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

Katrin Haeussler

Department of Statistical Science

University College London

June 12th, 2014
Outline of presentation

1. Aim of the research
2. Literature review
3. General introduction
   – Bayesian Markov models
4. Model assumptions
   – Reference population and follow-up
   – Cervical screening and HPV vaccination
   – Model structure
   – The process of sexual mixing
     • Herd immunity
   – Distributional assumptions and sources of prior information
   – Transition probabilities
5. Preliminary results
   – Convergence and autocorrelation
   – Cost-effectiveness analysis
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Aim of the research

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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1. Incorporating the effects of herd immunity into the Bayesian Markov model
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3. Considering a great variety of HPV-induced diseases
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
HPV-induced disease burden in the UK

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Cervical cancer
- Yearly 2,890 new cervical cancer diagnoses
- Cervical cancer 11th most frequent cancer in females
HPV-induced disease burden in the UK

HPV prevalence
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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
Economic impact

Yearly costs borne by the NHS
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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

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.

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Bayesian Markov models

1. Define a structure

- Exhaustive and mutually exclusive health states
2. Estimate the transition probabilities

- Transition probabilities $\lambda$ are functions of $\theta$
- Assigning flat and informative distributions to parameters $\theta$
Bayesian Markov models

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
Bayesian Markov models

3. Run the simulation: \( t = 2 \)
3. Run the simulation: $t = 3$
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
Reference population and follow-up

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Interventions

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
   - Sensitivity analysis to catch-up coverage rate
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$S_f = 36$ health states
Cervical cancer

- Infection
- Clearance
- Reinfection

CIN I
CIN II
CIN III

Year 1
Year 2
Year 3

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Presentation at Bayes Pharma
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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Average-risk sexual activity

- 80% of the population
- 2-10 lifetime sex partners
HPV transmission probabilities

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 HPV transmission probabilities

- **Density**
  - Average-risk
  - High-risk

**Axes**
- **x-axis**: ε
- **y-axis**: Density

**Legend**
- **o average-risk**
- **o high-risk**
### Sexual Mixing Matrix

#### Sexual Partnership Matrix for Female (Average-Risk Group)

<table>
<thead>
<tr>
<th>Age</th>
<th>12-19</th>
<th>15</th>
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| 65-80   | 0%    | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 14%| 86%|...

- Consider a 20 year old female in the average-risk group.
- 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 $a' = 25-29$;
  - $m_{g,s,s}',a,a' = 12\% \times 1.38 = 0.1656$, for $a' = 30-34$;
  - $m_{g,s,s}',a,a' = 2\% \times 1.38 = 0.0276$, for $a' = 35-39$;
  - $m_{g,s,s}',a,a' = 0$, for any other age group $a'$. 

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Presentation at Bayes Pharma 16/25
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### Annual max, average and mean partner acquisition rate for females

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<th>Males</th>
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<td>Min</td>
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<td>12-19</td>
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Sexual mixing matrix

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<td>60-</td>
<td>0.05</td>
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</table>

- Consider a 20 year old female in the average-risk group and assume the maximum partner acquisition rate
### Sexual partnership matrix for female (average-risk group)

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<tbody>
<tr>
<td>12-19</td>
<td>1%</td>
<td>26%</td>
<td>58%</td>
<td>15%</td>
<td>1%</td>
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<td>20-24</td>
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<td>14%</td>
<td>86%</td>
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### Annual max, average and mean partner acquisition rate for females

<table>
<thead>
<tr>
<th>Age</th>
<th>Min</th>
<th>Mean</th>
<th>Max</th>
<th>Min</th>
<th>Mean</th>
<th>Max</th>
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<td>1.78</td>
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<td>20-24</td>
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<td>0.96</td>
<td>1.38</td>
<td>0.68</td>
<td>1.38</td>
<td>2.09</td>
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<tr>
<td>60-</td>
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<td>0.10</td>
<td>0.15</td>
<td>0.04</td>
<td>0.11</td>
<td>0.18</td>
</tr>
</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 
  \[- m_{g,s,s',a,a'} = 36\% \times 1.38 = 0.4968, \text{ for } a' = 20-24;\]
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

\[ m_{g,s,s',a,a'} = 36\% \times 1.38 = 0.4968, \text{ for } a' = 20-24; \]

\[ m_{g,s,s',a,a'} = 49\% \times 1.38 = 0.6762, \text{ for } a' = 25-29; \]
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 \( a' = 25-29 \);
- \( m_{g,s,s',a,a'} = 12\% \times 1.38 = 0.1656 \), for \( a' = 30-34 \);
### Sexual mixing matrix

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

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**Annual max, average and mean partner acquisition rate for females**

<table>
<thead>
<tr>
<th>Age</th>
<th>Females</th>
<th>Males</th>
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<tbody>
<tr>
<td></td>
<td>Min</td>
<td>Mean</td>
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<tr>
<td>12-19</td>
<td>0.74</td>
<td>1.26</td>
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<td>20-24</td>
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<td>60-</td>
<td>0.05</td>
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</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 \( a' = 20-24 \);
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  - \( m_{g,s,s',a,a'} = 12\% \times 1.38 = 0.1656 \), for \( a' = 30-34 \);
  - \( m_{g,s,s',a,a'} = 2\% \times 1.38 = 0.0276 \), for \( a' = 35-39 \);
**Sexual mixing matrix**

Sexual partnership matrix for female (average-risk group)

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Annual max, average and mean partner acquisition rate for females

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  - $m_{g,s,s',a,a'} = 2\% \times 1.38 = 0.0276$, for $a' = 35-39$;
  - $m_{g,s,s',a,a'} = 0$, for any other age group $a'$. 
Equation introduced by Korostil et al.

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

- \( \epsilon \) represents the HPV transmission probability per partnership
- \( m_{g,s,s',a,a'} \) represents the sexual mixing matrix
- \( I_{g',s',a'} \) indicates the number of infected individuals of gender \( g' \), sexual activity \( s' \) and age \( a' \)
- \( N_{g',s',a'} \) indicates the total number of individuals of gender \( g' \), sexual activity \( s' \) and age \( a' \).

At each time point \( t \), the probability of HPV infection depends on the pool of opposite sex partners

a) available for mating, depending on age and sexual activity

b) currently infected by HPV, accounting for herd immunity in interventions with vaccination.
Sexual mixing equation

Equation introduced by Korostil et al.

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

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Transformation of rates into probabilities

Equation introduced by Cooper et al.

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

- The HPV infection rates \( \kappa_{g,s,a} \) have to be transformed into probabilities \( \lambda_{g,s,a} \).
- Cooper et al.’s formula is based on the assumption of constant transition probabilities over the whole observation period.
- \( \lambda_{g,s,a} \) are the transition probabilities from the health states Exposure to Infection.
- These are directly integrated into the health state allocation algorithm of the MM.
- Health economic analysis by means of output of MM.
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- \( \rightarrow \) Health economic analysis by means of output of MM.
Preliminary results

1. Running the MCMC simulations to obtain the posterior distributions of all model parameters.
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2. Investigating convergence and the amount of autocorrelation to identify critical parameters
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1. Running the MCMC simulations to obtain the posterior distributions of all model parameters
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4. Running the algorithm of sexual mixing and allocating all individuals to their corresponding health states throughout the full observation time horizon
Preliminary results

1. Running the MCMC simulations to obtain the posterior distributions of all model parameters
2. Investigating convergence and the amount of autocorrelation to identify critical parameters
3. Computing the transition probabilities according to the specified formulae
4. Running the algorithm of sexual mixing and allocating all individuals to their corresponding health states throughout the full observation time horizon
5. Calculating overall costs and utilities, resulting in the cost-effectiveness analysis
Running the model

- **Just Another Gibbs Sampler (JAGS)**
- Integrated into R by means of package R2jags
- 2 parallel chains \( n_{chains} = 2 \)
- \( n_{iter} = 40,000 \) simulations
- burn-in of \( n_{burn} = 4,000 \)
- thinning step of \( n_{thin} = 360 \)

\[
\text{n}_{sims} = n_{chains} \frac{(n_{iter} - n_{burn})}{n_{thin}} = 2 \frac{(40,000 - 4,000)}{360} = 200
\]
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\[
\begin{align*}
    n_{sims} &= n_{chains} \frac{(n_{iter} - n_{burn})}{n_{thin}} \\
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    &= 200
\end{align*}
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\[
n_{sims} = n_{chains} \left( \frac{n_{iter} - n_{burn}}{n_{thin}} \right) = 2 \left( \frac{40,000 - 4,000}{360} \right) = 200
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- thinning step of $n_{thin} = 360$

\[
n_{sims} = n_{chains} \frac{(n_{iter} - n_{burn})}{n_{thin}} = 2 \frac{(40,000 - 4,000)}{360} = 200\]
Running the model

- **Just Another Gibbs Sampler (JAGS)**
- Integrated into R by means of package R2jags
- 2 parallel chains ($n_{chains} = 2$)
- $n_{iter} = 40,000$ simulations
- burn-in of $n_{burn} = 4,000$
- thinning step of $n_{thin} = 360$

\[ n_{sims} = n_{chains} \left( \frac{n_{iter} - n_{burn}}{n_{thin}} \right) = 2 \left( \frac{40,000 - 4,000}{360} \right) = 200 \]
Running the model

- Just Another Gibbs Sampler (JAGS)
- Integrated into R by means of package R2jags
- 2 parallel chains ($n_{chains} = 2$)
- $n_{iter} = 40,000$ simulations
- burn-in of $n_{burn} = 4,000$
- thinning step of $n_{thin} = 360$

$$n_{sims} = n_{chains} \frac{(n_{iter} - n_{burn})}{n_{thin}} = 2 \frac{40,000 - 4,000}{360} = 200$$
Gelman-Rubin statistics $\hat{R}$ for $\theta$

Convergence evaluation with $\hat{R}$ for all model parameters $\theta$

Gelman-Rubin statistic $\hat{R}$

Parameters $\theta$

Katrin Haeussler

Presentation at Bayes Pharma
Gelman-Rubin statistics $\hat{R}$ for $\theta$

Convergence evaluation with $\hat{R}$ for all model parameters $\theta$

\[
\hat{R} = \sqrt{\frac{\text{Var}(\theta_k | y)}{W(\theta_k)}}
\]
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 $\nu_c = 0.03$

$$\text{PVC}_i = \sum_{t=1}^{t=55} \frac{C_{i,t}}{(1 + \nu_c)^{t-1}}$$
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PVC_i = \sum_{t=1}^{t=55} \frac{C_{i,t}}{(1 + \nu_c)^{t-1}}
\]

#### The PVU
- Sum of overall utilities in intervention \( i \) for time \( t = 1 \) to \( t = 55 \)
- Commonly discounted by \( \nu_u = 0.015 \)

\[
PVU_i = \sum_{t=1}^{t=55} \frac{U_{i,t}}{(1 + \nu_u)^{t-1}}
\]
Present values of cost (PVC) and utility (PVU)

The PVC

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Comparison of universal to female-only vaccination

- $\Delta_c = PVC_3 - PVC_2$
- $\Delta_e = PVU_3 - PVU_2$
Present values of cost (PVC) and utility (PVU)

The PVC

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Comparison of universal to female-only vaccination

- $\Delta_c = \text{PVC}_3 - \text{PVC}_2$
- $\Delta_e = \text{PVU}_3 - \text{PVU}_2$
Cost-effectiveness plane vs ICER

Cost-effectiveness plane

Effectiveness differential
Cost differential $\Delta e$
Cost differential $\Delta c$

ICER = $\frac{\Delta c}{\Delta e}$

Effectiveness differential
Cost-effectiveness plane vs ICER

Cost-effectiveness plane

Effectiveness differential

Cost differential

\[ \Delta_c \]

\[ \Delta_e \]

ICER = \[ \frac{E[\Delta_c]}{E[\Delta_e]} \] = Cost per QALY
Universal versus female-only vaccination

Cost effectiveness plane
Universal vs Female-only

- Effectiveness differential
- Cost differential

ICER = 6330.56

k = 25000
Thank you very much for your attention.
Appendix
Other HPV-induced cancers

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
Other HPV-induced cancers

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

- Multifactorial diseases
- HPV-induced:
  - more than 90% of anal cancers
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Other HPV-induced cancers

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  - 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 continuous 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**
Hybrid model structures

- **Combination of**
  - natural history of disease infection and progression models
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  - these probabilities inform the disease progression model afterwards

- **Alternative: the process of sexual mixing can be integrated directly into the static disease progression model**
$S_m = 22$ health states
Anal cancer

Infection → Clearance → Reinfection

Anal cancer
Anal LSIL
Anal HSIL

Year 1 → Year 2 → Year 3
Head and neck cancer

- Infection
- Clearance
- Reinfection

Head & neck cancer

Year 1 → Year 2 → Year 3
Vaginal cancer

- Infection
- Clearance
- Reinfection

- VaIN I
- VaIN II
- VaIN III

- Year 1
- Year 2
- Year 3
Penile cancer

Infection

Clearance

Reinfection

PeIN

Penile cancer

Year 1

Year 2

Year 3
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 $1 - \sum p_{i,a,j,h} \quad \forall h \in \mathcal{H}$

- 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 \((h = 1)\)

\[
p_{i,a,1,h} = 0 \forall h \notin \{1, 2, 9\}
p_{i,a,1,2} = s_a
p_{i,a,1,9} = d_{a,0}
p_{i,a,1,1} = 1 - \sum_{h \neq 1} p_{i,a,1,h}
\]
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 (\( h = 2 \))

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

\[
p_{2,a,2,h} = 0 \quad \forall h \notin \{2, 3, 9\}
\]

\[
p_{2,a,2,3} = \alpha_1[\omega_3(1 - \gamma_1)\lambda_{0,s,a} + (1 - \omega_3)(1 - \zeta \gamma_1)\lambda_{0,s,a}] + (1 - \alpha_1)\lambda_{0,s,a}
\]

\[
p_{2,a,2,9} = d_{a,0}
\]

\[
p_{2,a,2,2} = 1 - \sum_{h \neq 2} p_{2,a,2,h}
\]

- $\alpha_1$ represents the vaccine coverage in female-only vaccination
- $\gamma_1$ represents the vaccine efficacy
- $\omega_3$ represents the vaccine compliance
- $\zeta$ represents the reduction in effectiveness due to noncompliance
### Population dynamics

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

\[
\hat{\text{Var}}(\theta_k | y) = \frac{n_{\text{sims}} - 1}{n_{\text{sims}}} W(\theta_k) + \frac{1}{n_{\text{sims}}} B(\theta_k)
\]
The Gelman-Rubin statistic $\hat{R}$

Convergence is monitored by assessing the *potential scale reduction*

\[ \hat{R} = \sqrt{\frac{\text{Var}(\theta_k|y)}{W(\theta_k)}} \]

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

\[ n_{\text{eff}} = \frac{n_{\text{sims}}}{1 + 2 \sum_{t=1}^{\infty} \text{corr}_t} \]

- \( \text{corr}_t \) is the \textit{lag} \( t \) autocorrelation
- \( n_{\text{eff}} \approx n_{\text{sims}} \) indicates negligible autocorrelation
- In case of high autocorrelation
  - convergence can still be reached
  - extreme quantiles of the posterior distribution are typically estimated without precision
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

- diagnostic 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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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.

\[
C_{i,t} = C_{i,t}^{\text{scr}} + C_{i,t}^{\text{vac}} + C_{i,t}^{\text{gw}} + C_{1,i,t}^{\text{cin}} + C_{2,i,t}^{\text{cin}} + C_{3,i,t}^{\text{cin}} + C_{i,t}^{\text{cerv}} + C_{i,t}^{\text{lsil}} \\
+ C_{i,t}^{\text{hsil}} + C_{i,t}^{\text{an}} + C_{i,t}^{\text{hn}} + C_{i,t}^{\text{vin}} + C_{i,t}^{\text{vulv}} + C_{1,i,t}^{\text{vain}} + C_{2,i,t}^{\text{vain}} + C_{3,i,t}^{\text{vain}} \\
+ C_{i,t}^{\text{pein}} + C_{i,t}^{\text{pen}}
\]

\[
U_{i,t} = U_{i,t}^{\text{health}} + U_{i,t}^{\text{inf}} + U_{i,t}^{\text{gw}} + U_{1,i,t}^{\text{cin}} + U_{2,i,t}^{\text{cin}} + U_{3,i,t}^{\text{cin}} + U_{r,i,t}^{\text{cerv}} + U_{i,t}^{\text{lsil}} \\
+ U_{i,t}^{\text{hsil}} + U_{r,i,t}^{\text{an}} + U_{r,i,t}^{\text{hn}} + U_{i,t}^{\text{vin}} + U_{r,i,t}^{\text{vulv}} + U_{1,i,t}^{\text{vain}} + U_{2,i,t}^{\text{vain}} + U_{3,i,t}^{\text{vain}} \\
+ U_{r,i,t}^{\text{vag}} + U_{i,t}^{\text{pein}} + U_{r,i,t}^{\text{pen}}
\]
Incremental Cost-Effectiveness Ratio (ICER)

- Standard measure in cost-effectiveness analyses
- Incremental cost per QALY gained
  - Quality-Adjusted Life Year
  - Utility of health state is multiplied with amount of time spent within
- All model parameters in vector $\theta = (\theta^3, \theta^2)$
  - $\theta^3$ representing parameters in $i = 3$ (universal vaccination)
  - $\theta^2$ representing parameters in $i = 2$ (female-only vaccination)
- Ratio of expectations of cost- and effectiveness-differentials
  - $\Delta_c = \text{PVC}_3 - \text{PVC}_2$
  - $\Delta_e = \text{PVU}_3 - \text{PVU}_2$

\[
\text{ICER} = \frac{E[\text{PVC}|\theta^3] - E[\text{PVC}|\theta^2]}{E[\text{PVU}|\theta^3] - E[\text{PVU}|\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 → 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.
Description of the graph

- The x-axis is the effectiveness differential $\Delta_e$
- The y-axis is the cost differential $\Delta_c$
- 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
New Chemotherapy vs Old Chemotherapy

Effectiveness differential
Cost differential

\[ \text{ICER} = 6497.10 \] $k = 1000$
Cost-effectiveness plane vs ICER

Cost effectiveness plane
New Chemotherapy vs Old Chemotherapy

Effectiveness differential
Cost differential

$\text{ICER} = 6497.10$

$k = 25000$
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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Including layers of uncertainty

Vaccine booster application

Generalization of R code

Cost-effectiveness analysis

Final results

Writing paper on results

Comparing methodologies

Writing paper on methodology

Writing up PhD thesis