Dynamic Bayesian Markov model for health economic evaluations of interventions in infectious disease

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University of Oxford

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Disclaimer...

Before I begin:

- My **personal** view of the world:

  Statisticians should be in charge of everything.

- And actually, come to think about it:

  Bayesian *Statisticians should be in charge of all Statisticians.*

- So I probably will be very annoying in the next hour or so...[1]

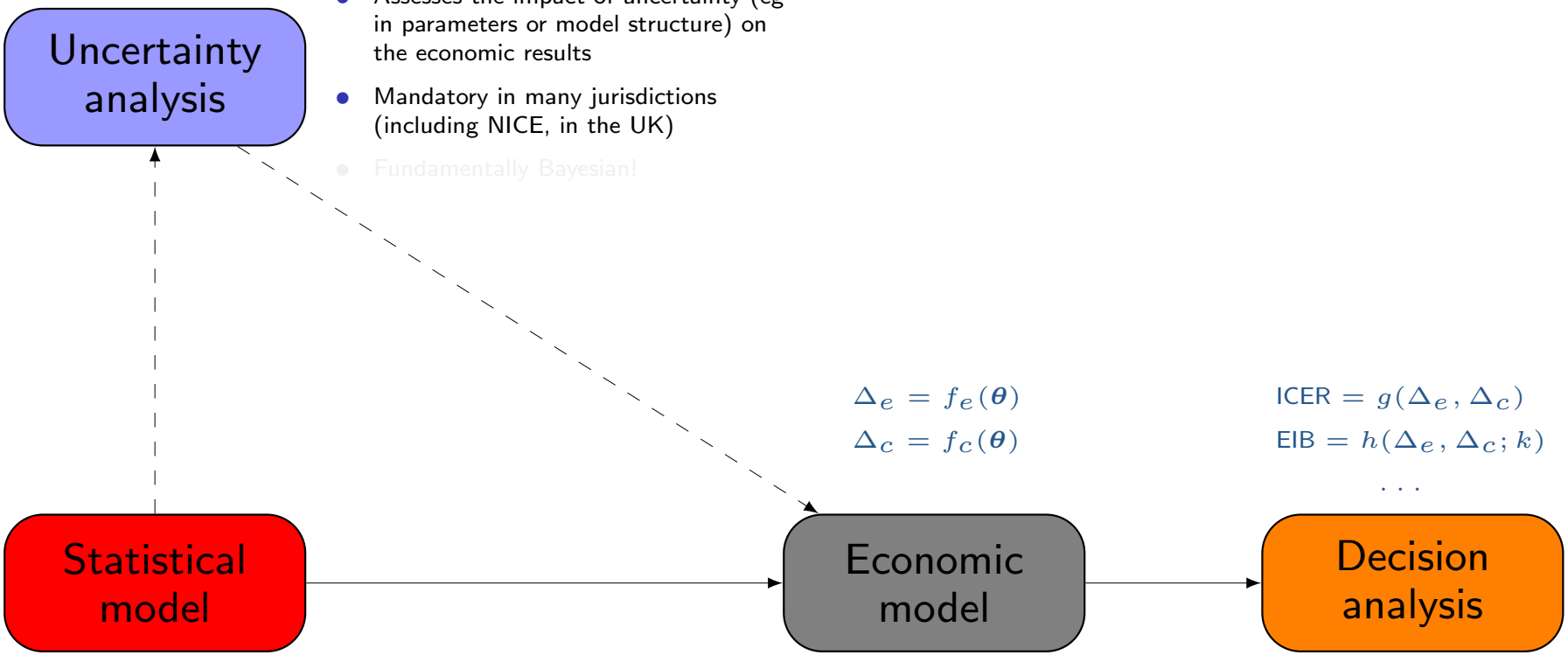
[1] But luckily no non-Bayesian Statistician has been harmed in the making of this slides

Outline

1. **Health technology assessment (HTA)**
   - What is it? How does it work?
   - HTA for infectious diseases
2. **Motivating example**
   - HPV vaccination model
   - Complex structure & uncertain inputs...
3. **Toy example (simulations)**
   - ODE-based models vs discrete time approximations
   - ODE vs Bayesian ODE vs Dynamic Bayesian MM
   - Results
4. **HPV model**
   - Epidemiological results
   - Cost-effectiveness analysis
5. **Conclusions**

Health technology assessment (HTA)

Objective: Combine costs & benefits of a given intervention into a rational scheme for allocating resources



- Assesses the impact of uncertainty (eg in parameters or model structure) on the economic results
- Mandatory in many jurisdictions (including NICE, in the UK)
- Fundamentally Bayesian!

- Estimates relevant **population** parameters
- Varies with the type of available data (& statistical approach!)

- Combines the parameters to obtain a population average measure for costs and clinical benefits
- Varies with the type of available data & statistical model used

- Summarises the economic model by computing suitable measures of "cost-effectiveness"
- Dictates the best course of actions, given current evidence
- Standardised process

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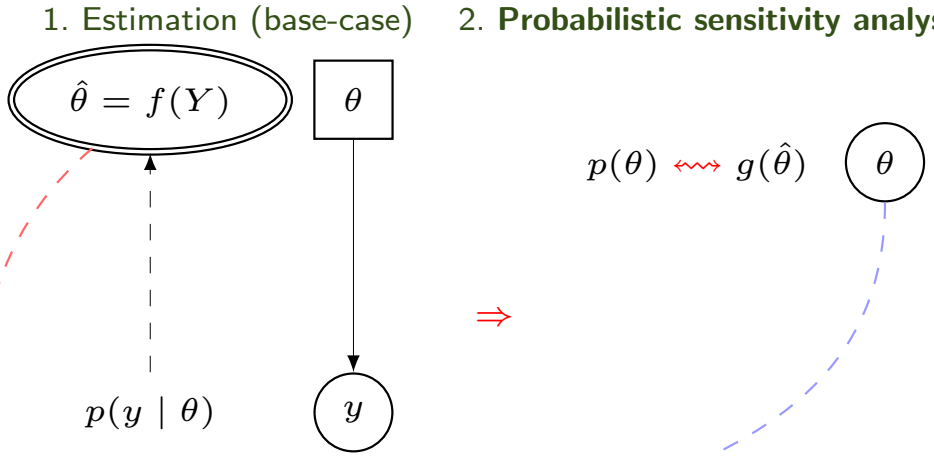

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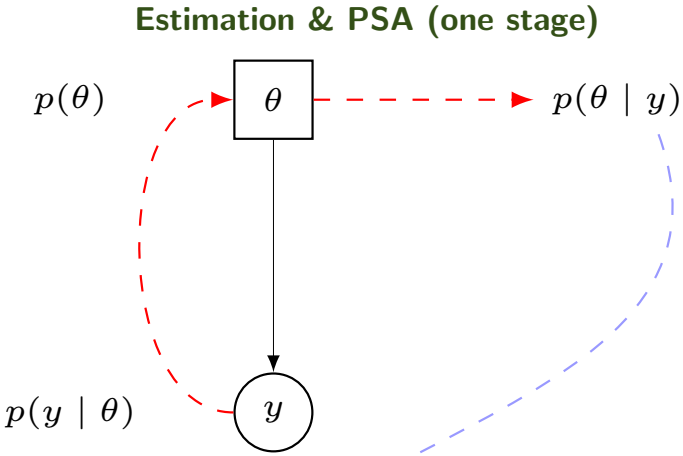

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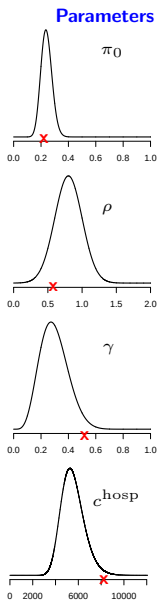

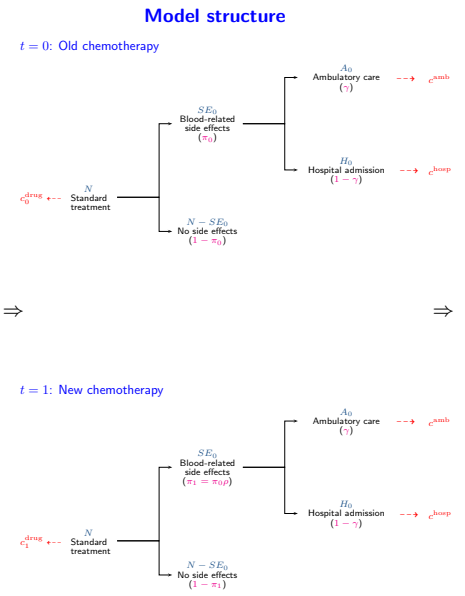

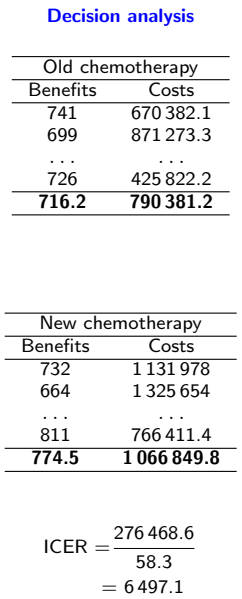

Old chemotherapy	
Benefits	Costs
741	670 382.1
699	871 273.3
...	...
726	425 822.2
716.2	**790 381.2**

New chemotherapy	
Benefits	Costs
732	1 131 978
664	1 325 654
...	...
811	766 411.4
774.5	**1 066 849.8**

$$\text{ICER} = \frac{276\,468.6}{58.3} = 6\,497.1$$

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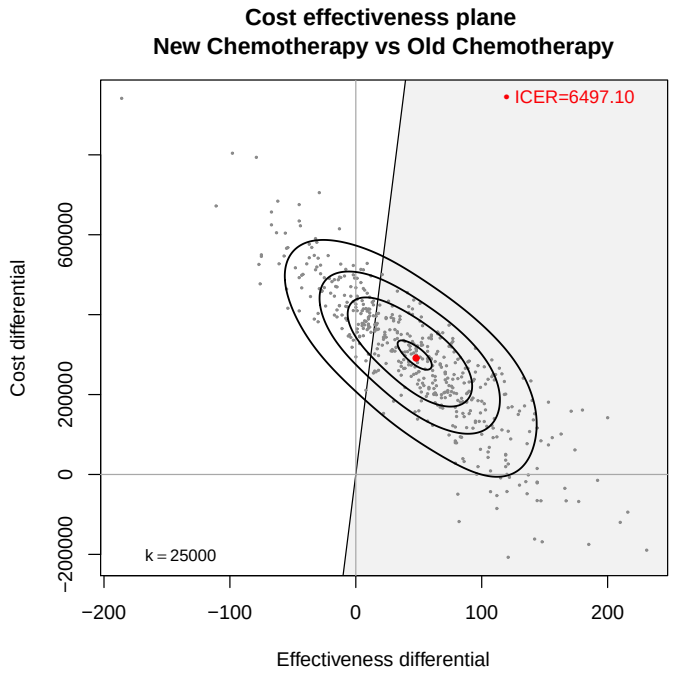

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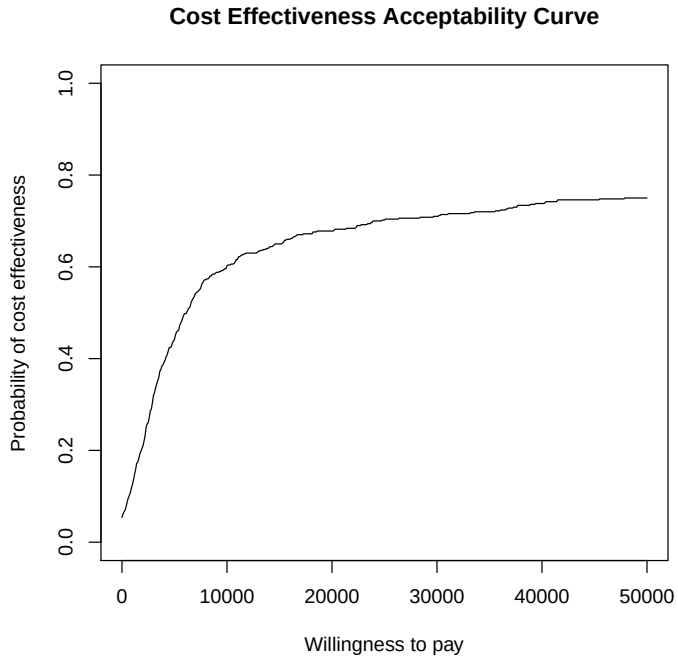

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Health technology assessment (HTA)

- **In the UK**, bodies such as NICE are responsible for guidance and advice (to DoH and NHS) on whether interventions should be publicly funded
- This applies to many types of health-care interventions
  - (First and foremost...) **Pharmaceuticals**
  - Behavioural change/complex interventions (e.g. mental health)
  - ...
- Canada and Australia have very similar set-ups — CADHTA and PBAC are almost exact counterparts to NICE
- Other jurisdictions (eg France, Italy, Spain) have slightly different (less formal?) processes — but there is a(n increasing) drive in following in NICE's footsteps
  - As of yesterday, Denmark has decided to adopt QALYs for CEAs...
  - (...unless/until Brexit breaks that too)

- **But what about vaccines and interventions for infectious diseases?**

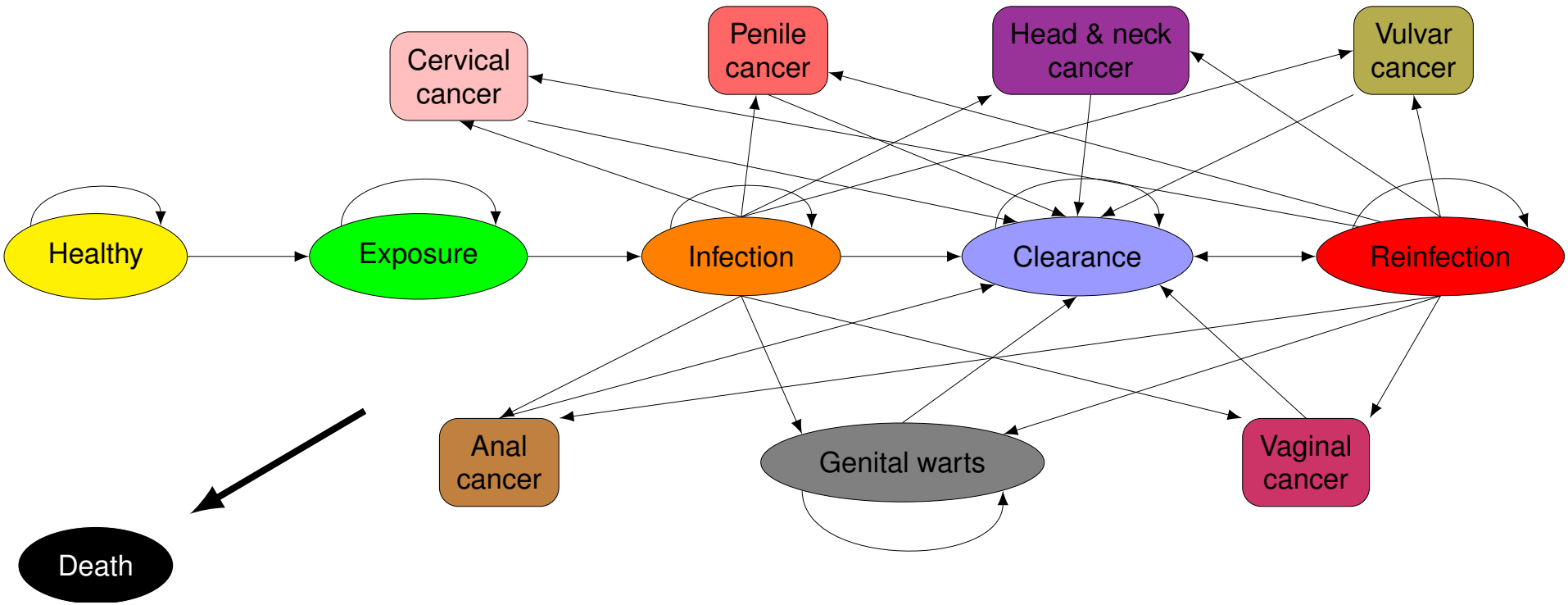
HTA for infectious diseases

- In the UK, appraisal of vaccines is under the remit of a different body (JCVI)
  - Since 2009/10, the Health Protection Regulation **obliges** the Health Secretary to ensure that recommendations for national vaccination programmes are based on an assessment demonstrating cost-effectiveness *(assuming they have time left after all the fridges buying...)*

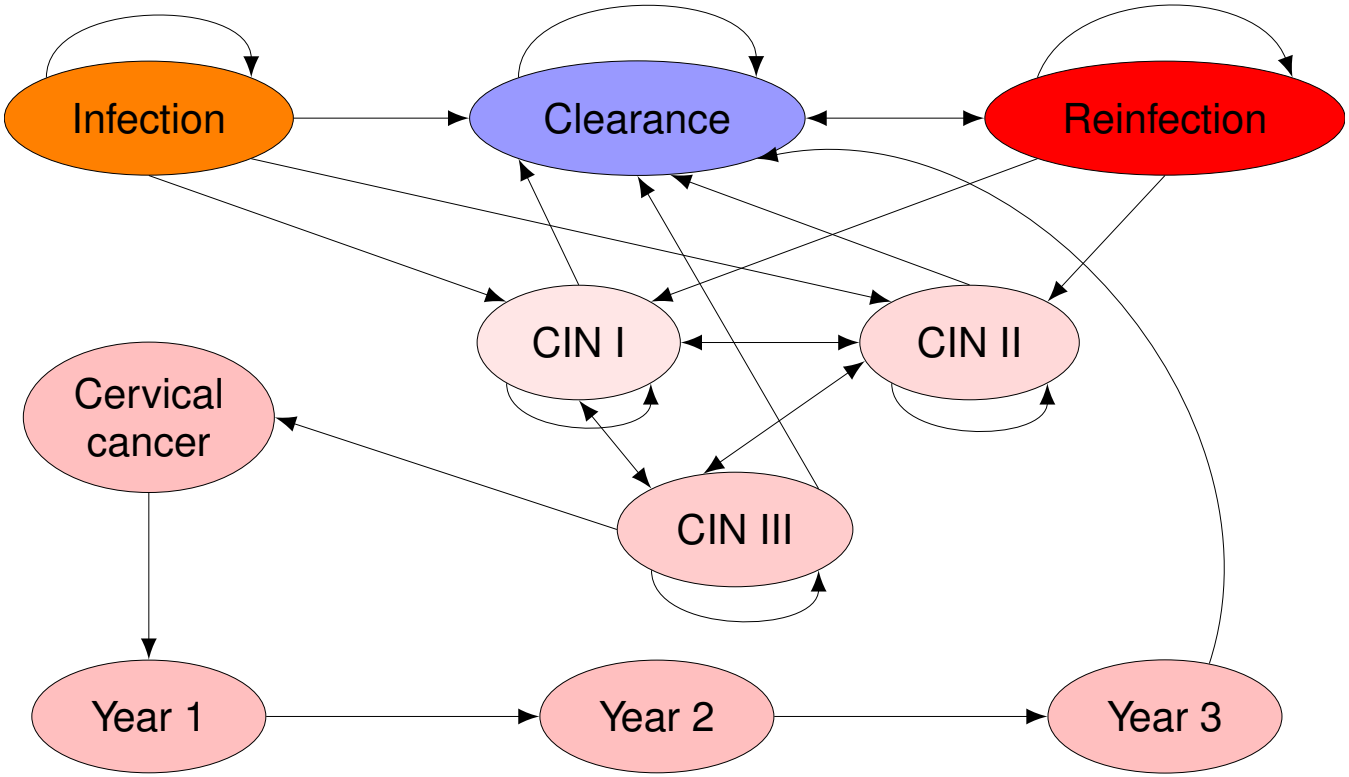
- **However**, there are currently no vaccine-specific guidelines for developing clinical or cost-effectiveness evidence
  - Modelling for infectious disease arguably more complex than it is for "normal" pharmaceutical interventions
  - Compartmental models need to account for **herd immunity** and **dynamic transmission**

- Typical "compromise" (especially in industry!)
  - Epidemiologic component: up to standard
    - Usually based on **ODEs** and advanced mathematical modelling
  - Cost-effectiveness analysis: sub-optimal
    - (Economic) Modellers only access output of complex mathematical modelling and combines with ad-hoc procedures

Females compartment model: $S_f = 36$ health states
Males compartment model: $S_m = 22$ health states



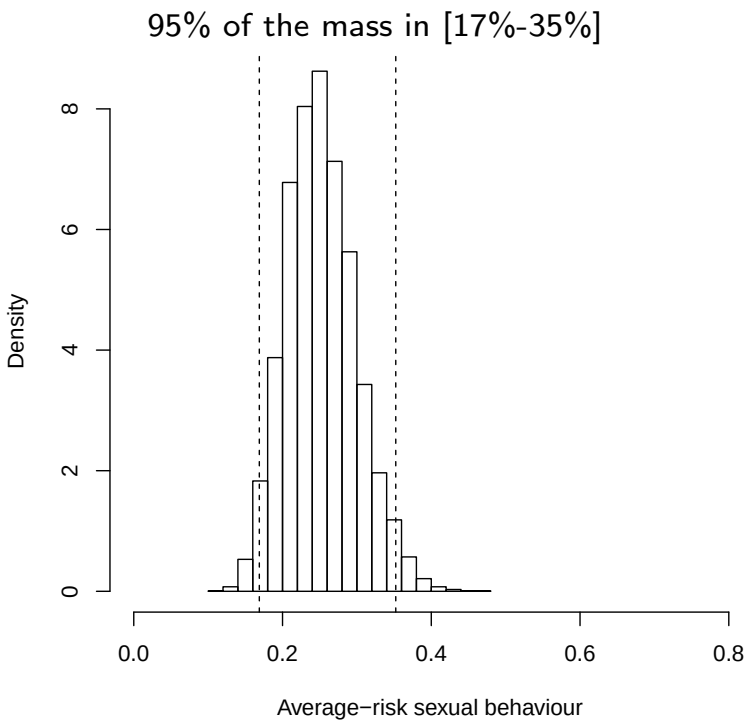
Cervical cancer module (blown up)

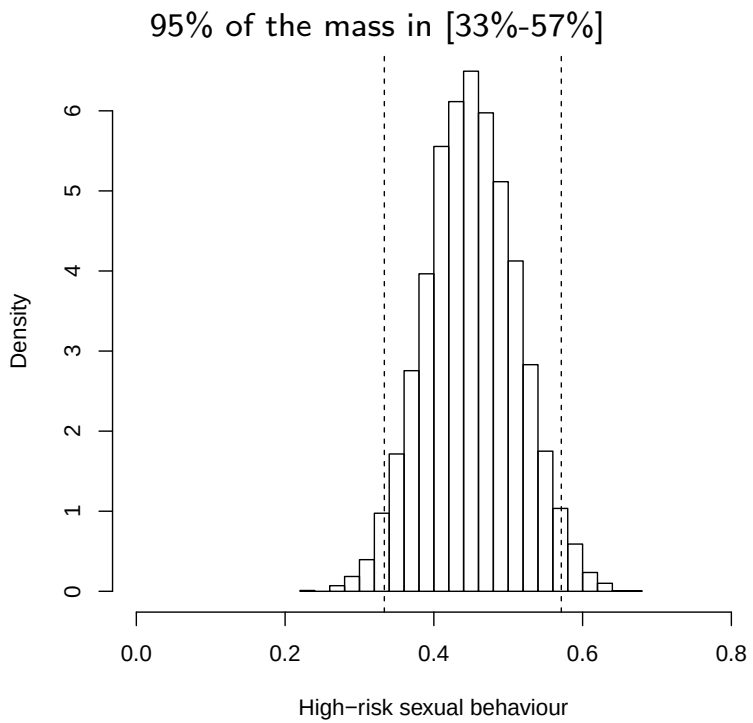


Lots of uncertainty in the model inputs...

- **HPV transmission rate**: crucial parameter, limited/inconclusive evidence available
  - Uniform distribution in [0;1] (Korostil et al, 2012)?
  - Per *sex act*: $\sim$ 40% with a range of 5-100% (Dunne et al, 2006)?
  - Per *partnership*: $\sim$ 42% with a range of 36-47% (Burchell et al, 2011)?
  - Affected by external factors (eg average- vs high-risk sexual behaviour)?

- Bayesian modelling useful to include expert opinion and relatively straightforward for (probabilistic) sensitivity analysis



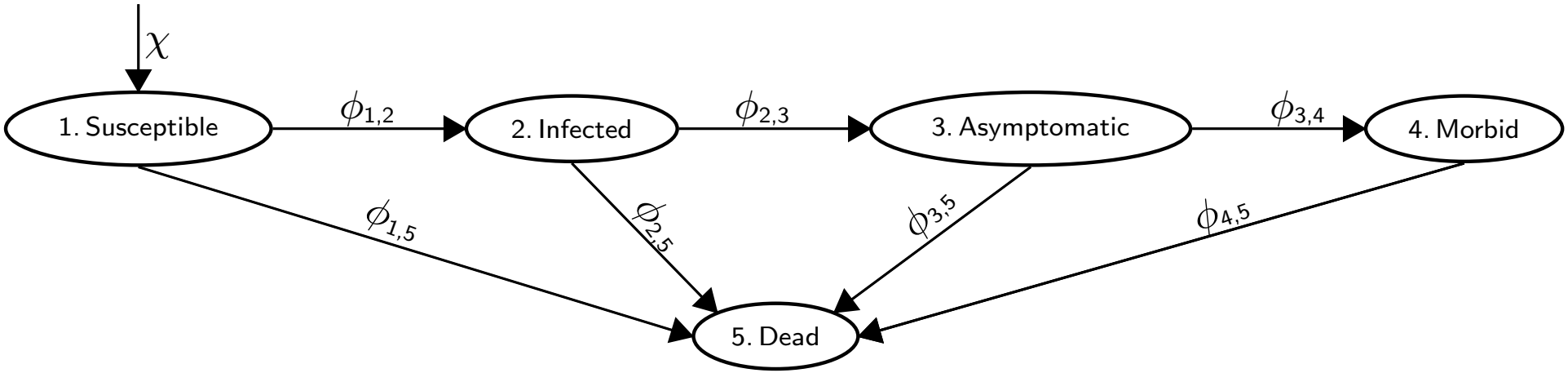


The problem with ODEs(?)

Well — there's really no problem with ODEs-based dynamic transmission models... **BUT**:

1. They can be very computationally intensive
2. Often requires specialised software (e.g. Berkeley Madonna), which the average Economic Modeller is most likely not familiar with
   - Steps towards world domination no. 1: http://www.statistica.it/gianluca/teaching/r-hta-workshop/
3. Crucially, because of the potential computational complexity, the process of **uncertainty/probabilistic sensitivity analysis** (PSA) is much less straightforward (then in "normal" HTAs)!
   - Notably, PSA is often conducted "retrospectively" using procedures such as Latin Hypercube Sampling or Monte Carlo sampling
4. HTA models often involve very complex structures (usually more complex than standard "clinical" comparisons)
   - And this exhacerbates the potential for computational complexity...

Consider an infectious disease, e.g. HIV



- $\phi_{r,s}$ are the **transition parameters**, governing movements across the states

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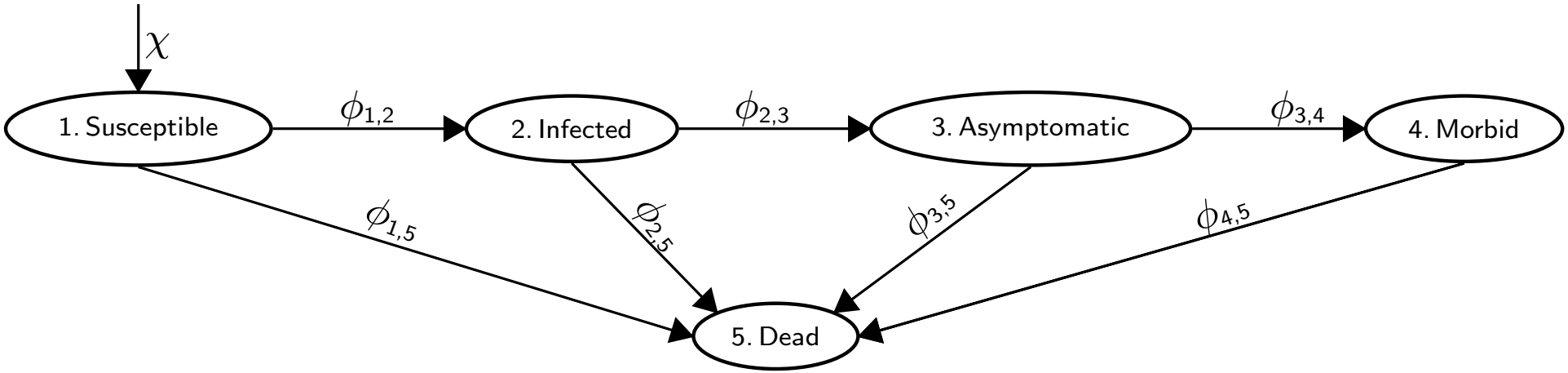
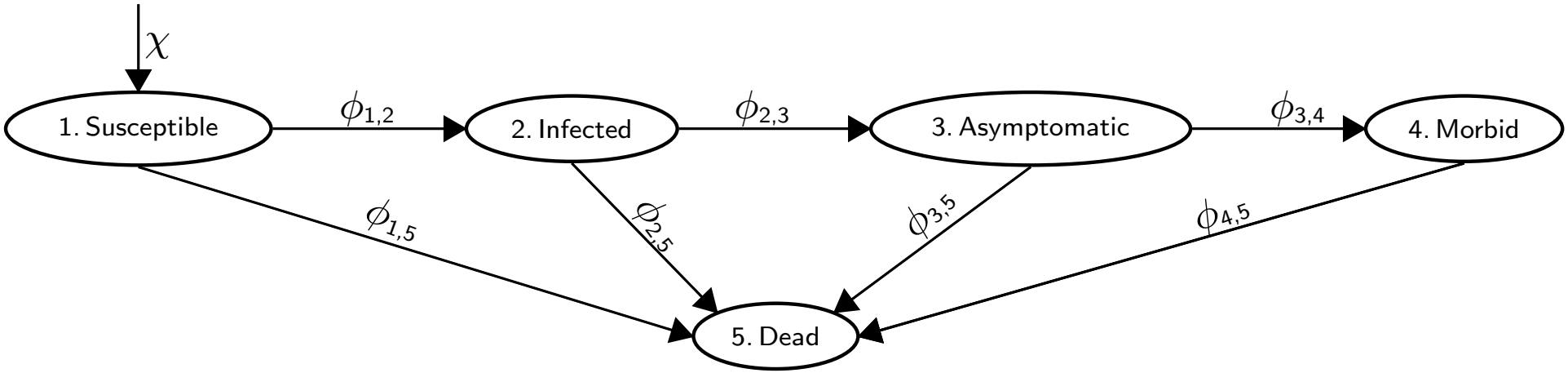


$$\frac{dn_1(t)}{dt} = \chi[n_1(t) + n_2(t) + n_3(t) + n_4(t)] - \rho_{1,2}(t)n_1(t) - \rho_{1,5}n_1(t)$$
$$\frac{dn_2(t)}{dt} = \rho_{1,2}(t)n_1(t) - \rho_{2,3}n_2(t) - \rho_{2,5}n_2(t)$$
$$\frac{dn_3(t)}{dt} = \rho_{2,3}n_2(t) - \rho_{3,4}n_3(t) - \rho_{3,5}n_3(t)$$
$$\frac{dn_4(t)}{dt} = \rho_{3,4}n_3(t) - \rho_{4,5}n_4(t)$$
$$\frac{dn_5(t)}{dt} = \rho_{1,5}n_1(t) + \rho_{2,5}n_2(t) + \rho_{3,5}n_3(t) + \rho_{4,5}n_4(t)$$

$\phi_{r,s} = \rho_{r,s} =$ transition **rates** (continuous times)

Consider an infectious disease, e.g. HIV



$$\mathbf{\Pi} = \begin{pmatrix} \pi_{1,1} & \pi_{1,2} & 0 & 0 & \pi_{1,5} \\ 0 & \pi_{2,2} & \pi_{2,3} & 0 & \pi_{2,5} \\ 0 & 0 & \pi_{3,3} & \pi_{3,4} & \pi_{3,5} \\ 0 & 0 & 0 & \pi_{4,4} & \pi_{4,5} \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$\phi_{r,s} = \pi_{r,s} =$ transition **probabilities** (in discrete consecutive times)

1. **"Standard" ODE**
   - Solve ODE system to estimate the model parameters
   - Characterise population dynamics & accounts for herd immunity
   - Feed point estimate from the transmission model to the economic model to obtain the "best-case" scenario
   - Re-run economic model for different configuration of the transmission model to do PSA
2. **Bayesian ODE (BODE)**
   - ODE system embedded in wider Bayesian model — typically including the economic component
   - Directly allows for evidence synthesis and functional relationships across parameters
   - Fully characterises population dynamics & accounts for herd immunity
   - Gold standard — when it can be used (as it may become very computationally intensive)
   - Recent development (e.g. Stan) alleviates computational issues
3. **Dynamic Bayesian Markov Model (BMM)**
   - Simplifies the temporal resolution and consider discrete time intervals
   - Simpler to run — and more in line with Economic Modeller's knowledge
   - **Can** approximate population dynamics & account for herd immunity
   - PSA comes from free as a byproduct of the estimation procedure

BMM — shaking things up...

- A "standard" version of a Markov Model (MM) cannot account for population dynamics & herd immunity
  - In fact, MMs are popular in health economics to model chronic diseases (e.g. cardiovascular or cancer)

- Need to model the transition between *Susceptible* to *Infected* to vary over time
  - β = probability of pathogen transmission
  - ω = rate of contacts between susceptibles
  - $\phi_t = \frac{I_t}{N_t}$ = time-dependent pathogen prevalence (=infected/alive in a time interval)
  - $\lambda_t = \beta\omega\phi_t$ = force of infection (varies with time & population composition)

- Can **approximate** the underlying continuous transition to infection using

$$\pi_{1,2,t} = 1 - \exp(-\lambda_t)$$

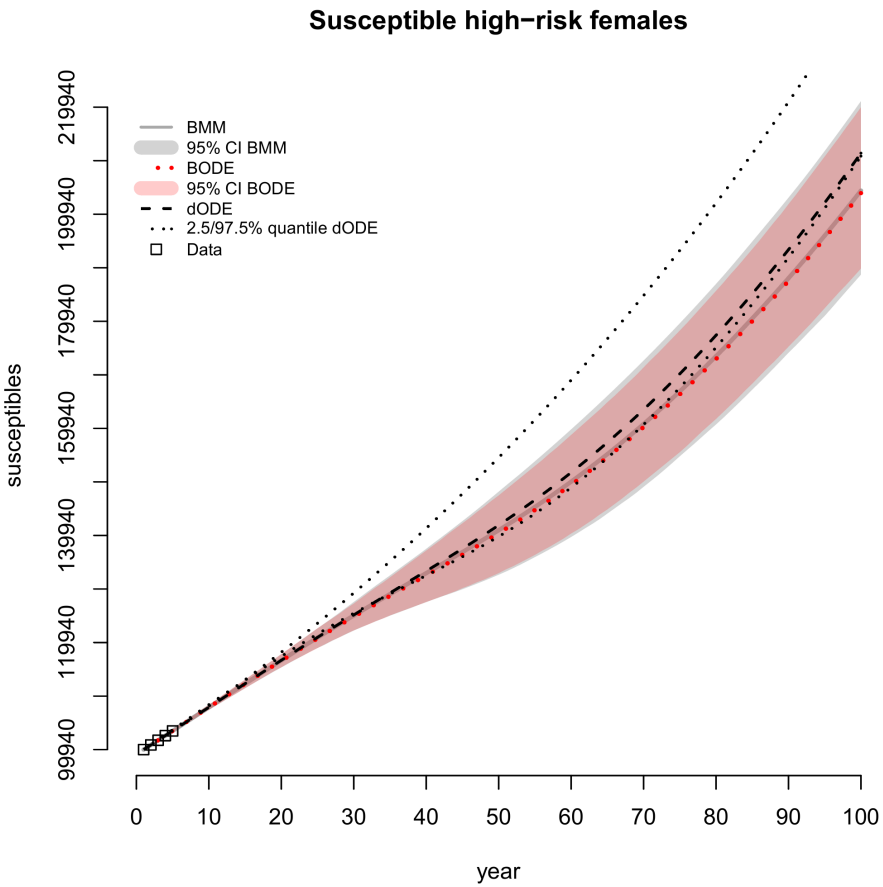
  - The approximation can be gross due to competing risks and the assumption of uniformity for the event probabilities in the time intervals
  - Can use short cycle lengths (potentially increase computational time)
  - Does not need any specialised software (can be fitted using `BUGS/JAGS` and then post-processed in `R` — or *even* `Excel`)

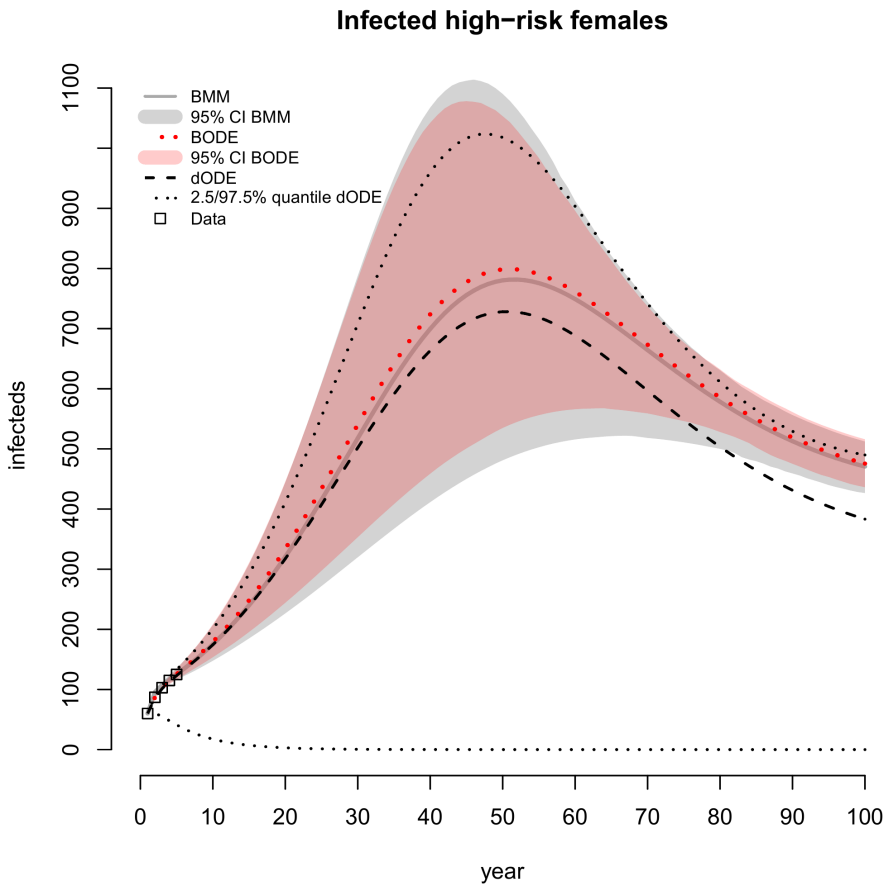
Parameter	Description	Distribution BMM	Distribution BODE	Mean	95% interval
ω_{MH}	Partner acquisition rate (high-risk males)	Poisson-Gamma model	equivalent to BMM	9.10	[8.77;9.29]
ω_{ML}	Partner acquisition rate (low-risk males)	Poisson-Gamma model	equivalent to BMM	2.98	[2.82;3.12]
ω_{FH}	Partner acquisition rate (high-risk females)	Poisson-Gamma model	equivalent to BMM	9.00	[8.71;9.26]
ω_{FL}	Partner acquisition rate (low-risk females)	Poisson-Gamma model	equivalent to BMM	1.96	[1.86;2.09]
χ	Proliferation parameter	Gamma(1111.1,111111.1)	Gamma(1111.1,111111.1)	0.01	[0.01;0.01]
β	STI transmission probability per partnership	Beta-Binomial model	equivalent to BMM	0.16	[0.15;0.16]
$\pi_{2,3}$	Transition parameter from state 2 to state 3	Beta(5119.2, 1279.8)	Gamma(25600,32000)	0.80	[0.79;0.81]
$\pi_{3,4}$	Transition parameter from state 3 to state 4	Beta(1842.66, 18631.34)	Gamma(2025,22500)	0.09	[0.09;0.09]
$\pi_{4,5}$	Transition parameter from state 4 to state 5	Beta(1535.96, 36863.04)	Gamma(1600,40000)	0.04	[0.04;0.04]
$\pi_{1,5}$	Transition parameter from state 1 to state 5	Beta(156.171, 312186.6)	Gamma(156.25,312500)	<0.01	$[<0.01;<0.01]$
η	Probability of STI diagnosis	Beta-Binomial model	equivalent to BMM	0.90	[0.88;0.92]
σ	Screening probability	Beta-Binomial model	equivalent to BMM	0.90	[0.87;0.92]
α	Vaccine coverage parameter	Beta-Binomial model	equivalent to BMM	0.90	[0.87;0.92]
γ	Vaccine efficacy parameter	Beta-Binomial model	equivalent to BMM	0.90	[0.87;0.92]
c_{screen}	Unit cost of screening in £	Lognormal(2.996, 0.693)	equivalent to BMM	25.39	[5.19;77.53]
c_{vac}	Unit cost of vaccination in £	Lognormal(5.011, 0.01)	equivalent to BMM	150.02	[147.14;152.98]
c_{test}	Unit cost of STI test in £	Lognormal(2.996, 0.03)	equivalent to BMM	20.01	[18.83;21.19]
c_{blood}	Unit cost of blood test in £	Lognormal(3.401, 0.03)	equivalent to BMM	30	[28.26;31.79]
c_{treat}	Unit cost of treatment in £	Lognormal(8.517, 0.015)	equivalent to BMM	4999.78	[4853.56;5149.24]
c_{dis}	Unit cost of disease treatment in £	Lognormal(9.210, 0.01)	equivalent to BMM	9999.95	[9802.97;10198.10]
c_{gp}	Unit cost of visit to general practitioner in £	Lognormal(3.912, 0.02)	equivalent to BMM	50.01	[48.08;52.01]
u_2	Health utility of infected (min=0, max=1)	Beta(1469.3, 629.7)	equivalent to BMM	0.70	[0.68;0.72]
u_3	Health utility of asymptomatic (min=0, max=1)	Beta(1439.4, 959.6)	equivalent to BMM	0.60	[0.58;0.62]
u_4	Health utility of morbid (min=0, max=1)	Beta(629.7, 1469.3)	equivalent to BMM	0.30	[0.28;0.32]

- ODE model (`EpiModel/deSolve`): 1 hour 15 mins
- BODE model (`WinBUGS+WBDiff`): 1 hour 50 mins (MCMC using 2 chains) — no issues with convergence
- BMM model (`WinBUGS/JAGS`): 9 mins / 2.5 mins (MCMC using 2 chains) — no issues with convergence

NB: We chose to use more or less standard software, which was available/usable for/in `R`. `Stan` is likely to make the BODE faster to run (but its ODE solver was not fully implemented by the time we did this...)

Results (simulations)





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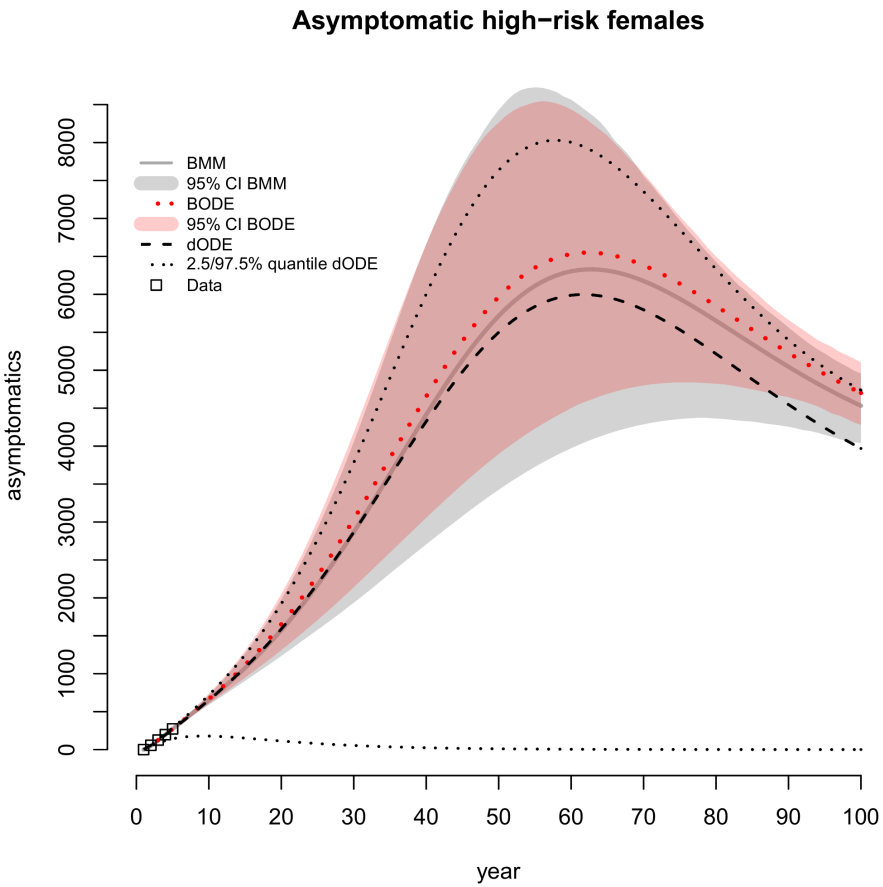
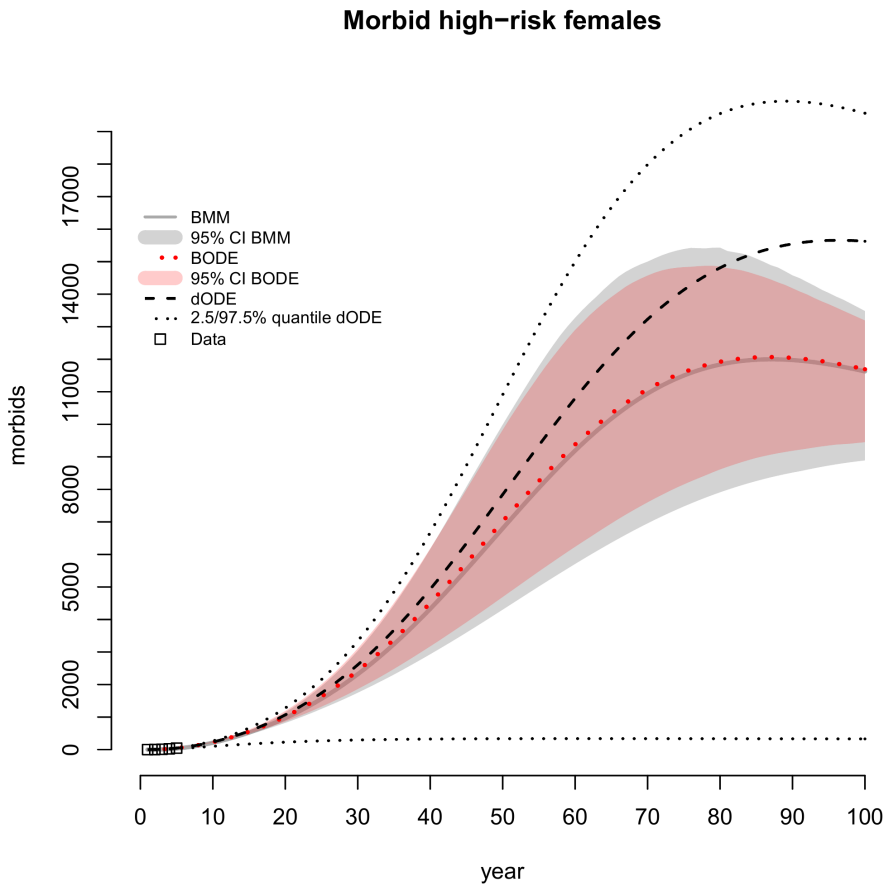
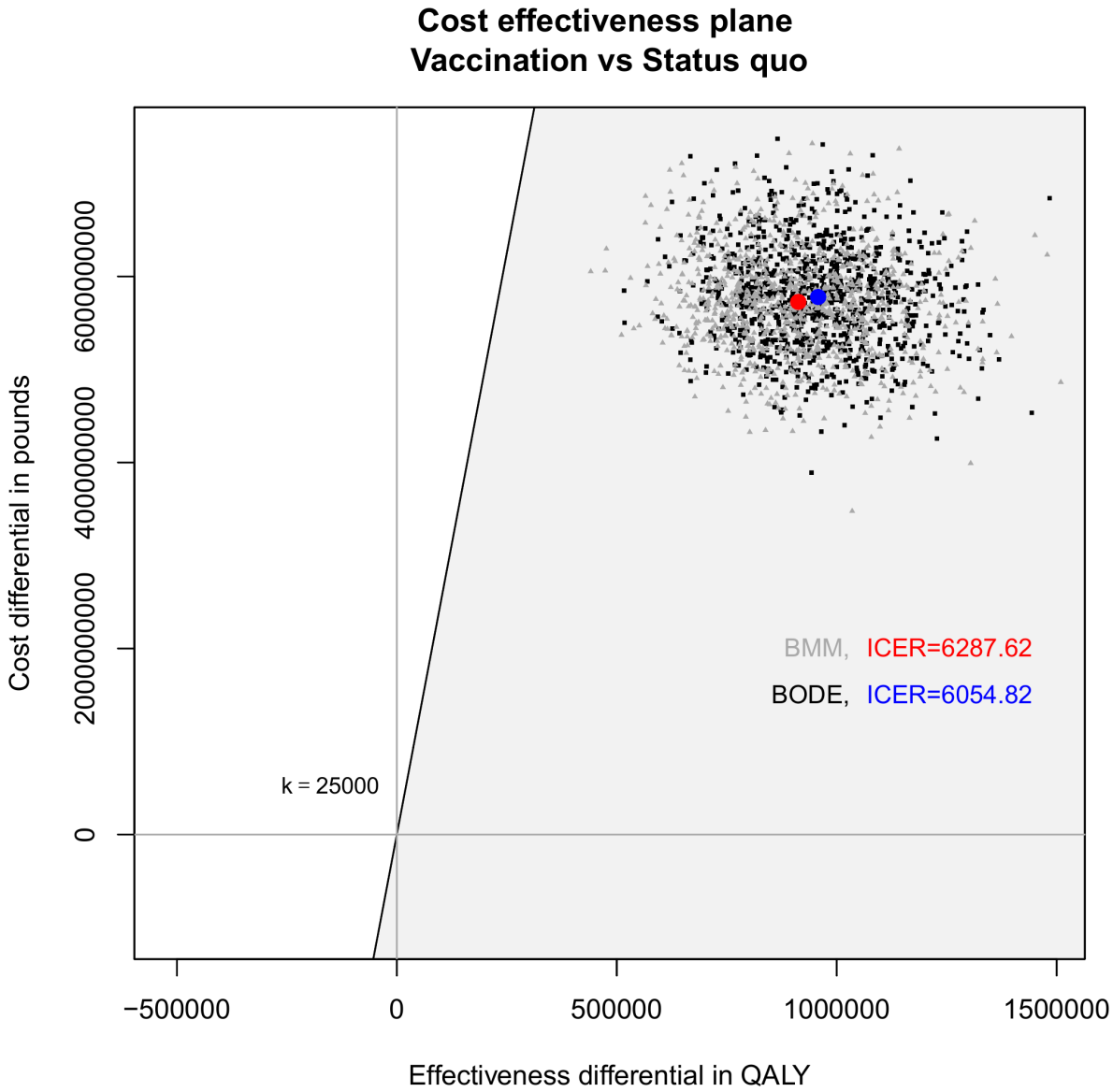
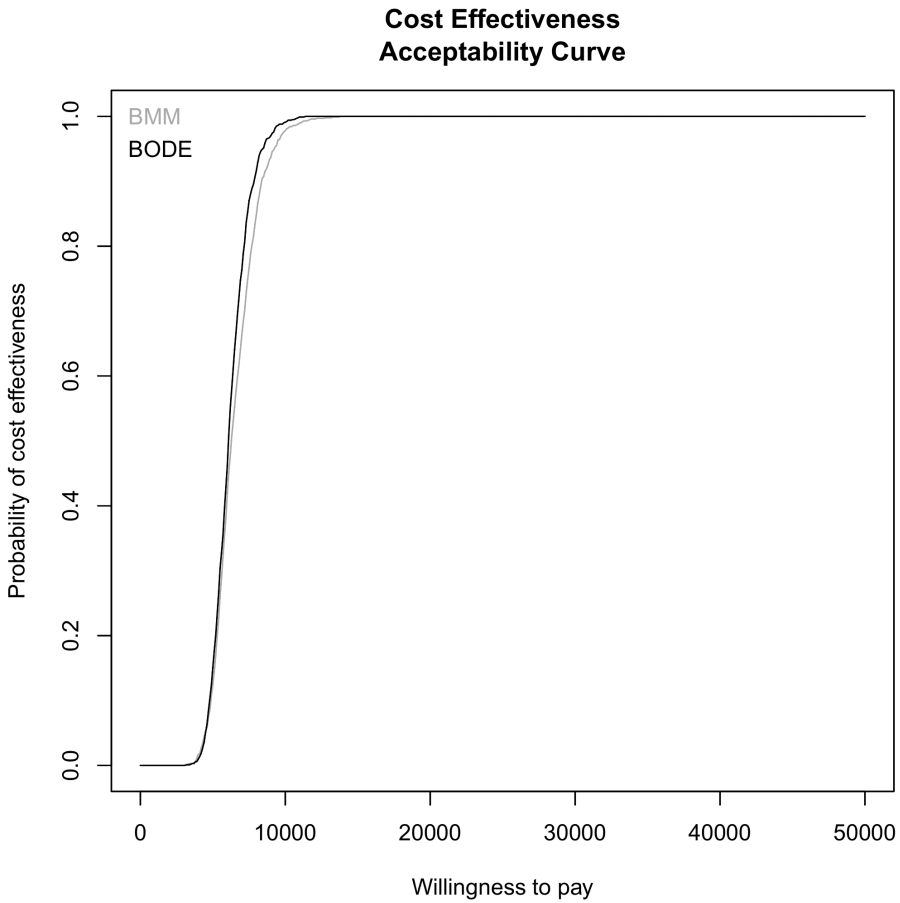
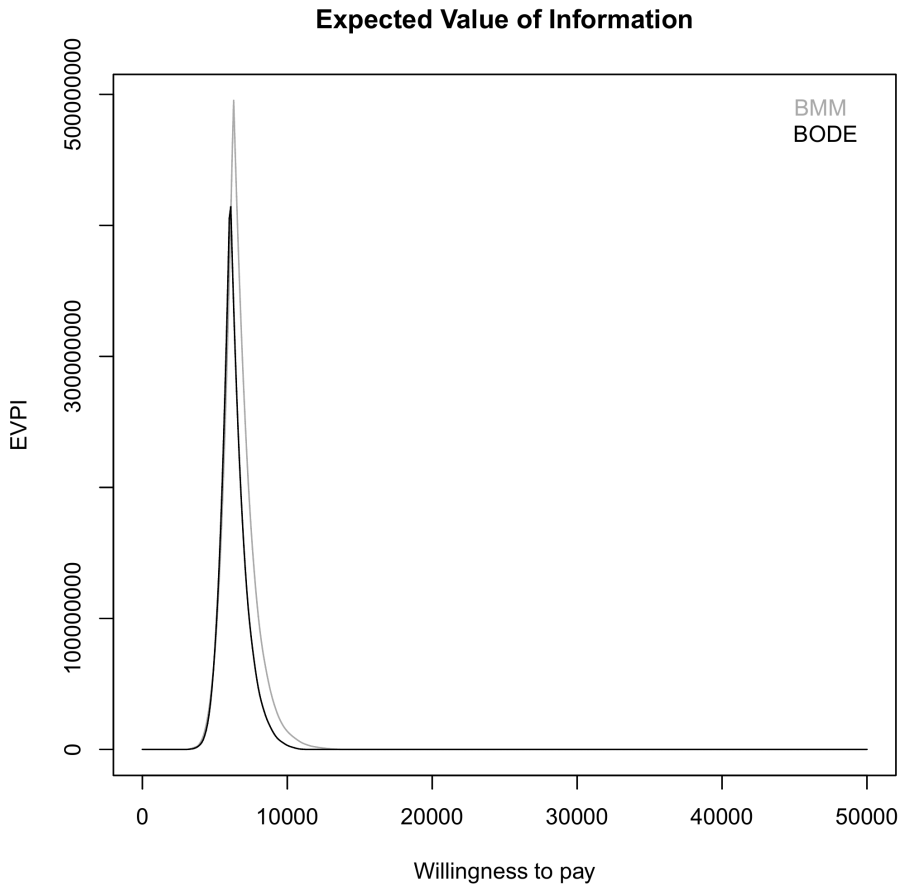


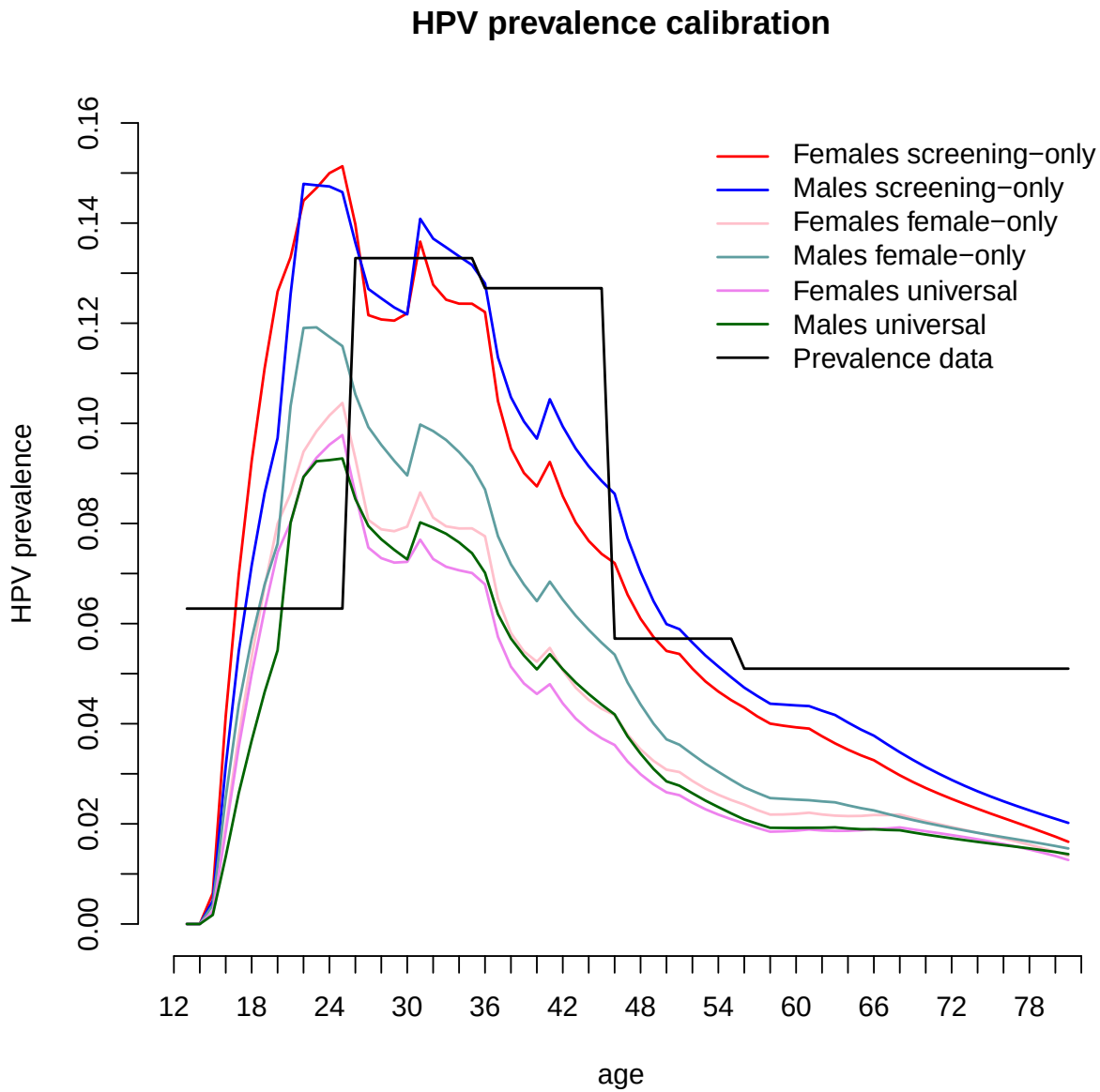



Cost effectiveness plane
Vaccination vs Status quo
Cost differential in pounds
0
200000000
400000000
600000000
−500000
0
500000
1000000
1500000
Effectiveness differential in QALY
k = 25000
BMM, ICER=6287.62
BODE, ICER=6054.82

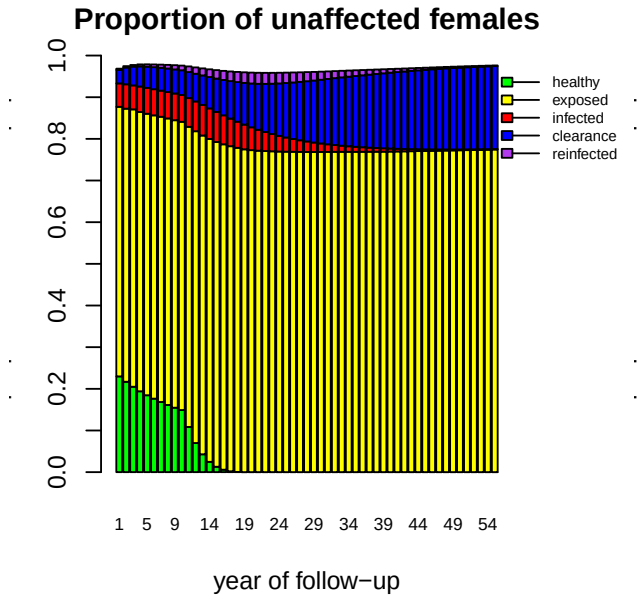

Cost Effectiveness
Acceptability Curve
BMM
BODE
Probability of cost effectiveness
0.0
0.2
0.4
0.6
0.8
1.0
0
10000
20000
30000
40000
50000
Willingness to pay

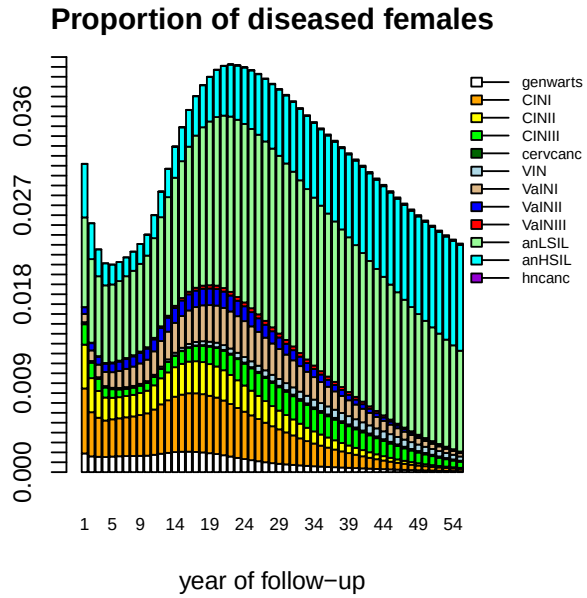

Expected Value of Information
BMM
BODE
EVPI
0
100000000
300000000
500000000
0
10000
20000
30000
40000
50000
Willingness to pay

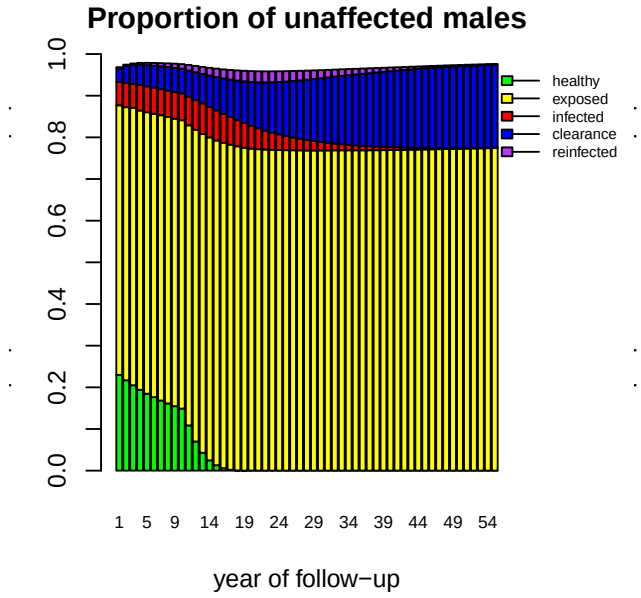
Results (HPV model)

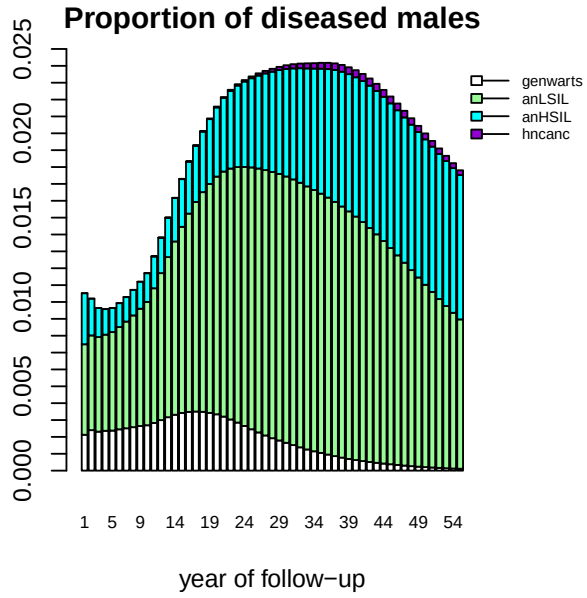


Results (HPV model)

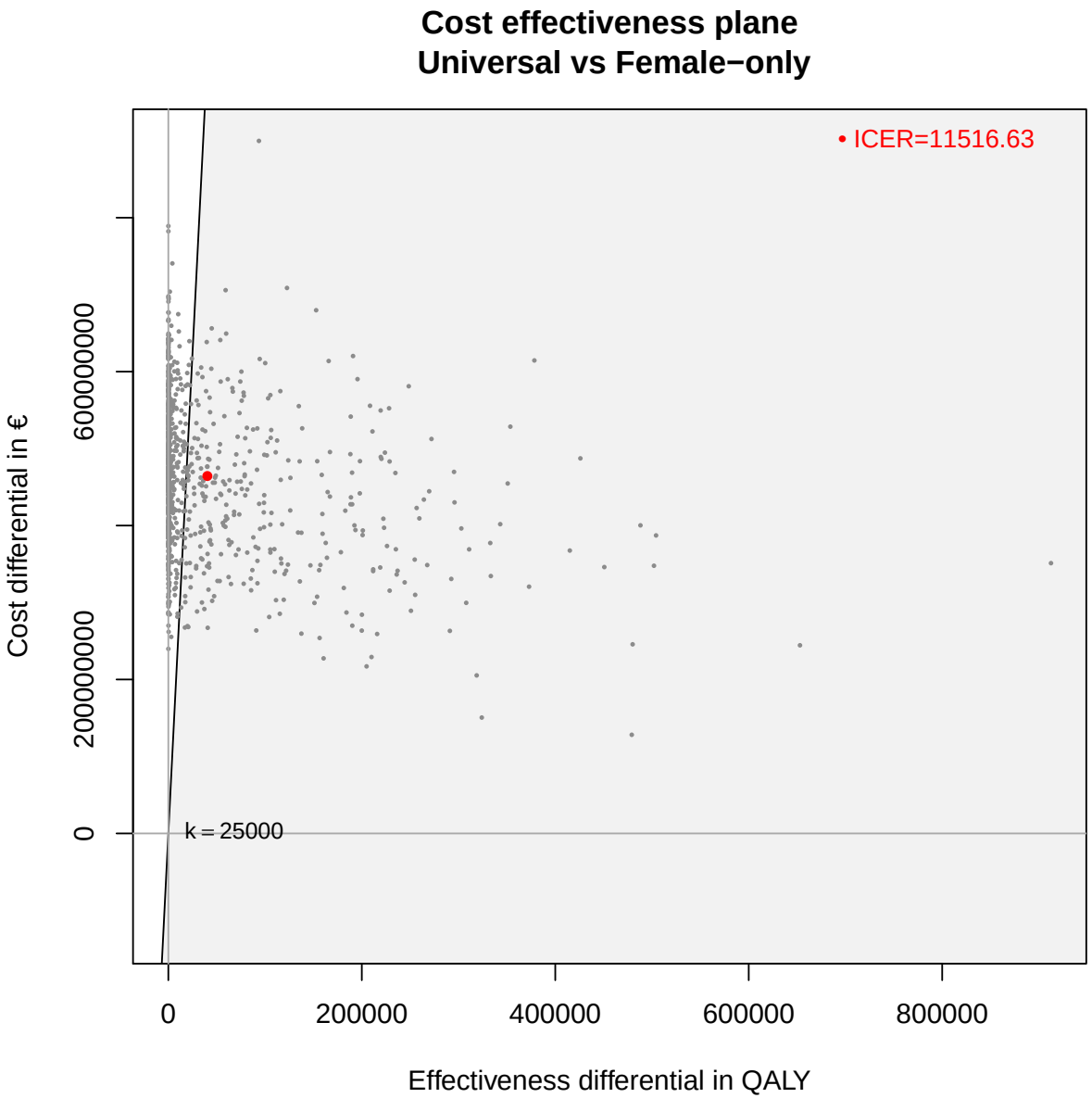




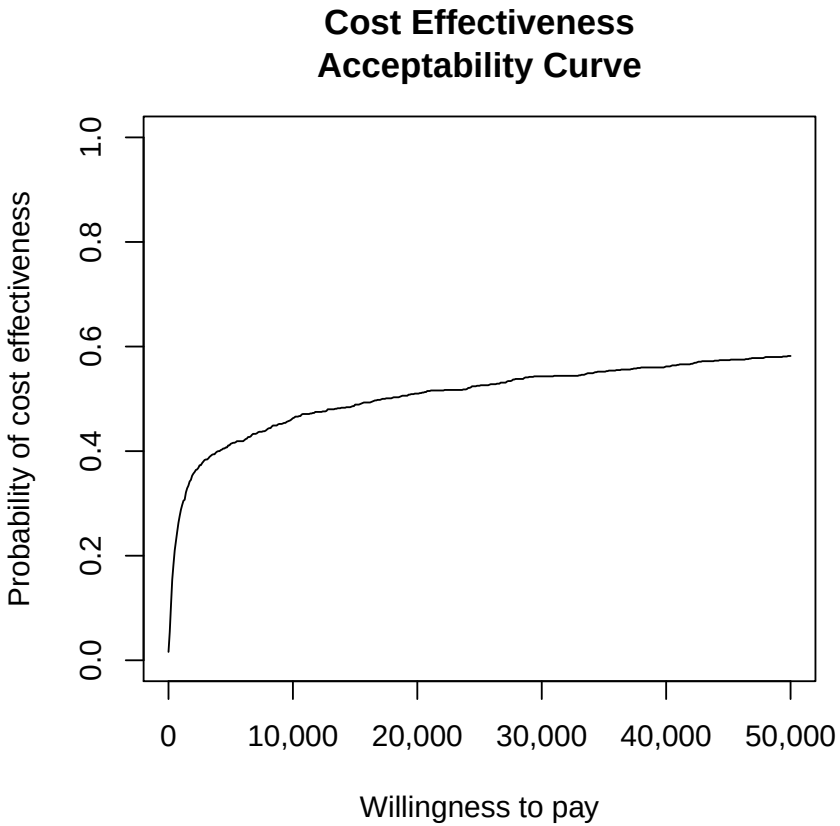


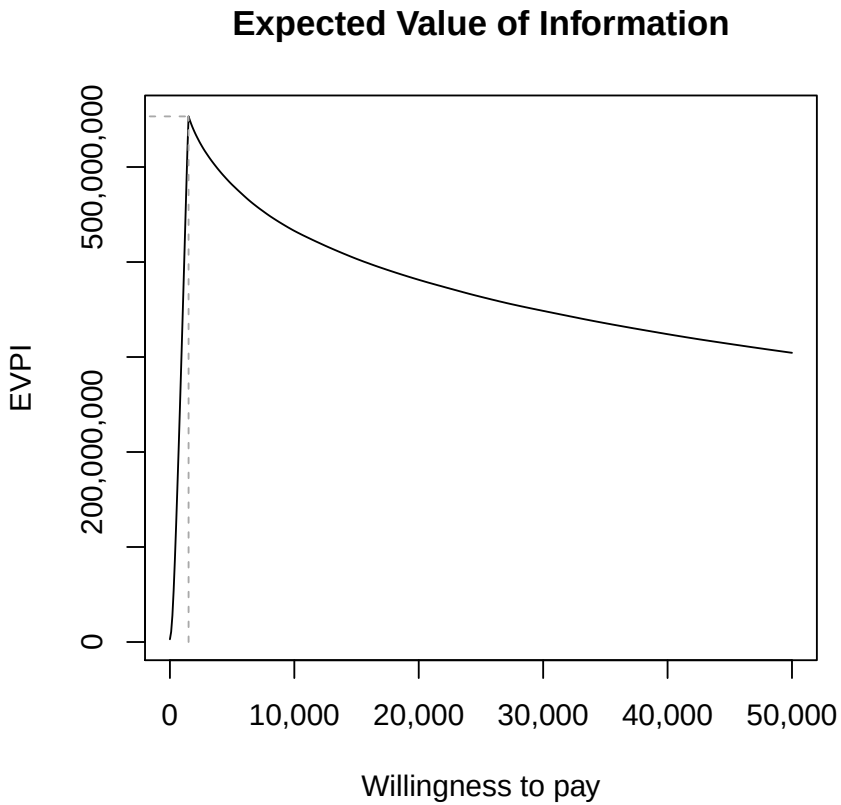


Results (HPV model)



Results (HPV model)





Conclusions

- HTA of interventions for infectious disease typically characterised by
  1. (More) complex underlying modelling
  2. Need to account for specific features (e.g. population dynamics)
  3. Large uncertainty and potentially correlation in/across inputs parameters

- "Industry" standard to model transmission fit for purpose. But: wider economic modelling often miss out on important aspects
  - Full characterisation of uncertainty in model parameters and PSA

- Bayesian modelling and some simplifications (e.g. reduce temporal resolution/model structure) can be efficient
  - Arguably sub-optimal modelling (in some respects). But allows us to get where we **need** to be in a more straightforward way

Thank you!