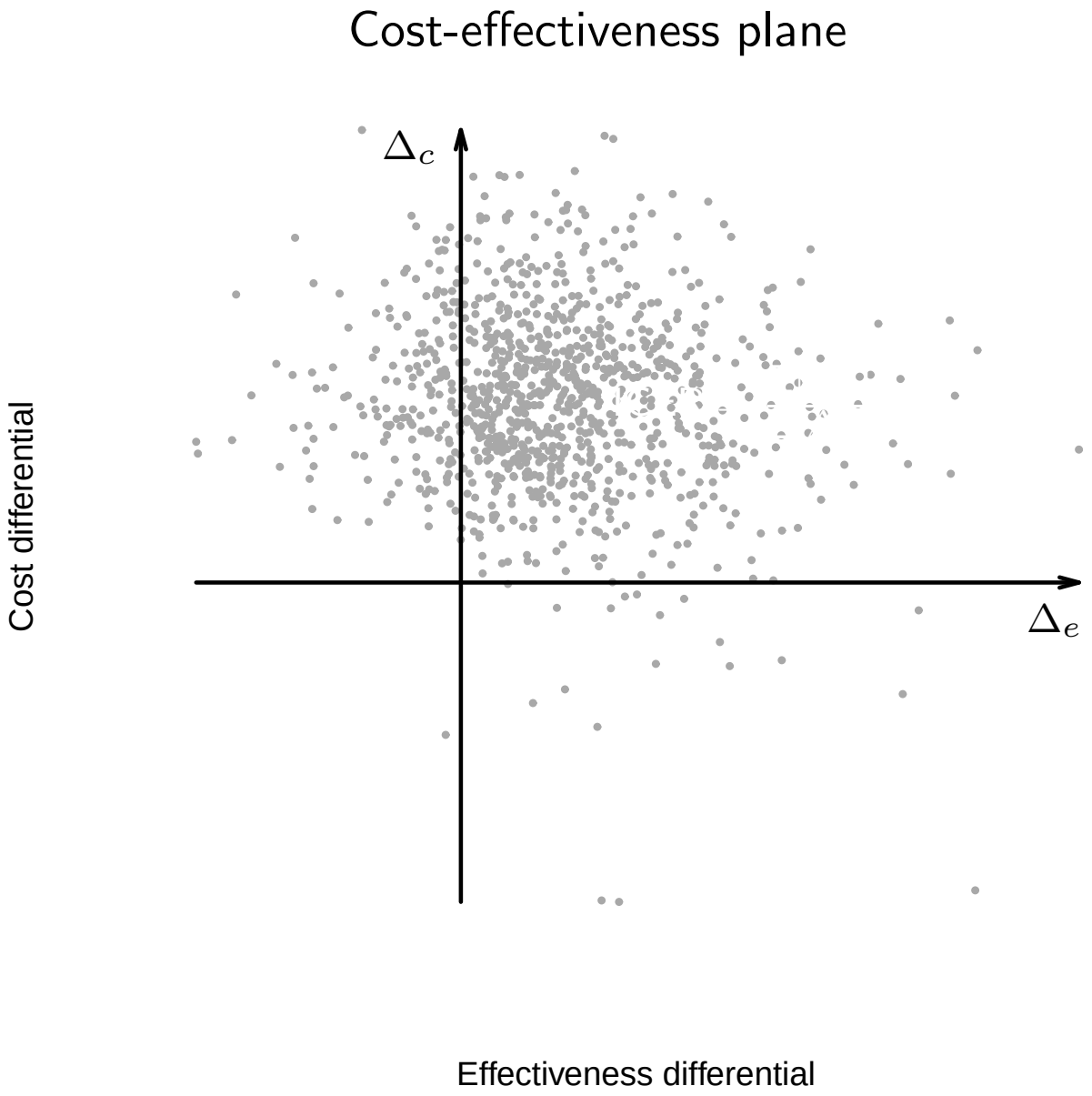
Cost-effectiveness plane vs ICER



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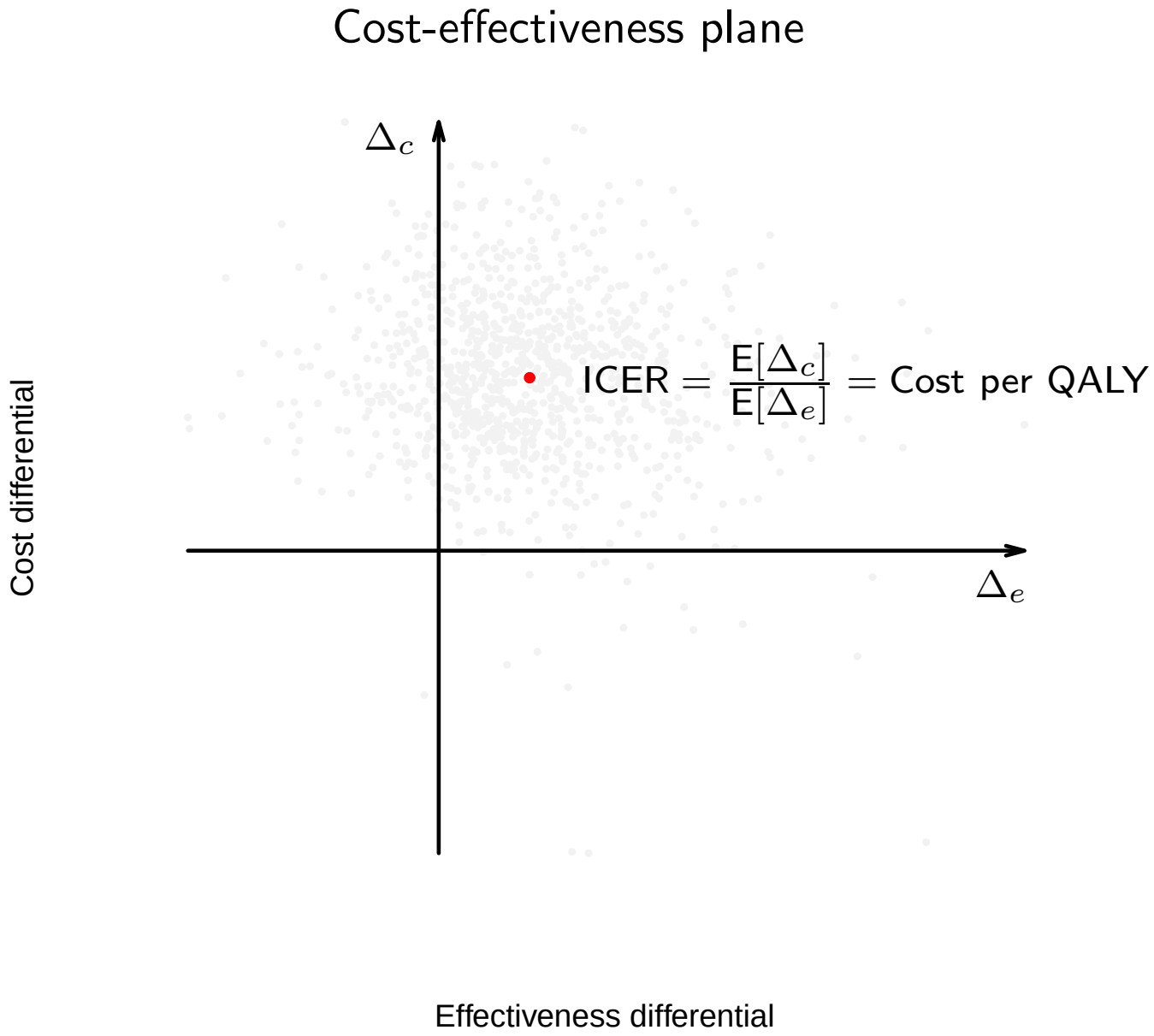
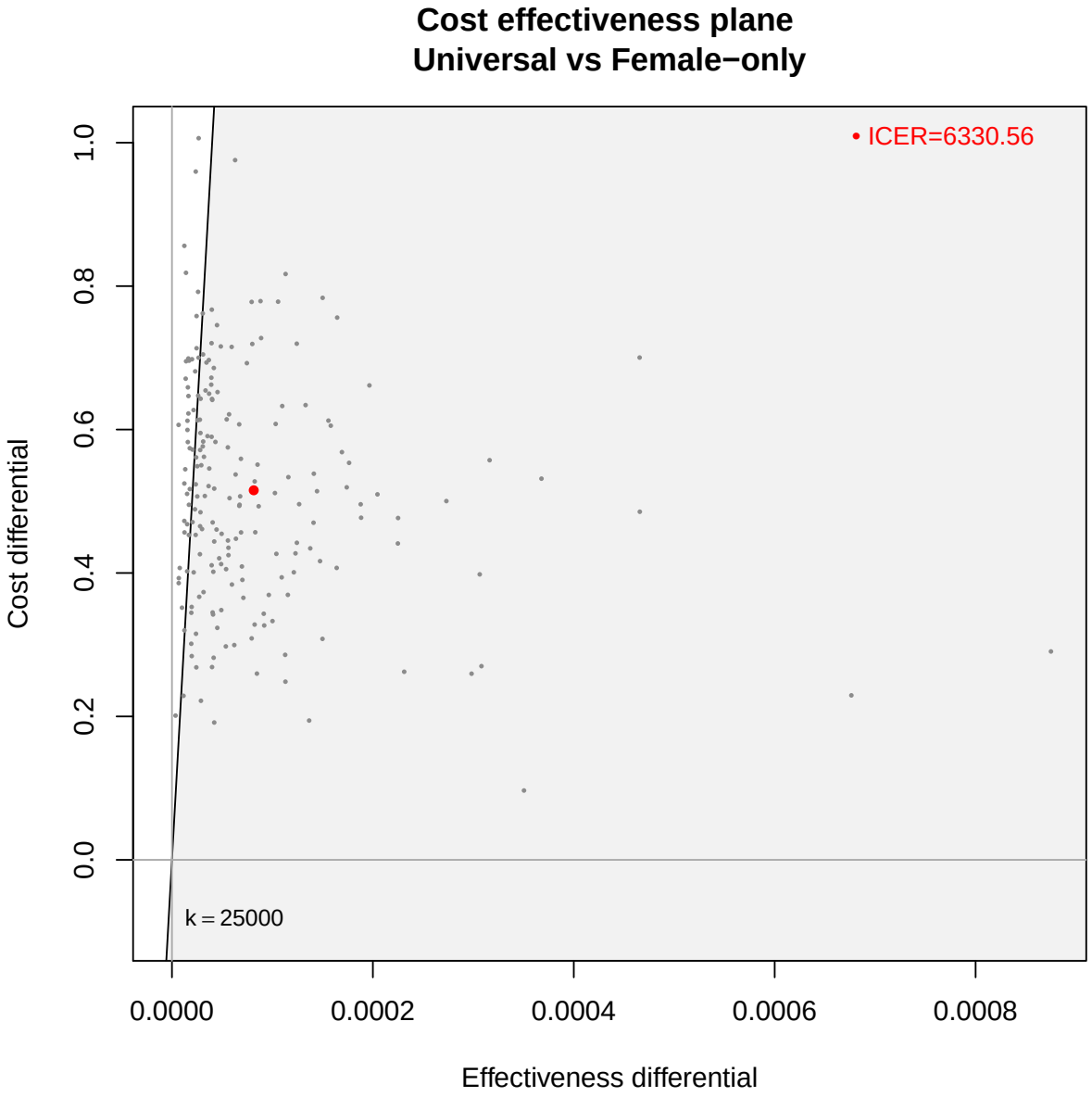
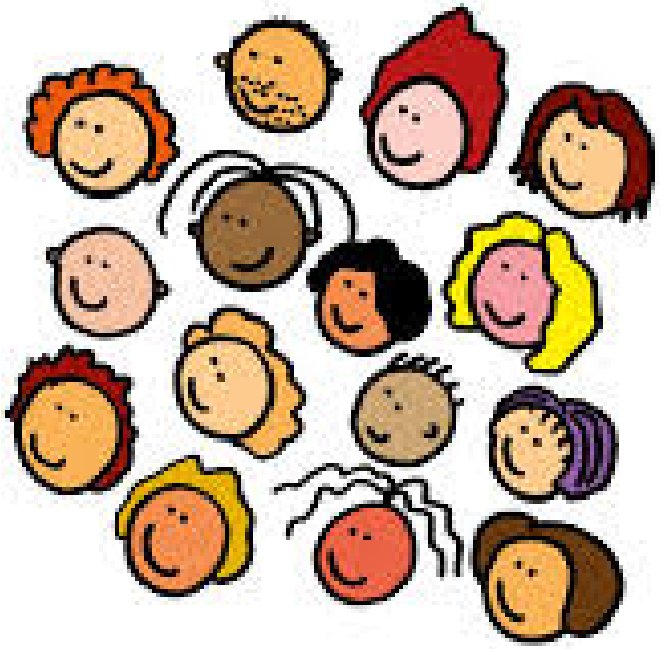


Universal versus female-only vaccination



Thank you very much for your attention.



Appendix

Anal, head/neck, vaginal, vulvar, and penile cancer

- Multifactorial diseases
- HPV-induced:
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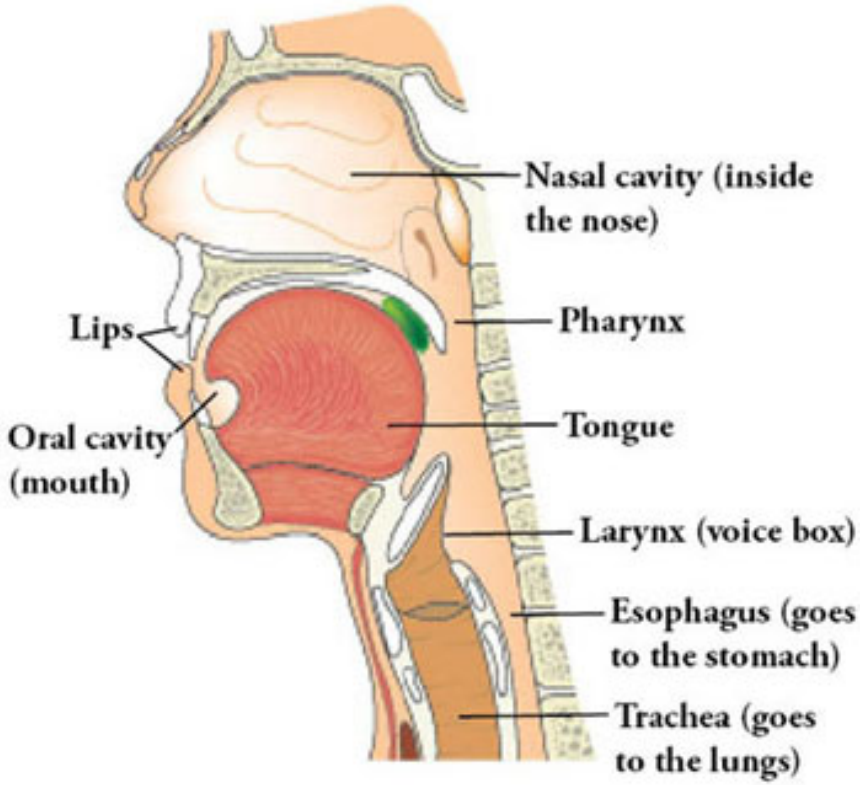
  - more than 50% of vaginal, vulvar and penile cancers
  - 60–70% of oropharyngeal cancers
- Other head/neck cancers mainly attributed to tobacco and alcohol



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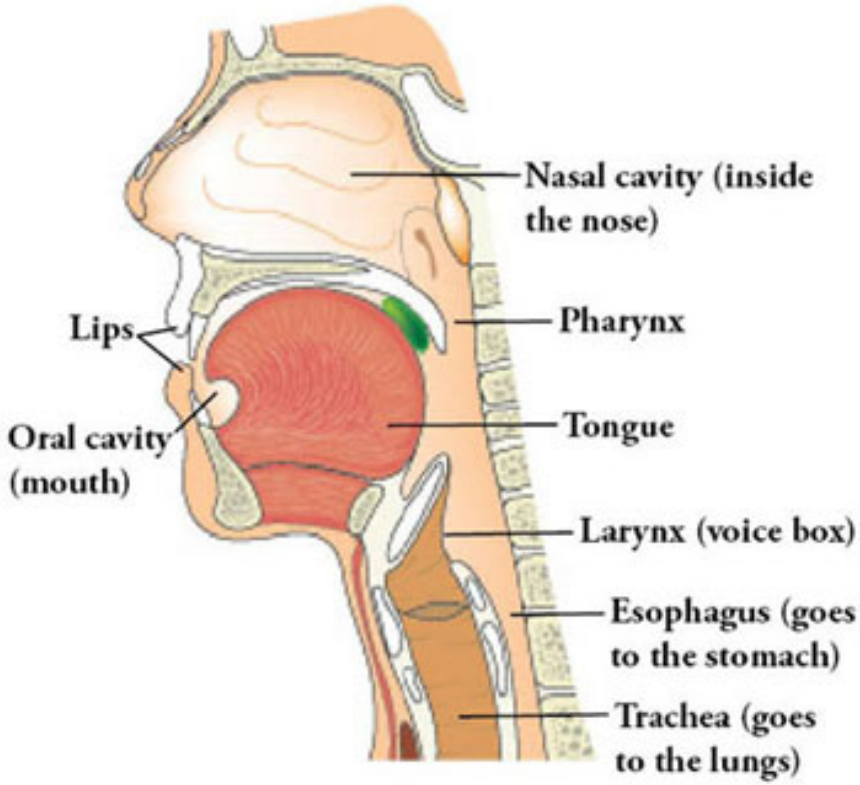
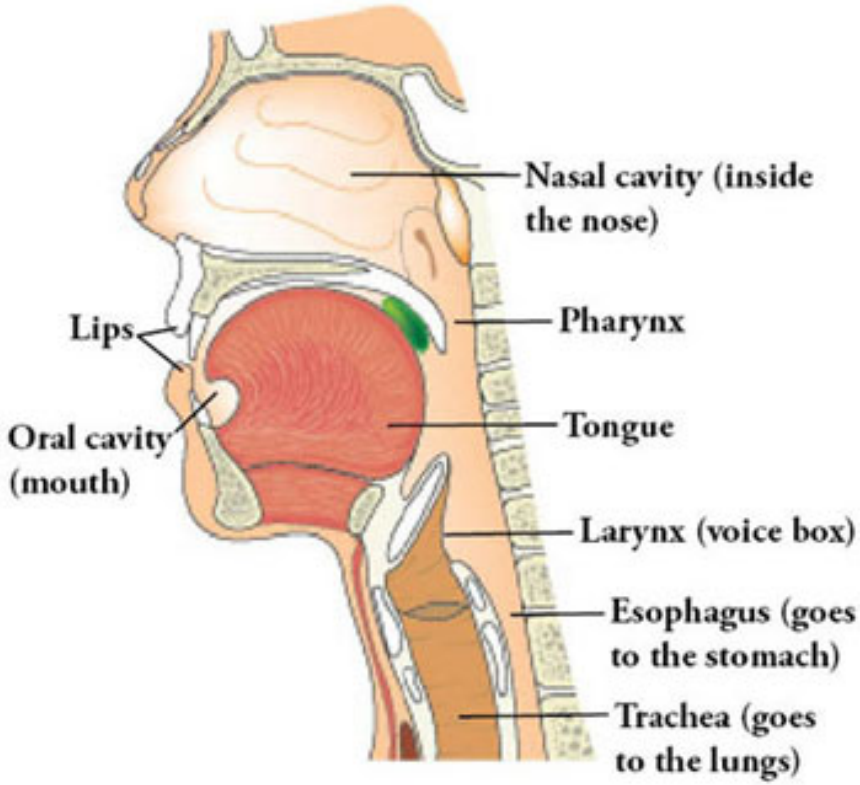


Anal, head/neck, vaginal, vulvar, and penile cancer

- Multifactorial diseases
- HPV-induced:
  - more than 90% of anal cancers
  - more than 50% of vaginal, vulvar and penile cancers
  - 60–70% of oropharyngeal cancers
- Other head/neck cancers mainly attributed to tobacco and alcohol



Databases

- Scopus
- Pubmed
- Cochrane Library
- Web of Science
- Centre for Review and Dissemination (CRD)
  - Database of Abstracts of Reviews of Effects (DARE)
  - NHS Economic Evaluation Database (EED)
  - Health Technology Assessment (HTA)

Search word combinations

```
((cost-effectiveness) OR (cost-utility) OR (cost-benefit))
AND ((HPV vaccine) OR (human papillomavirus vaccine) OR
HPV or (human papillomavirus))
```

For universal vaccination extended by

```
AND (boys OR male)
```

Checklist for literature review

Methodology

- Static vs. dynamic
- Deterministic vs. stochastic
- Ordinary differential equation (ODE) vs. Markov model vs. hybrid model
- Population-based vs. individual-based vs. microsimulation model

Model assumptions

- Country of investigation
- HPV types involved
- HPV-induced diseases
- Vaccine coverage rate
- Vaccine efficacy
- Vaccination age
- Male vaccination
- Duration of immunity
- Application of booster
- Levels of sexual activity
- Sexual mixing strategy
- Cervical screening strategy
- Duration of follow-up
- Time step of follow-up

Research outcome

- Cost-effectiveness analysis
- HPV-prevalence reduction

Summary of methodologies

Universal HPV vaccination: 26 publications

- 8 reuse methodology
- 8 ordinary differential equation (ODE) models
- 1 static Markov model
- 2 network models
- 3 difference equation models
- 3 hybrid models
- 1 prevalence-based model

Female-only HPV vaccination: 90 publications

- $\approx$ 50% reuse methodology
- 25 static Markov models
- 4 microsimulation models
- 3 cohort models
- 1 prevalence-based model
- 2 difference equation models
- 1 network model
- 10 ODE models
- 8 hybrid models

Summary of research outcomes

Universal vaccination

- 8 publications: cost-effective results
- 7 publications: non-cost-effective results
- 11 publications: only HPV prevalence reductions

Female-only vaccination

- 75 publications: cost-effective results
- 1 publication: non-cost-effective results
- 10 publications: only HPV prevalence reductions
- 4 publications: no research outcomes

Universal vaccination

- Taira et al.
  - Difference equation model for HPV transmission
  - Static Markov disease progression model
- Kim et al.
  - ODE model for HPV transmission
  - Microsimulation disease progression model
- Horn et al.
  - ODE model for HPV transmission
  - Static Markov disease progression model

Bayesian Markov models

- Probabilistic nature
- Exhaustive and mutually exclusive health states
- Moving between health states according to specified transition probabilities
  - Assigning flat and informative distributions with suitable ranges
  - Prior information out of the literature or from expert opinion
  - Updating posterior distributions with available data
  - Propagating parameter uncertainty by Markov Chain Monte Carlo estimations (MCMC)
- Model calibration with age- and gender-specific data on prevalence of HPV infection and induced diseases
- Each health state is assigned a value of utility
  - Ranging between 0 and 1
  - 0 represents death, 1 perfect health
  - Specified with Time Trade-Off (TTO) method
- Health economic analysis of multi cohort HPV vaccination strategy

Hybrid model structures

- **Combination of**
  - natural history of disease infection and progression models
  - dynamic sexual disease transmission models
- **Age- and gender-specific HPV prevalence can be calculated beforehand**
  - by means of discrete or continous time models
  - these probabilities inform the disease progression model afterwards
- **Alternative: the process of sexual mixing can be integrated directly into the static disease progression model**

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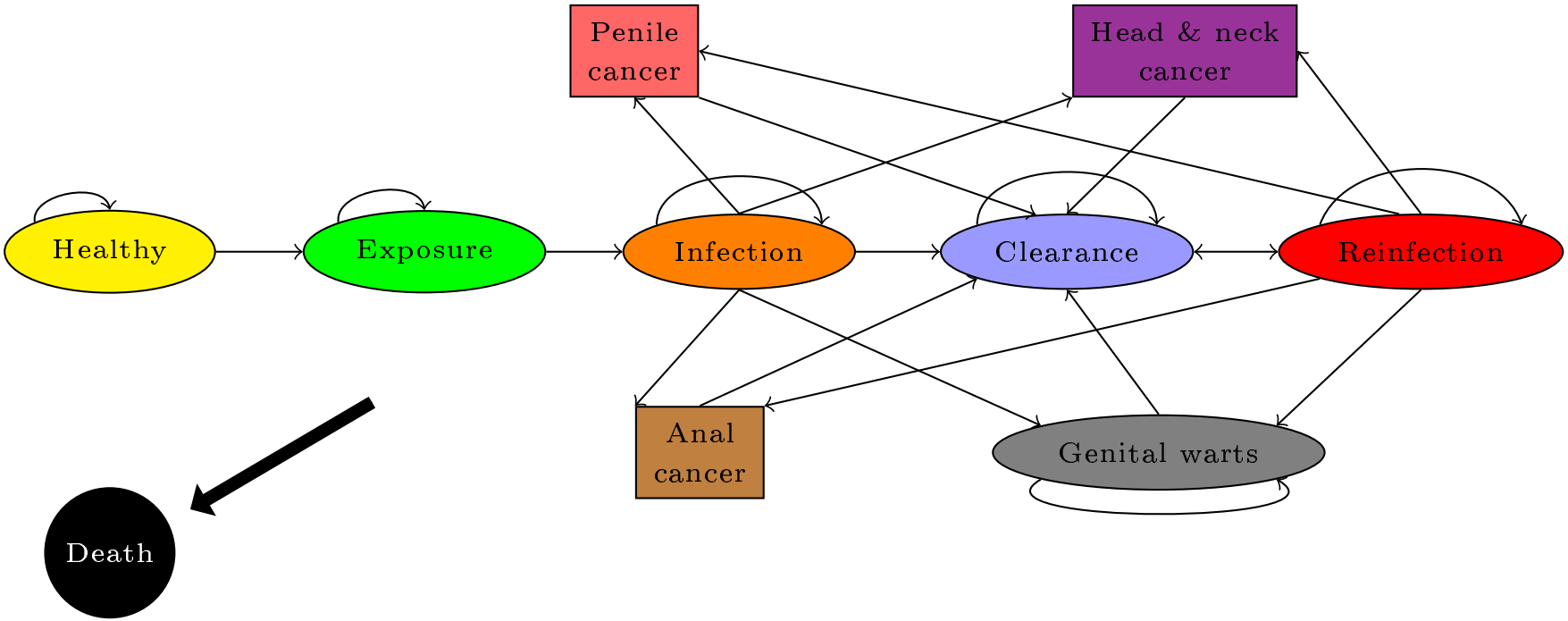
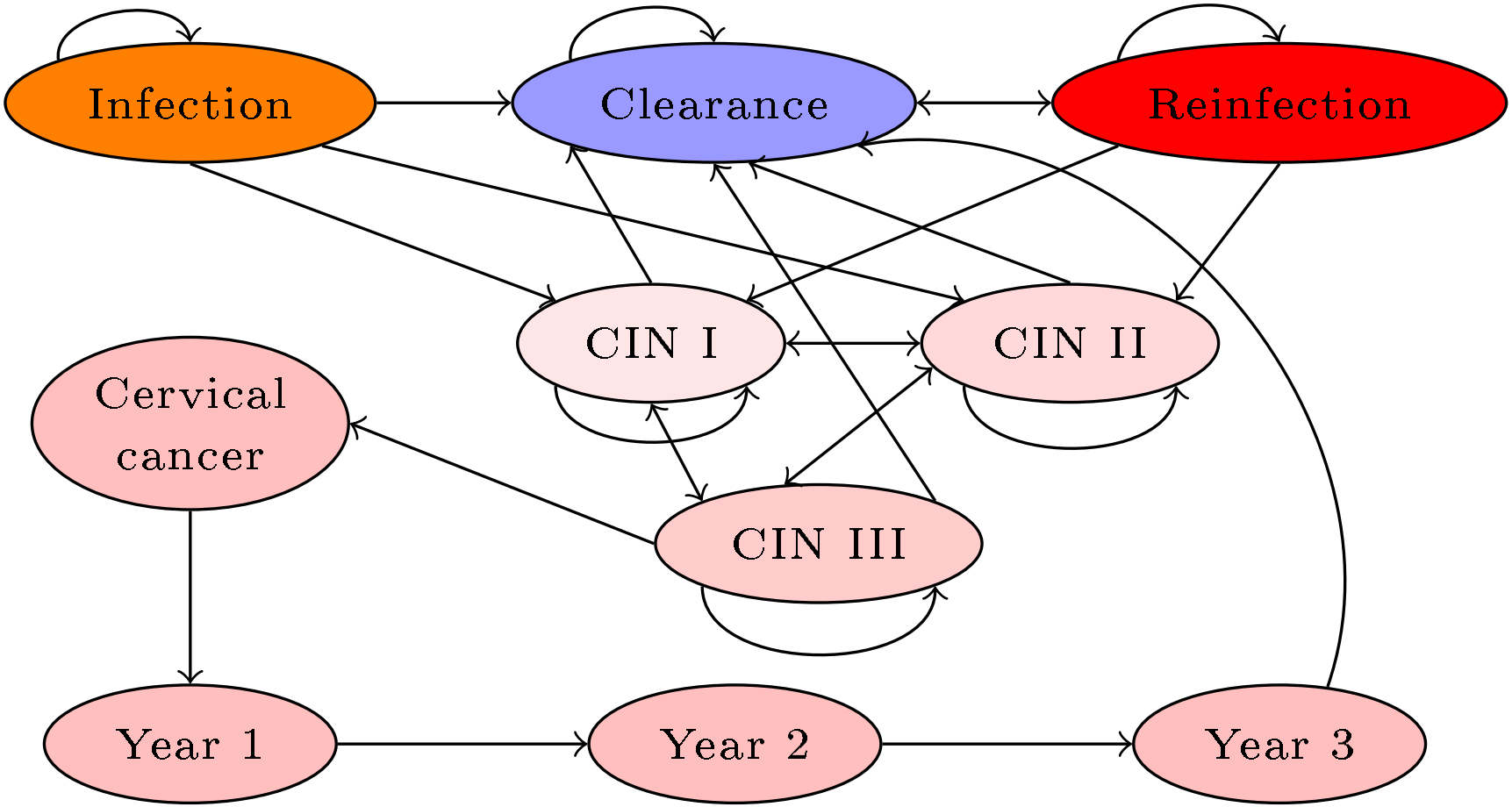
Male model compartment

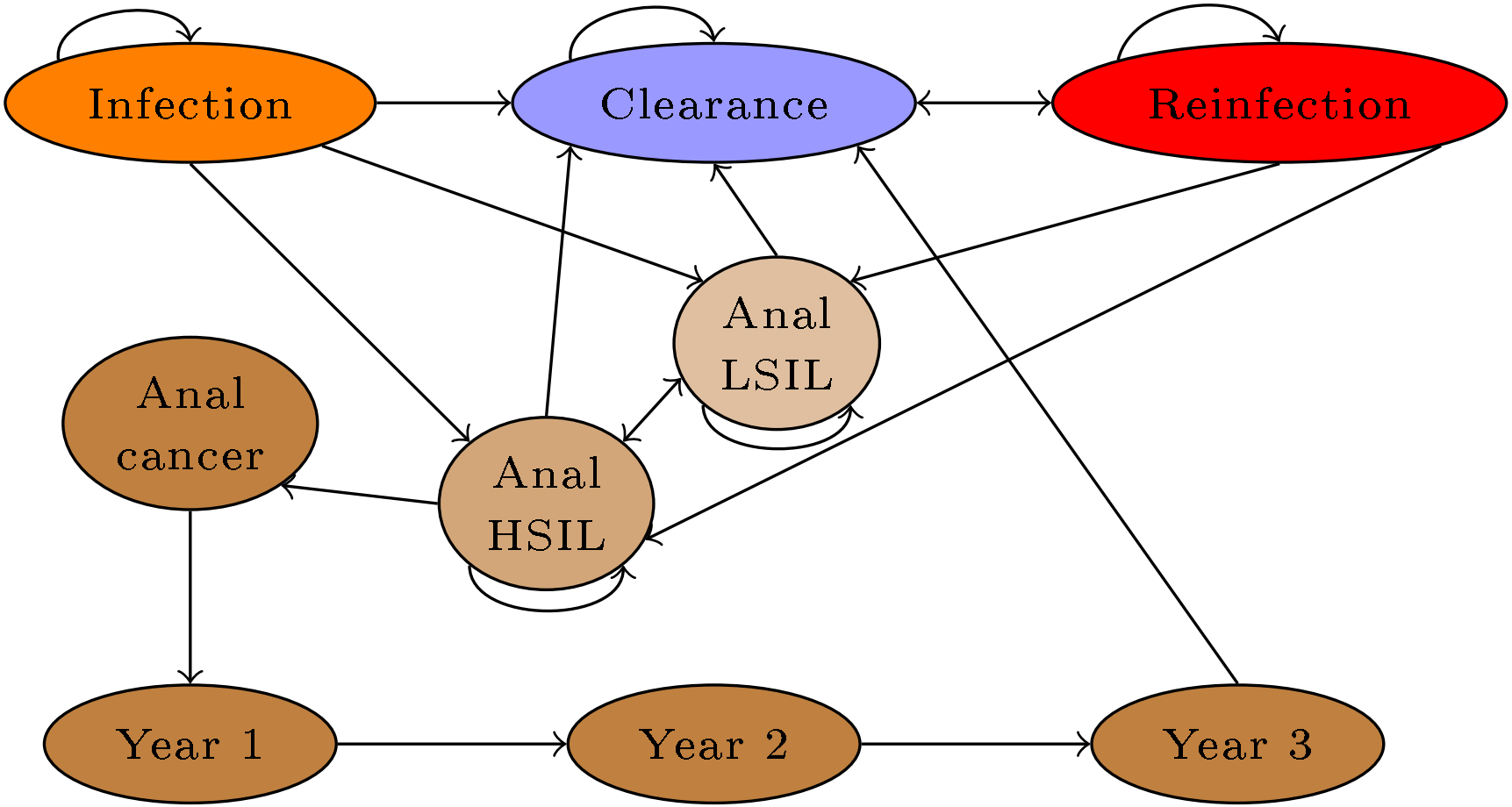
$S_m = 22$ health states



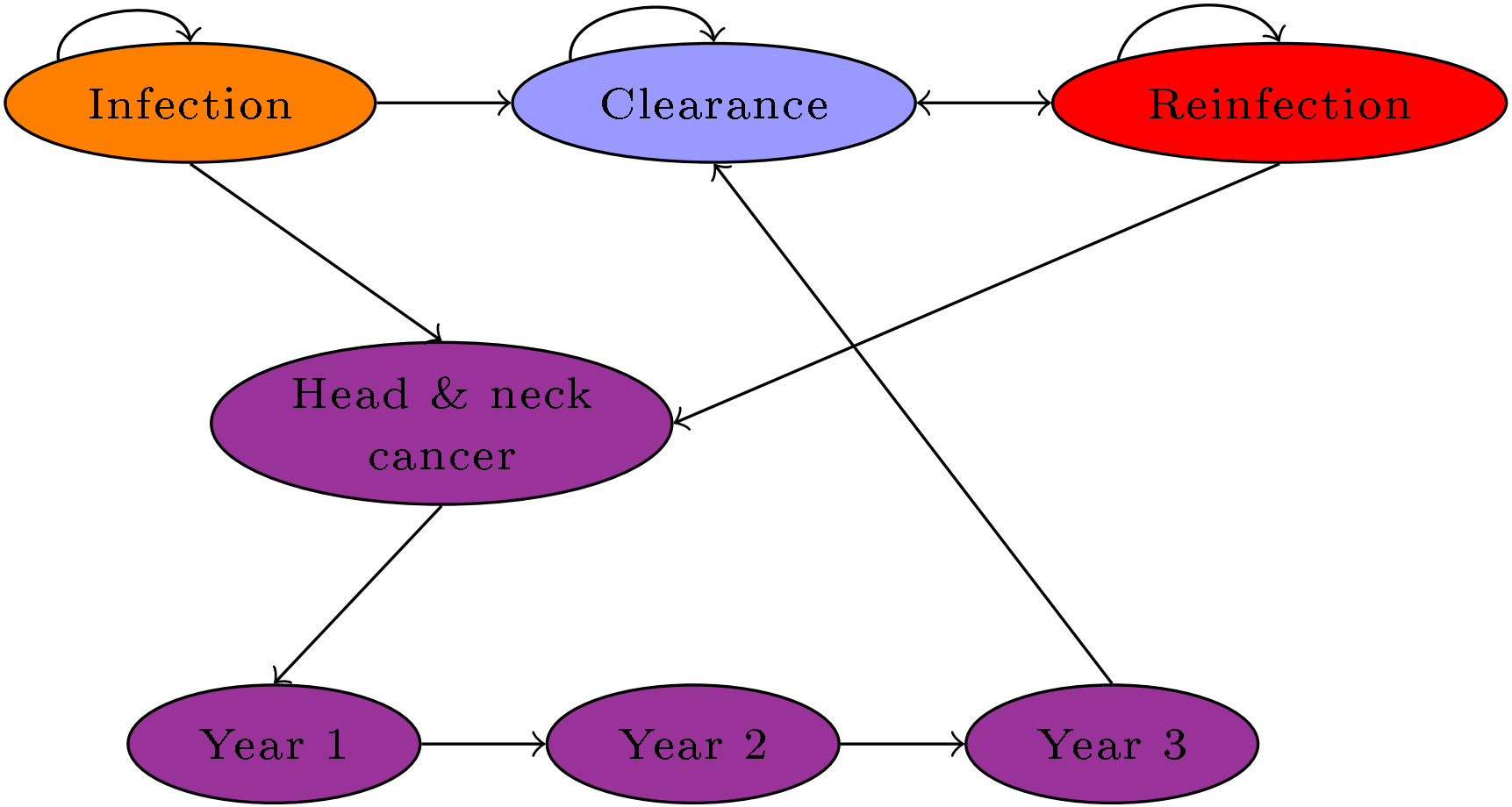
Cervical cancer



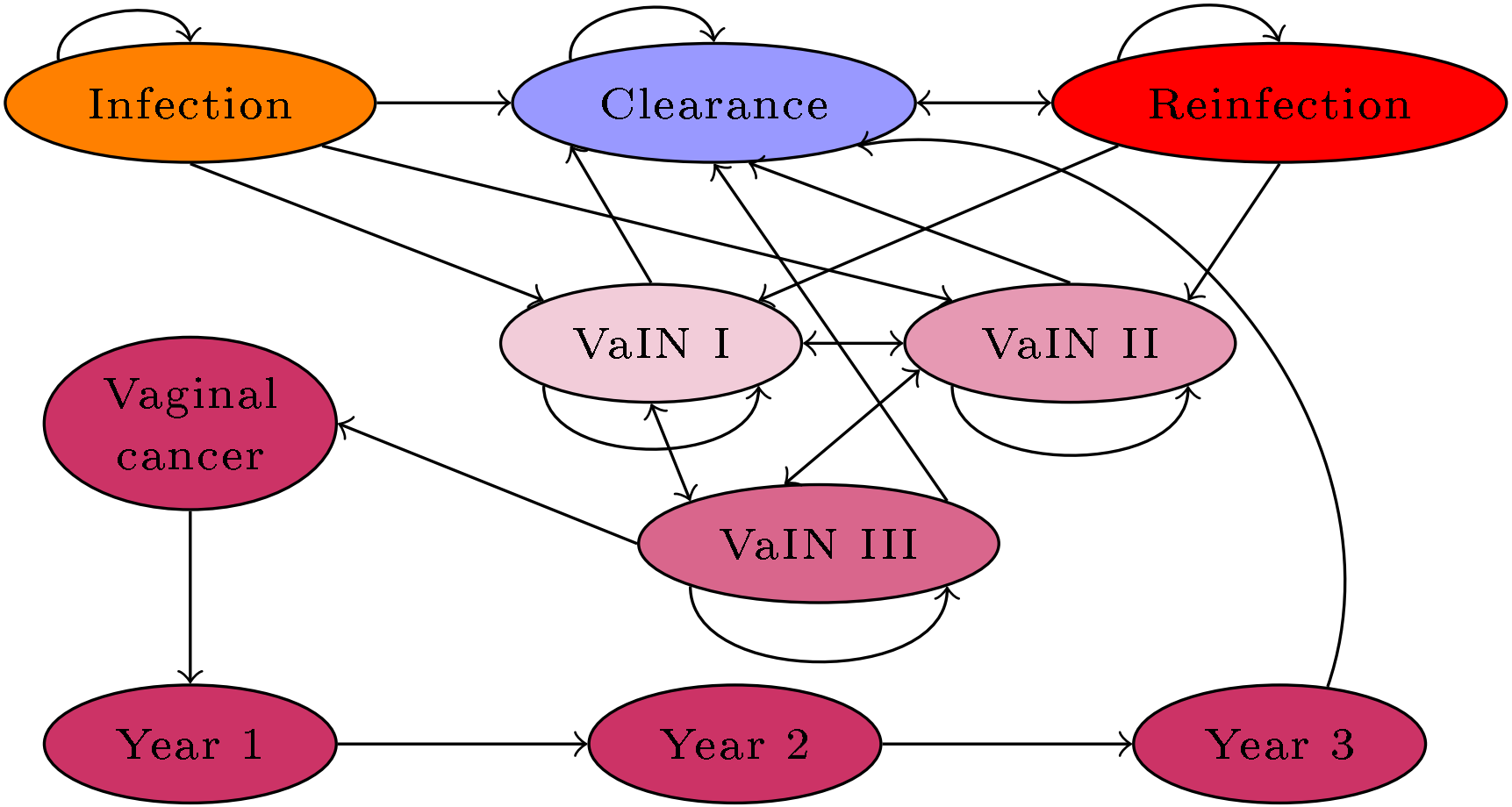
Anal cancer


Infection
Clearance
Reinfection
Anal LSIL
Anal cancer
Anal HSIL
Year 1
Year 2
Year 3

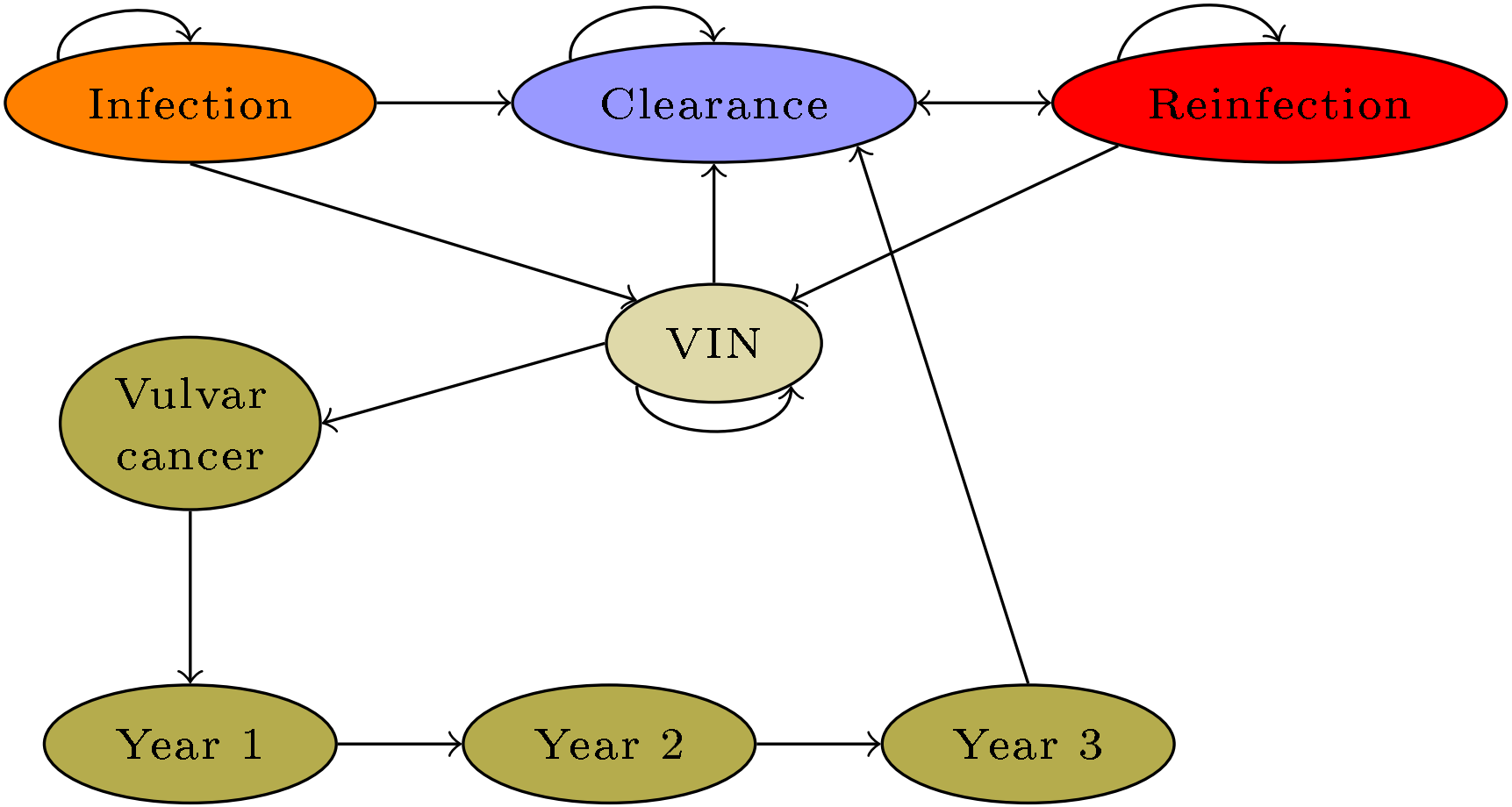
Head and neck cancer



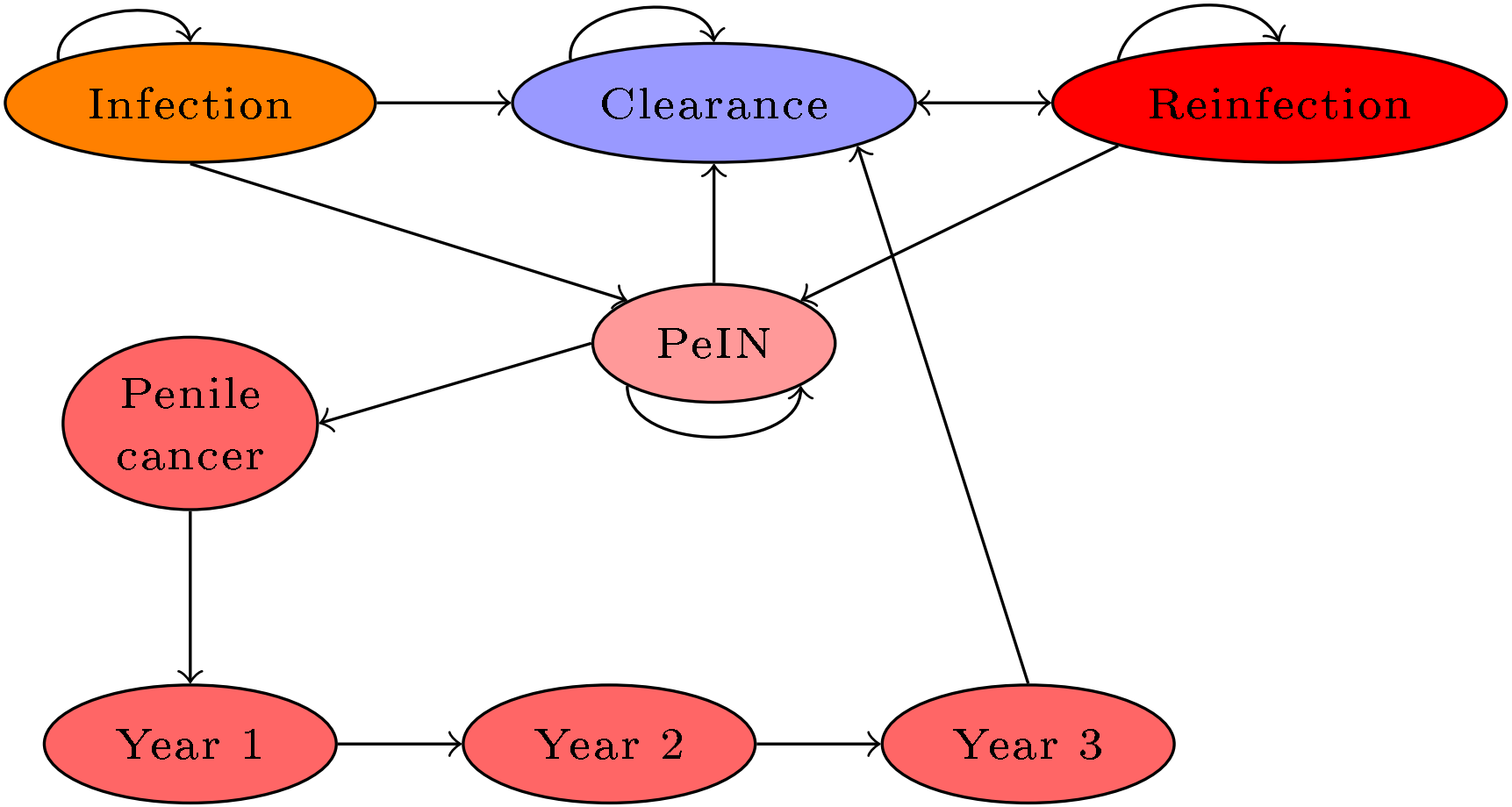
Vaginal cancer



Vulvar cancer



Penile cancer



Transition probabilities

- Individuals move across health states according to $p_{i,a,j,h}$, where
  - i indexes the respective health intervention;
  - a indexes the individual's age;
  - j indexes the original health state;
  - h indexes the target health state.
- All transitions from one health state have to sum up to 1 (constraint of probabilities)
- Transitions to the set of health states $\mathcal{H}$ are possible
- Transitions to health states outside of $\mathcal{H}$ are set to 0
- Remaining in respective state is induced by $1 - \sum_{p_{i,a,j,h}} \forall\, h \in \mathcal{H}$
- Different transition probabilities for females and males as a consequence of different numbers of health states and gender-specific parameters
- Gender-specific parameters with the index $g = 0$ represent females

Examples: From the state *Healthy* ($j = 1$)

- Individuals can have sex (indicated by s_a) and move to $h = 2$
- Individuals can die (indicated by $d_{a,0}$) and move to $h = 9$
- Individuals can remain in perfect health ($h = 1$)

$$
\begin{aligned}
p_{i,a,1,h} &= 0 \,\forall\, h \notin \{1, 2, 9\} \\
p_{i,a,1,2} &= s_a \\
p_{i,a,1,9} &= d_{a,0} \\
p_{i,a,1,1} &= 1 - \sum_{h \neq 1} p_{i,a,1,h}
\end{aligned}
$$

From the state *Exposed* (screening-only)

- Individuals in $j = 2$ can have acquire HPV infection (indicated by $\lambda_{0,s,a}$) and move to $h = 3$
- Individuals in $j = 2$ can die (indicated by $d_{a,0}$) and move to $h = 9$
- Individuals in $j = 2$ can remain in exposure ($h = 2$)

$$
\begin{aligned}
p_{1,a,2,h} &= 0 \, \forall \, h \notin \{2, 3, 9\} \\
p_{1,a,2,3} &= \lambda_{0,s,a} \\
p_{1,a,2,9} &= d_{a,0} \\
p_{1,a,2,2} &= 1 - \sum_{h \neq 2} p_{1,a,2,h}
\end{aligned}
$$

From the state *Exposed* (vaccination)

- Individuals in $j = 2$ can have acquire HPV infection (indicated by $\lambda_{0,s,a}$) and move to $h = 3$
- Individuals in $j = 2$ can die (indicated by $d_{a,0}$) and move to $h = 9$
- Individuals in $j = 2$ can remain in exposure ($h = 2$)

$$p_{2,a,2,h} = 0 \, \forall \, h \notin \{2, 3, 9\}$$
$$p_{2,a,2,3} = \alpha_1[\omega_3(1-\gamma_1)\lambda_{0,s,a} + (1-\omega_3)(1-\zeta\gamma_1)\lambda_{0,s,a}] + (1-\alpha_1)\lambda_{0,s,a}$$
$$p_{2,a,2,9} = d_{a,0}$$
$$p_{2,a,2,2} = 1 - \sum_{h \neq 2} p_{2,a,2,h}$$

- α_1 represents the vaccine coverage in female-only vaccination
- γ_1 represents the vaccine efficacy
- ω_3 represents the vaccine compliance
- ζ represents the reduction in effectiveness due to noncompliance

Population dynamics

	Time of follow-up												
Cohort	0	1	2	3	4	5	6	7	8	9	10	**...**	55
1	25	26	27	28	29	30	31	32	33	34	35	...	80
2	24	25	26	27	28	29	30	31	32	33	34		79
3	23	24	25	26	27	28	29	30	31	32	33		78
4	22	23	24	25	26	27	28	29	30	31	32		77
5	21	22	23	24	25	26	27	28	29	30	31		76
6	20	21	22	23	24	25	26	27	28	29	30		75
7	19	20	21	22	23	24	25	26	27	28	29		74
8	18	19	20	21	22	23	24	25	26	27	28		73
9	17	18	19	20	21	22	23	24	25	26	27		72
10	16	17	18	19	20	21	22	23	24	25	26		71
11	15	16	17	18	19	20	21	22	23	24	25		70
12*	14	15*	16	17	18	19	20	21	22	23	24	...	69
13*	13	14	15*	16	17	18	19	20	21	22	23		68
14*	*12*	13	14	15*	16	17	18	19	20	21	22		67
15		*12*	13	14	15	16	17	18	19	20	21		66
16			*12*	13	14	15	16	17	18	19	20		65
17				*12*	13	14	15	16	17	18	19		64
18					*12*	13	14	15	16	17	18		63
19						*12*	13	14	15	16	17		62
20							*12*	13	14	15	16		61
21								*12*	13	14	15		60
22									*12*	13	14		59
23										*12*	13		58
24											*12*	...	57

Convergence

- Running 2 chains in parallel to calculate posterior distributions of parameters $\boldsymbol{\theta} = (\theta_1, ..., \theta_k)$
- Choosing two different starting points with larger variance compared to the underlying data
- Comparing within-chain variance $W(\theta_k)$ to between-chain variance $B(\theta_k)$
- n_{sims} represents the length of the MCMC sample

$$\widehat{Var}(\theta_k|y) = \frac{n_{sims}-1}{n_{sims}} W(\theta_k) + \frac{1}{n_{sims}} B(\theta_k)$$

The Gelman-Rubin statistic $\hat{R}$

Convergence is monitored by assessing the *potential scale reduction*

$$\hat{R} = \sqrt{\frac{\widehat{Var}(\theta_k|y)}{W(\theta_k)}}$$

- $\hat{R}$ is the factor by which the scale of the posterior distribution of θ_k can be further reduced
- A longer MCMC run will possibly improve convergence
- $R \hat{\leq} 1.1$ represents sufficient convergence

Autocorrelation

- MCMC iterations are by definition correlated
- Current observation depends on previous one
- The higher the autocorrelation, the lower the equivalence between MCMC output and a proper iid sample

$$n_{eff} = \frac{n_{sims}}{1+2\sum_{t=1}^{\infty} corr_t}$$

- $corr_t$ is the *lag t* autocorrelation
- $n_{eff} \approx n_{sims}$ indicates negligible autocorrelation
- In case of high autocorrelation
  - convergence can still be reached
  - extreme quantiles of the posterior distribution are typically estimated without precision

Cost-effectiveness analysis

Presentation of preliminary results under baseline assumptions

- vaccination of 12 year old females and males
- high vaccine coverage rate in the catch-up vaccination

Detailed explanation of calculation process including

- overall costs and utilities
- present values of cost (PVC) and utility (PVU)
- *Incremental Cost-Effectiveness Ratio* (ICER)
- cost-effectiveness plane

Overall costs and utilities

Costs include

- diagnosic procedures of health states
  - 2 pap smears and 2 colposcopies in females with CIN I-III
  - 1 HPV DNA test in females with CIN III and cervical cancer
  - anoscopy, biopsy, cytology in individuals with anal LSIL and HSIL
  - diagnostic costs of other HPV-induced diseases already included in treatment costs
- treatment of HPV-induced precancerous lesions and cancers
- vaccine administration and product costs in female-only, universal and catch-up interventions

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Utilities are considered stage- and gender-specific.

- Utility loss in certain health state only occurs after its diagnosis

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Overall costs and utilities

Unit costs and utilities are multiplied by the number of individuals in intervention i at time t in the respective health state, and by the probabilities of diagnosis, to result in **overall** measures.

$$
\begin{aligned}
C_{i,t} = & C^{scr}_{i,t} + C^{vac}_{i} + C^{gw}_{i,t} + C^{cin}_{1,i,t} + C^{cin}_{2,i,t} + C^{cin}_{3,i,t} + C^{cerv}_{i,t} + C^{lsil}_{i,t} \\
& + C^{hsil}_{i,t} + C^{an}_{i,t} + C^{hn}_{i,t} + C^{vin}_{i,t} + C^{vulv}_{i,t} + C^{vain}_{1,i,t} + C^{vain}_{2,i,t} + C^{vain}_{3,i,t} \\
& + C^{pein}_{i,t} + C^{pen}_{i,t}
\end{aligned}
$$

$$
\begin{aligned}
U_{i,t} = & U^{health}_{i,t} + U^{inf}_{i,t} + U^{gw}_{i,t} + U^{cin}_{1,i,t} + U^{cin}_{2,i,t} + U^{cin}_{3,i,t} + U^{cerv}_{r,i,t} + U^{lsil}_{i,t} \\
& + U^{hsil}_{i,t} + U^{an}_{r,i,t} + U^{hn}_{r,i,t} + U^{vin}_{i,t} + U^{vulv}_{r,i,t} + U^{vain}_{1,i,t} + U^{vain}_{2,i,t} + U^{vain}_{3,i,t} \\
& + U^{vag}_{r,i,t} + U^{pein}_{i,t} + U^{pen}_{r,i,t}
\end{aligned}
$$

Incremental Cost-Effectiveness Ratio (ICER)

- Standard measure in cost-effectiveness analyses
- Incremental cost per QALY gained
  - **Q**uality-**A**djusted **L**ife **Y**ear
  - Utility of health state is multiplied with amount of time spent within
- All model parameters in vector $\boldsymbol{\theta} = (\boldsymbol{\theta^3}, \boldsymbol{\theta^2})$
  - $\boldsymbol{\theta^3}$ representing parameters in $i = 3$ (universal vaccination)
  - $\boldsymbol{\theta^2}$ representing parameters in $i = 2$ (female-only vaccination)
- Ratio of expectations of cost- and effectiveness-differentials
  - $\Delta_c = \text{PVC}_3 - \text{PVC}_2$
  - $\Delta_e = \text{PVU}_3 - \text{PVU}_2$

$$ICER = \frac{E[\text{PVC}|\boldsymbol{\theta^3}] - E[\text{PVC}|\boldsymbol{\theta^2}]}{E[\text{PVU}|\boldsymbol{\theta^3}] - E[\text{PVU}|\boldsymbol{\theta^2}]} = \frac{E[\Delta_c]}{E[\Delta_e]}$$

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Interpretation of the ICER

Positive algebraic sign

- Universal vaccination both higher costs and effects than female-only vaccination
- Universal vaccination both lower costs and effects than female-only vaccination

Negative algebraic sign

- Universal vaccination higher costs and lower effects than female-only vaccination
- Universal vaccination lower costs and higher effects than female-only vaccination $\rightarrow$ cost-saving ICER

ICER values between €30,000 and €45,000 are deemed to be cost-effective according to the Italian Health Economics Association (AEIS). In contrast, the NHS in the UK define ICERs under £25,000 to be cost-effective.

Cost-effectiveness plane

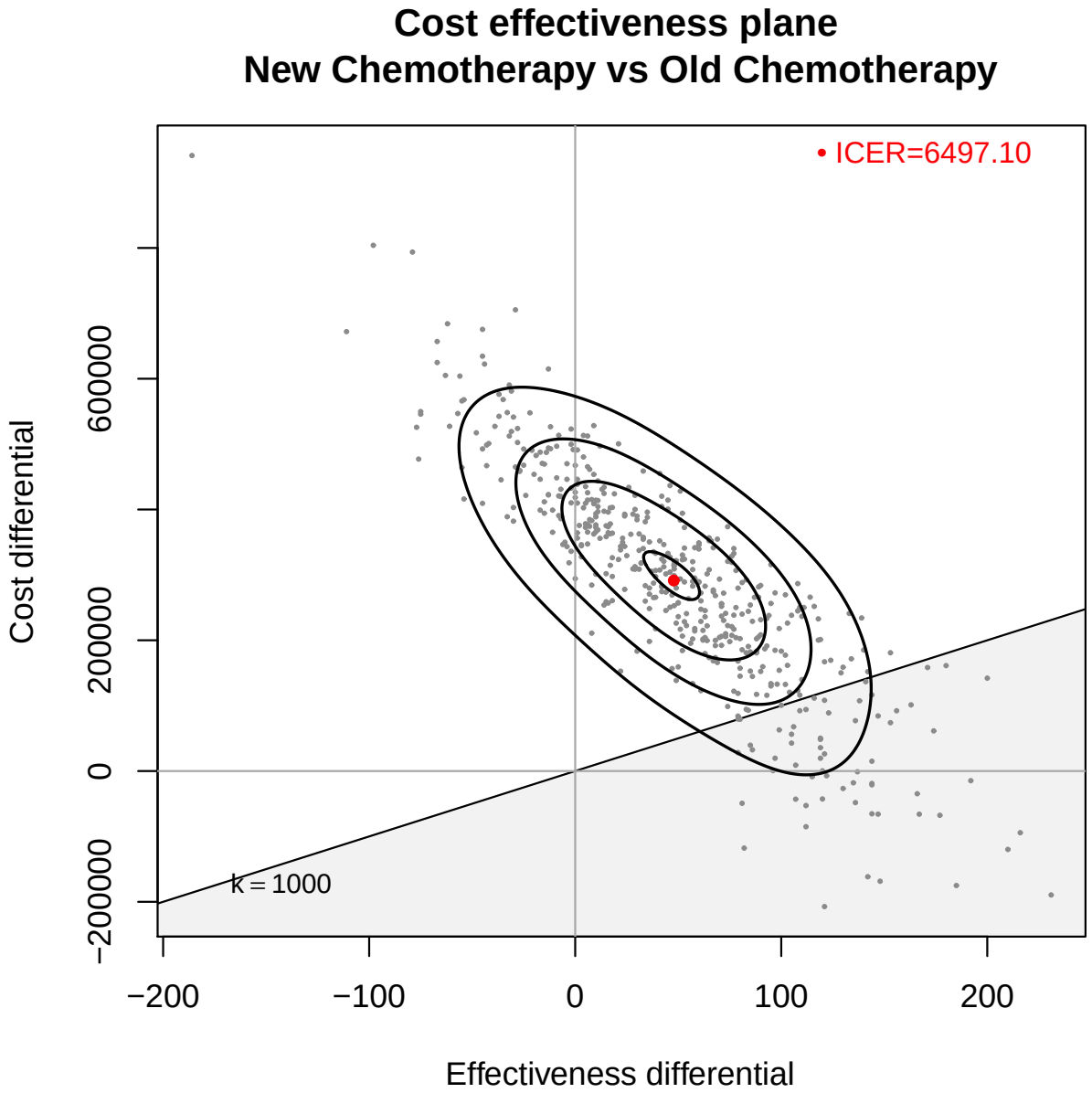
Description of the graph

- The x-axis is the effectiveness differential Δ_e
- The y-axis is the cost differential Δ_c
- Each point represents a possible future in terms of the expected measures of differential cost and benefit
- The spread of the distribution of points accounts for uncertainty
- The shaded part of the plane indicates the sustainability area (ICERs below the threshold of cost-effectiveness)
- The ICER is displayed as a red dot with its corresponding value

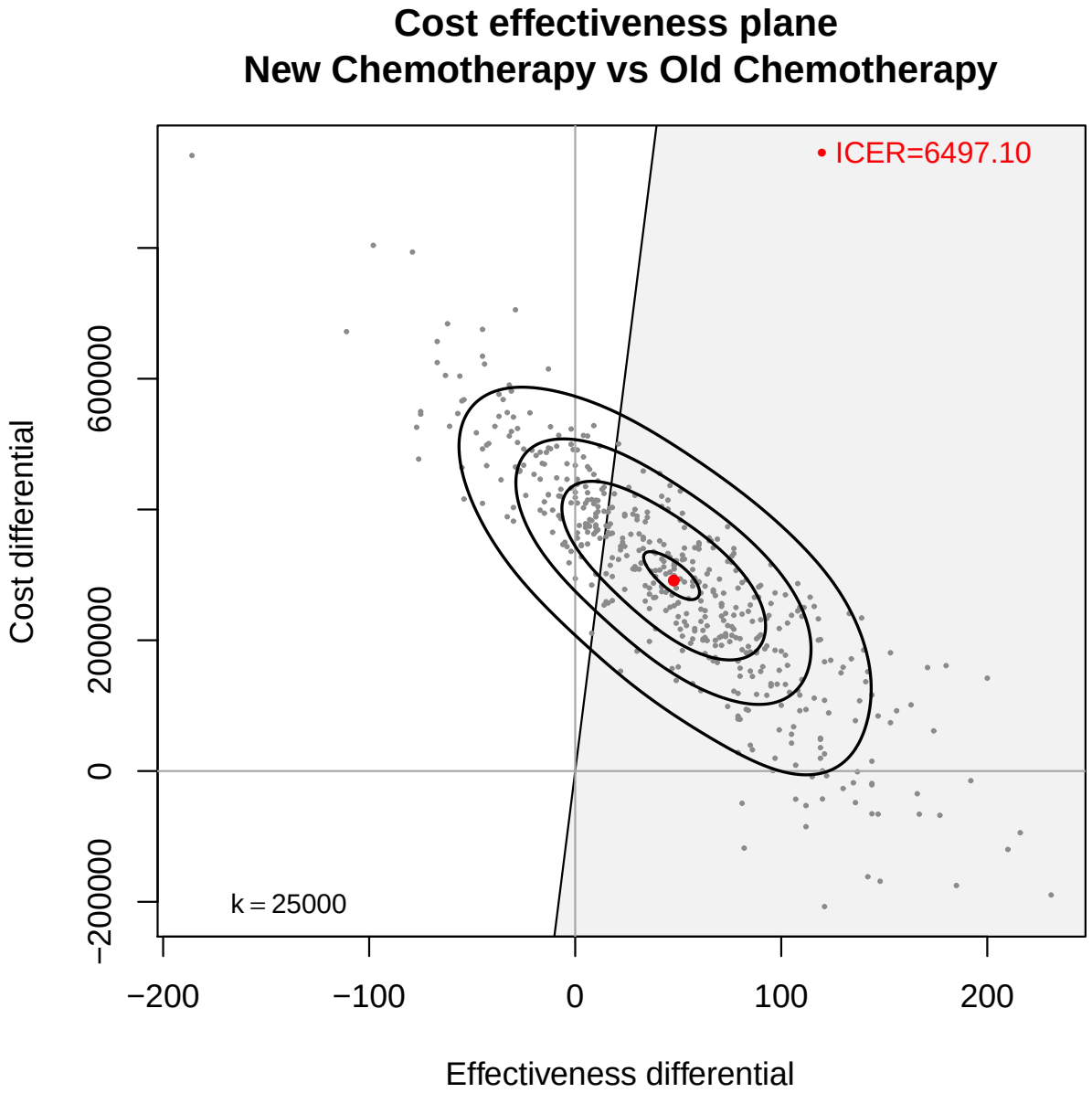
Interpretation of the graph

- Points lying in the north-eastern quadrant (i.e. when $\Delta_e > 0$ and $\Delta_c > 0$) suggest that universal vaccination proves more effective as well as more expensive than female-only vaccination.
- Points lying in the north-western quadrant (i.e. when $\Delta_e < 0$ and $\Delta_c > 0$) suggest that universal vaccination proves less effective and more expensive than female-only vaccination.
- Points lying in the south-western quadrant (i.e. when $\Delta_e < 0$ and $\Delta_c < 0$) suggest that universal vaccination proves less effective as well as less expensive than the reference intervention.
- Finally, points lying in the south-eastern quadrant (i.e. when $\Delta_e > 0$ and $\Delta_c < 0$) suggest that universal vaccination proves more effective and less expensive than female-only vaccination.

Cost-effectiveness plane vs ICER



Cost-effectiveness plane vs ICER



Future work

- **Programming tasks**
  - Including layers of uncertainty in the deterministic age- and gender-specific mixing matrices and partner acquisition rates
  - Implying the necessity of a booster application
  - Generalizing the R code to enable an easier calculation of scenarios next to the baseline
  - Conducting a full cost-effectiveness analysis
- **Reading literature** on standard methodology in infectious disease transmission modelling
- **Writing tasks**
  - Publishing the cost-effectiveness analysis results, focusing especially on the finding of staggered male vaccination age
  - Publishing the methodology of the hybrid Bayesian Markov model
  - Writing up the final PhD thesis

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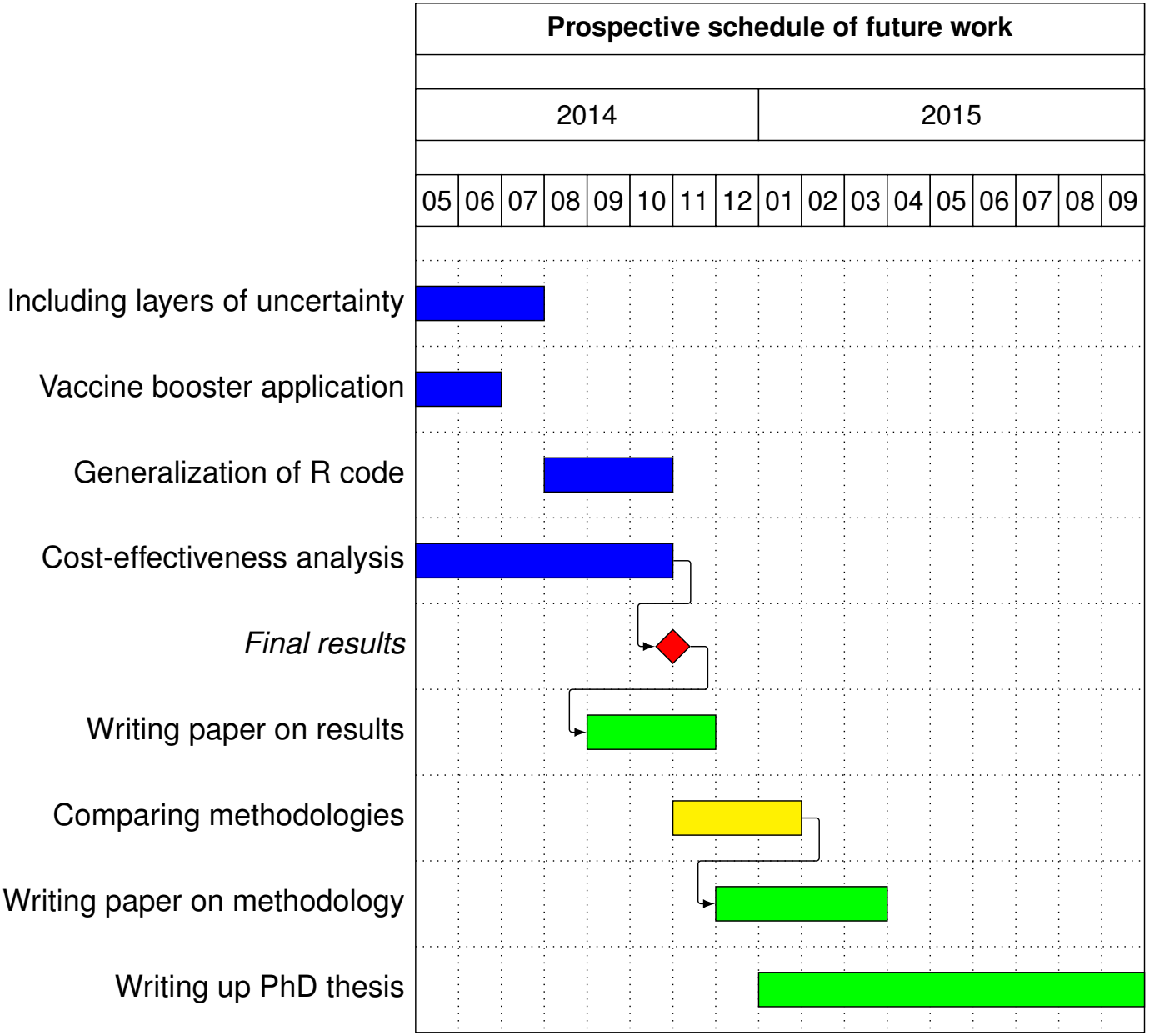
Gantt chart


Prospective schedule of future work
2014
2015
05 06 07 08 09 10 11 12 01 02 03 04 05 06 07 08 09
Including layers of uncertainty
Vaccine booster application
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Cost-effectiveness analysis
Final results
Writing paper on results
Comparing methodologies
Writing paper on methodology
Writing up PhD thesis