Bayesian health economic modelling of different human papillomavirus (HPV) vaccination strategies in a static and pseudo-dynamic setting: the BEST II study

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(Thanks to Katrin Haussler, UCL & the BEST II team)

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Background

- BEST I (2010-2012): model for the cost-effectiveness of HPV quadrivalent vaccine
  - Sanofi Pasteur MSD full financial support — international collaboration (includes UCL, University of Zürich, Stockholm SE, University of York, University of Rome)
  - **Static** Bayesian Markov model
  - No herd immunity
  - Females-only model
  - Simple comparisons (screening only vs multi-cohort vaccination)

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  - PhD studentship independently funded (at UCL)
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  - Herd immunity
  - Females + Males
  - Several interventions (screening vs **female-only** vs **universal vaccination**)

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- Both originated from applied perspective, but characterised by challenging methodological aspects
  - Focus on the methodology

Two words on HPV...

- **Human Papillomavirus** (HPV) is the *primum movens* both in the aetio-pathogenesis of invasive cervical cancer and in other malignant and benign neoplastic lesions
- Mainly sexually transmitted
  - **But**: large variability in the mode and force of infection
  - ∼40 identified genotypes, including 13 high-risk types
- HPV has a relatively large prevalence
  - ∼21% in females and ∼17% in males
- Impacts quite heavily on health-care systems
  - In the UK, annually: £17 million to treat genital warts[1]; £157 million to treat cervical cancer[2]

- Screening programmes established to detect and treat early instances of infection-related diseases
- Vaccination suggested as an effective addition
  - Disease process is complicated, so cost-effectiveness is uncertain

[1] Health Protection Agency (2011)
[2] NHS (2012)

Methodological challenges

- HPV has a heavy **indirect** impact on patients utility & health-care costs — infected patients are at higher risk of developing
  - Genital warts
  - Several types of cancer (especially cervical)
- Consequently, a proper health economic evaluation needs to consider a substantial amount of clinical outcomes and a sufficiently long time horizon
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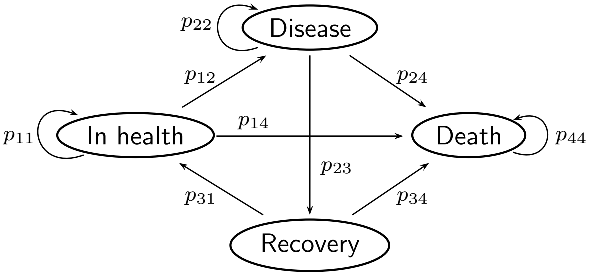
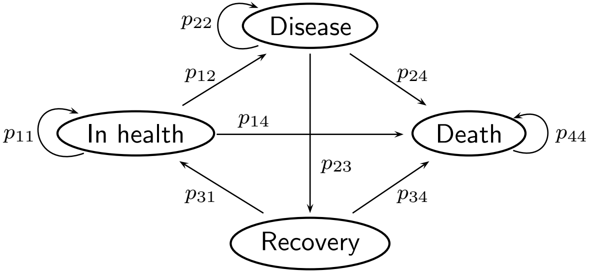
- At the same time, because the most likely mode of infection is sexual, need to consider
  - Effect of **herd immunity**
  - Differential impact of infection and outcomes, eg by age & sex
  - **Dynamic population** — effects may be more important for future patients at risk


Disease
In health
Death
Recovery
p_{22}
p_{12}
p_{24}
p_{11}
p_{14}
p_{44}
p_{23}
p_{31}
p_{34}



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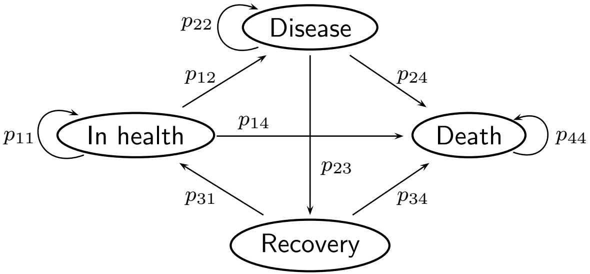

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- For example, under treatment t, we may assume $p_{12} = \pi\rho$
  - $\pi =$ population prevalence of the disease
  - $\rho =$ reduction in prevalence due to treatment, estimated by (meta-analysis of) published studies
- **NB**: Bayesian modelling particularly effective for this
  - Flexibile/modular structure
  - Propagates uncertainty throughout

Example: HPV Transmission rate

- Crucial parameter, but 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)?

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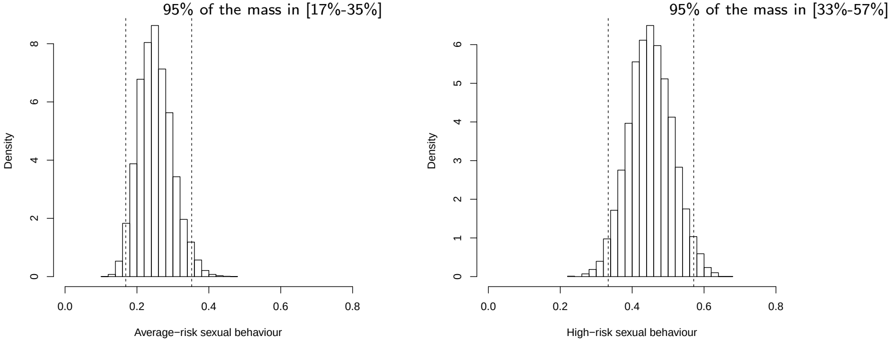
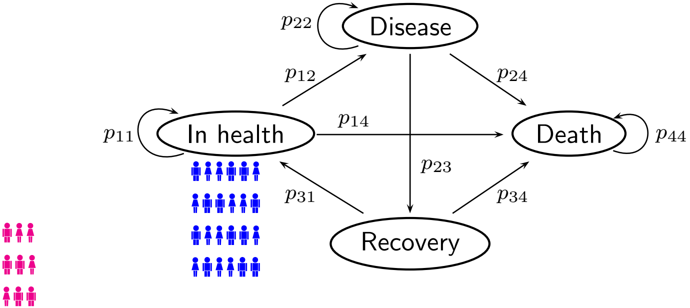
  - Affected by external factors (eg average- vs high-risk sexual behaviour)?
- Bayesian modelling useful to include expert opinion and relatively straightforward for (probabilistic) sensitivity analysis



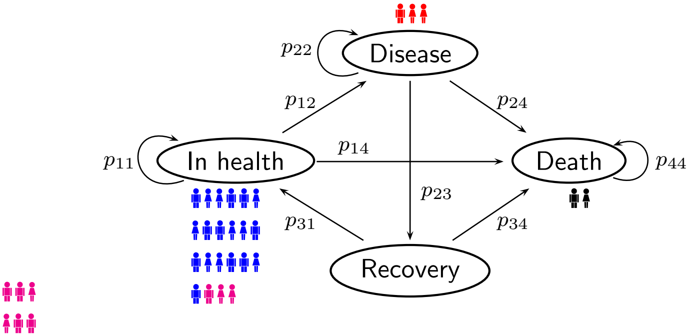
Markov models — dynamic population

$t = 0$



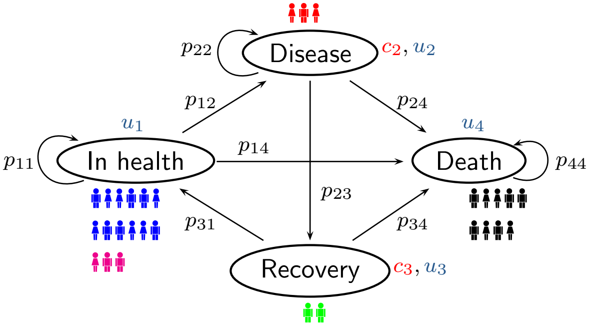
- 14 cohorts of males & females populate the model at time $t = 0$

$t = 1$



- 10 cohorts of new 12 year old enter the model sequentially
- The whole dynamic population is followed up over time

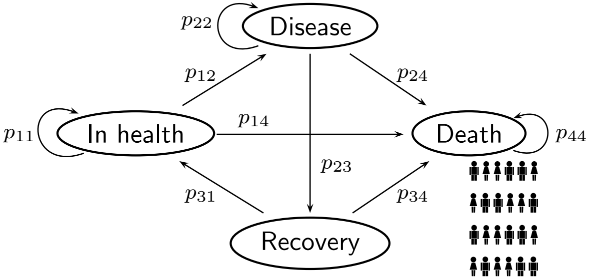
$t = 2$



- **Costs** and **utilities** attached to each status and added over time
  - Discounting is an important issue — results potentially sensitive to rates
  - In the base-case model, costs discounted @ 3% and utilities discounted @ 1.5% + sensitivity analysis performed to these choices

Markov models — dynamic population

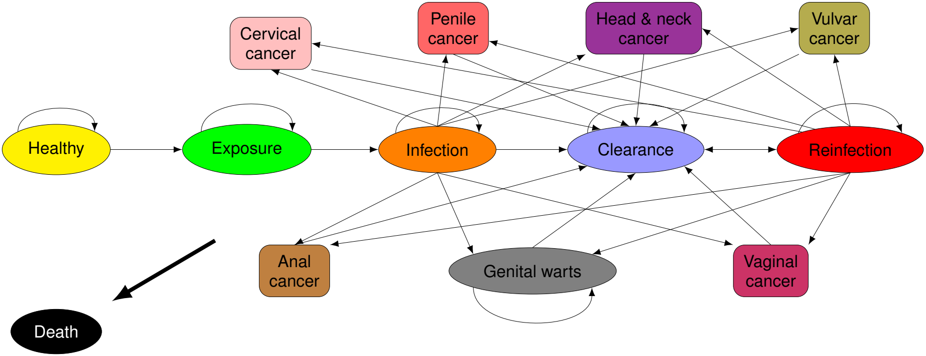
$t = T$



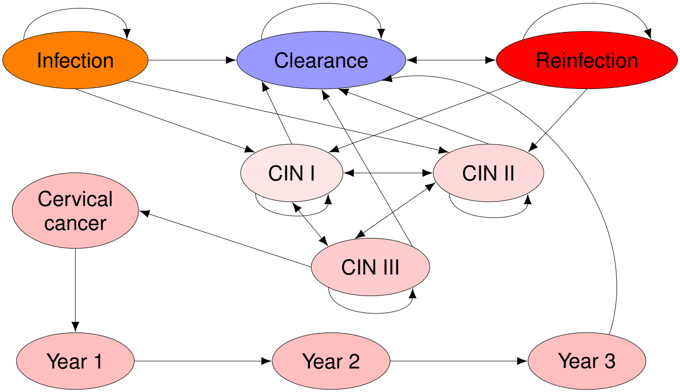
- In the base-case model, the follow up is set to 55 years — long enough to capture some of the long-term effects

Markov models — structure

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



Cervical cancer module (blown up)



Rate of HPV infection (Korostil et al, 2012):

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

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- Similarly, $N_{g',s',a'}$ indicates the total number of individuals of gender g', sexual activity level s' and age group a'

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
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Annual min, average and max partner acquisition rate for females

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  - $m_{g,s,s',a,a'} = 0$, for any other age group a'.

Markov models — herd immunity

- In practice, this construction implies that at each time point in the follow up, the probability of HPV infection depends on the pool of available partners of the opposite sex who are:
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- **NB**: The HPV infection rates $\rho_{g,s,a}$ can be transformed into probabilities

$$p_{g,s,a} = 1 - \exp^{-\rho_{g,s,a}}$$

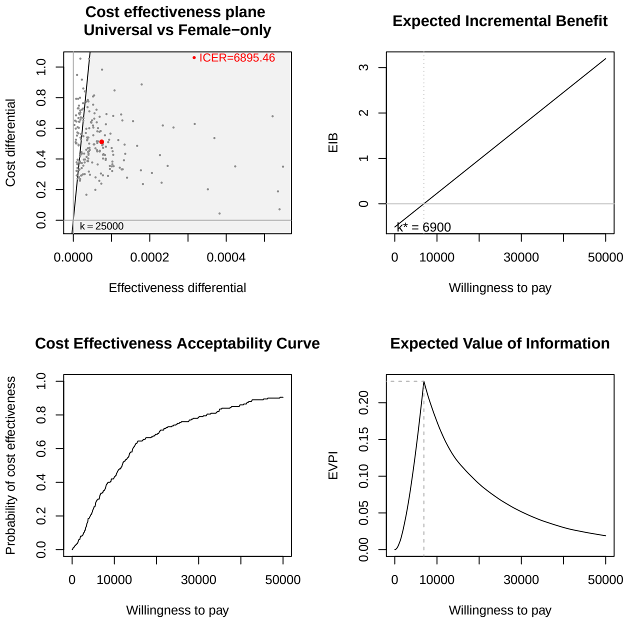
(assuming constant rates over the entire cycle)

Technical issues

Complex model specification, so helpful to break down for computational efficiency

1. Run the Bayesian model to estimate the parameters — performed in JAGS
   - Pre- and post-processing directly in R, but JAGS called to run the MCMC estimation
   - Relatively quick and easy convergence
2. Construct the transition probabilities as functions of the parameters — performed in R
   - Not too complex — only needs to write down a set of relationships among the parameters
3. Generate the "virtual follow up" — performed in R
   - Most computationally intensive part
   - Generates large arrays (dimension = number of states $\times$ number of MCMC simulations $\times$ number of cohorts $\times$ number of interventions)
4. Make the economic analysis — performed in R
   - Straightforward, using the BCEA (Bayesian Cost-Effectiveness Analysis) package — more details at www.statistica.it/gianluca/BCEA
   - Automatically obtain CEAC, CE plane, EVPI, EVPPI, ...

A glimpse at results...



Limitations & potential extensions

- The dynamic Markov model is capable of dealing with much of the complexity of the problem
  - Fundamental characteristics can be taken into account
  - Can use a full Bayesian approach — good thing!

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- The sexual partnership matrices and the partnership acquisition rates are considered as fixed (**for now**!)
- This is not ideal, as they are likely to be subject to uncertainty that should be further propagated through the model
  - Dirichlet priors for the entries of the sexual partnership matrices, to account for uncertainty
  - Gamma priors for the partner acquisition rates, to encode information about their range

- Speed up the computation process
  - Parallel computing

Thank you!