Dynamic Markov models for the health economic evaluation of human papillomavirus (HPV) vaccination

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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)
  - **Dynamic** model
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  - Females + Males
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- Both originated from applied perspective, but characterised by challenging methodological aspects
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
  - **Markov (multi-state) models** particularly helpful to deal with this kind of situations
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  - **Markov (multi-state) models** particularly helpful to deal with this kind of situations
- 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
Markov models — Bayesian modelling

- Disease
- In health
- Death
- Recovery

Transition probabilities:
- $p_{11}$
- $p_{12}$
- $p_{14}$
- $p_{22}$
- $p_{23}$
- $p_{24}$
- $p_{31}$
- $p_{34}$
- $p_{44}$

Gianluca Baio (UCL)
- Sometimes we have data to directly estimate the transition probabilities \( p \). Often, we do not — need to estimate them as functions of some random parameters for which data are available
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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
  - Flexible/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 (e.g., average- vs high-risk sexual behaviour)?
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- Bayesian modelling useful to include expert opinion and relatively straightforward for (probabilistic) sensitivity analysis

95% of the mass in [17%-35%]

95% of the mass in [33%-57%]
Markov models — dynamic population

\[ t = 0 \]

- 14 cohorts of males & females populate the model at time \( t = 0 \)
Markov models — dynamic population

$t = 1$

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

\[ t = 2 \]

- **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 and utilities discounted @ 3% + sensitivity analysis performed to these choices
In the base-case model, the follow up is set to 55 years — long enough to capture some of the long-term effects.
**Females** compartment model: $S_f = 36$ health states

**Males** compartment model: $S_m = 22$ health states
Cervical cancer module (blown up)
Data & distributional assumptions

“Hard” data

- Based on evidence synthesis or aggregated data from specific surveys
- Examples: vaccination coverage rates, questionnaires on quality of life
- Vague priors less of an issue
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- Examples: infection transmission rate, diagnosis of anal cancer
- Informative prior + sensitivity analysis
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“Unmodelled” data
- Examples: life tables, sexual partnership probabilities, partner acquisition rates
- Can extend the model to include uncertainty on these
  - May need to rely mainly subjective priors for some of these
### Markov models — herd immunity

#### Sexual partnership matrix for female (average-risk group)

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### Annual min, average and max partner acquisition rate for females

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Markov models — herd immunity

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Markov models — herd immunity

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• Consider a 20 year old female in the average-risk group and assume the maximum partner acquisition rate
• Then the sexual mixing matrices are defined as
  \[ m_{g,s,s',a,a'} = 36\% \times 1.38 = 0.4968, \text{ for } a' = 20-24; \]
Markov models — herd immunity

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Annual min, average and max partner acquisition rate for females

<table>
<thead>
<tr>
<th>Age</th>
<th>Min</th>
<th>Mean</th>
<th>Max</th>
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<tbody>
<tr>
<td>12-19</td>
<td>0.74</td>
<td>1.26</td>
<td>1.78</td>
<td>0.90</td>
<td>1.92</td>
<td>2.94</td>
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<td>20-24</td>
<td>0.54</td>
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<td>0.15</td>
<td>0.04</td>
<td>0.11</td>
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</tbody>
</table>

- Consider a 20 year old female in the average-risk group and assume the maximum partner acquisition rate
- Then the sexual mixing matrices are defined as
  - $m_{g,s,s',a,a'} = 36\% \times 1.38 = 0.4968$, for $a' = 20-24$;
  - $m_{g,s,s',a,a'} = 49\% \times 1.38 = 0.6762$, for $a' = 25-29$;
Consider a 20 year old female in the average-risk group and assume the maximum partner acquisition rate.

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\]

\[
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\]
Markov models — herd immunity

Sexual partnership matrix for female (average-risk group)

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Annual min, average and max partner acquisition rate for females

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Sexual partnership matrix for female (average-risk group)

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  \[ m_{g,s,s',a,a'} = 0, \text{ for any other age group } a'. \]
• 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:
  a) **available for mating**; this depends on the age and sex of the individual being considered, as well as on their own sexual activity level
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a) **available for mating**; this depends on the age and sex of the individual being considered, as well as on their own sexual activity level

b) **currently infected by HPV**; as vaccination is likely to reduce the number of people who originally become infected by the vaccine, because of this element, the probability of HPV infection will become smaller and will be affected by the impact of vaccination, thus mimicking the mechanism underlying herd immunity
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This effectively generates a form of **herd immunity**

- The rate of HPV infection varies with time and the population dynamics
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• This effectively generates a form of herd immunity
  − The rate of HPV infection varies with time and the population dynamics

• NB: the model has been calibrated against available data on age-specific incidence and prevalence from the literature
Interpreting cost-effectiveness analysis

Effectiveness differential

Cost differential

Effectiveness differential

SITIP, Florence 21 Mar 2015
Interpreting cost-effectiveness analysis

\[ \text{ICER} = \frac{\text{mean cost differential}}{\text{mean effectiveness differential}} \]
Interpreting cost-effectiveness analysis

Effectiveness differential

Cost differential

Dynamic MMs for HPV vaccination
Interpreting cost-effectiveness analysis

Effectiveness differential vs. Cost differential

Gianluca Baio (UCL)
A glimpse at results...

Cost effectiveness plane
Universal vs Female–only

\[ \text{ICER} = 11516.63 \]

\[ k = 25000 \]
A glimpse at results...

Cost Effectiveness
Acceptability Curve

Probability of cost effectiveness

Willingness to pay
A glimpse at results...

Expected Value of Information

Willingness to pay

EVPI

0.0 0.5 1.0 1.5 2.0

0 10000 20000 30000 40000 50000
Conclusions

- Universal vaccination is cost-effective when compared to female-only vaccination and cervical screening
  - The model recognises the substantial underlying uncertainty in some of the main parameters
  - Nevertheless we are able to assess directly whether this uncertainty is relevant to the decision-making process

- Positive features of the Dynamic MM
  - Incorporates the dynamic force of infection directly into the health state allocation algorithm, thus accounting for herd immunity
  - Combines the benefits of probabilistic multi-state models and dynamic transmission models
  - Conducting Probabilistic Sensitivity Analyses (PSA) is straightforward, once the model has been fitted
Thank you!