Deterministic Compartmental Models

Application: Modeling the Potential Benefit of HPV Vaccines

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Outline

• Human papillomavirus and cervical cancer
• Infectious disease epidemiology – mathematical modelling of sexually transmitted infections (STIs)
• Models of a single HPV type and vaccination
• SIR vs. SIS models
HPV and cervical cancer

• Human Papillomavirus (HPV) - a necessary cause of cervical cancer (CC)
• 500,000 new cases of cervical cancer annually worldwide
• 2nd most common cancer in women in the developing world
• HPV - ubiquitous sexually transmitted infection
• Most infections resolve spontaneously
• A minority go on to develop carcinoma of the cervix over years
Risk factors for HPV and CC

- **Susceptible**
  - Environmental cofactors
  - Host cofactors
  - Viral cofactors

- **HPV Infection**
  - Environmental cofactors
  - Host cofactors
  - Viral cofactors

- **Cervical Carcinoma**

- **Prevention**
  - HPV Vaccines

- **Screening and treatment**

- **Sexual behaviour**

- **High risk HPV type**
Questions about HPV vaccines

• Who should be immunised?
• How do vaccine delivery characteristics (such as coverage and age at vaccination) affect effectiveness?
  – Coverage: the percentage of the target population that is immunised
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$R_0 = 2$

Transmission

No Transmission

Infectious

Susceptible
\( R_0 = 2 \)
\( R_t = R_o \cdot \text{prop susceptible} = 0.5 \)

Transmission
No Transmission

Infectious
Susceptible
Immune
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• SIR vs. SIS models
An introduction to mathematical models

- Models are a framework for understanding and communicating infectious disease
- Explicit assumptions help delineate which parameters are based on evidence
- Quantitative or qualitative results are compared with observed or experimental data
- Validated models can be used to estimate the potential impact of interventions (e.g. vaccination)

An introduction to mathematical models

- Models are a framework for understanding and communicating infectious disease.
An introduction to mathematical models

- Explicit assumptions help delineate which parameters are based on evidence

Barnabas, RV et al; The potential impact of HPV vaccination; PLoS Med; 2006
Model description & assumptions

• Compartmental & deterministic
• Model population stratified for age & sexual activity (important for indirect vaccine effects)
• Model parameterised using demographic, sexual behaviour, smoking trends & HPV-16 serological data from Finland & HPV progression & regression rates from the literature
• Model HPV type 16 only
• Heterosexual mixing
• Validated against HPV 16 ICC incidence
• Explores the impact of waning immunity
An introduction to mathematical models

- Quantitative or qualitative results are compared with observed or experimental data

![Graph showing annual HPV ICC incidence per 100,000 women age 35-39 years from 1976 to 1996. The graph includes observed and model predicted incidence with and without behavior change and the effect of smoking.](image-url)
An introduction to mathematical models

- Validated models can be used to estimate the potential impact of interventions

![Graph showing decrease in HPV 16 cervical cancer incidence following vaccination.]

- Vaccinate 10% of women alone
- Vaccinate 10% of women and men
- Vaccinate 10% of 15 year old and 30% of 20 year old women
- Vaccinate 90% of women alone
- Vaccinate 90% of women and men
Results: Age at vaccination
Vaccinating 90% of women alone
Catch-up vaccination

- Vaccinating females at age 12 with different catch-up scenarios
- Vaccinating more than 6 years catch-up gives little additional benefit (French et al, 2007)
- Catch up can substantially reduce disease in the short term (Elbasha et al, 2007)
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Should boys be vaccinated?

• Would the indirect effects of vaccinating boys further reduce cervical cancer incidence among women?

• Different assumptions about model structure change the cost effectiveness of vaccinating boys
HPV model: men

Susceptible

\[ \lambda \]

HPV

Immune

Susceptible-Infected-Resistant (SIR) model
HPV model: men

Susceptible

\[ \lambda \]

HPV

Immune

Waning immunity

Susceptible-Infected-Resistant-Susceptible (SIRS) model

1. Van Velde et al; Modeling HPV vaccine effectiveness; AME; 2001
SIR vs SIRS

SIR: Higher transmission probability

SIRS: Lower transmission probability

Transmission probabilities are different for each model design
HPV model: women

French K, et al; Modeling the optimum age- & sex-specific pattern of vaccination in Finland; BJC; 2007
Vaccinating boys can increase % cervical cancer cases prevented

<table>
<thead>
<tr>
<th>% of males vaccinated in addition to 70% of girls</th>
<th>% of cervical cancers prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>71%</td>
</tr>
<tr>
<td>30%</td>
<td>76%</td>
</tr>
<tr>
<td>70%</td>
<td>85%</td>
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</tbody>
</table>
Impact of varying coverage changes with model structure

SIR model
Immunity lifelong

SIRS model
Can be reinfecced

% decrease in cervical cases

Women alone
Women and men

Vaccine coverage

10% 30% 90% 10% 30% 80%
Cost effectiveness of vaccinating boys

• Results depend on model assumptions
• To prevent HPV 16/18 infection & disease in women (SIS model, low heterogeneity)\(^1\):
  – Vaccination of 12 y/o girls - $14,583/QALY
  – Including boys ICER - $442,039/QALY
• To prevent HPV 6/11/16/18 infection & disease in women & men (SIR model, more heterogeneity)\(^2\)
  – Vaccination of 12-24 y/o females & males - ICER of $45,056/QALY (compared to $4,666/QALY for 12-24 y/o females)
  – Impact of vaccinating boys increased at lower coverage of girls

1. Taira AV et al; Evaluating HPV vaccination programs; Emerging Infect Dis; 2004
2. Elbasha et al; Model for assessing HPV vaccination strategies, Emerging Infect Dis; 2007
At high coverage, vaccinating women alone prevents more cancers per 100,000 vaccines.

**Cases ICC prevented per 100 vaccinations**

- **females only**
- **males and females**

**Age at vaccination**

- **age12**
- **age15**
- **age18**
- **age21**
Summary

- For transmission models to better assess the impact of vaccination data is needed on
  - HPV infection in older women
  - Natural history of HPV in men
  - Immunity to HPV infection over time
- Models differ widely in their structure, design and assumptions
  - Conclude that widespread HPV vaccination of girls, before sexual debut, with sufficient duration of protection has the potential to substantially reduce HPV precancer and cancer
- Underlying SIS or SIR model structure impacts cost effectiveness analyses
- Understanding model structure, assumptions and how uncertainties are handled helps interpret their results
Acknowledgements

- Imperial College London
  - Geoff Garnett
  - Kat French

- National Public Health Institute, Finland
  - Päivi Laukkanen
  - Matti Lehtinen

- PATH
  - Vivien Tsu

- Merck
  - Eliav Barr

- UW
  - Judy Wasserheit
  - Laura Koutsky

- Fred Hutchinson Cancer Research Center
  - Denise Galloway

- Duke University
  - Shalini Kulasingam