Provincial Canadian HPV vaccination: doses vs age of vaccination

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Outline

• Epidemiology of HPV
Outline

- Epidemiology of HPV
- Details of the vaccine
Outline

• Epidemiology of HPV
• Details of the vaccine
• Research questions
Outline

• Epidemiology of HPV
• Details of the vaccine
• Research questions
• The mathematical model
Outline

• Epidemiology of HPV
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• Research questions
• The mathematical model
• Derive thresholds
Outline

- Epidemiology of HPV
- Details of the vaccine
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- Derive thresholds
- Number of doses vs age
Outline

• Epidemiology of HPV
• Details of the vaccine
• Research questions
• The mathematical model
• Derive thresholds
• Number of doses vs age
• Applications to policy.
Human papillomavirus

• Over 100 different strains
Human papillomavirus

- Over 100 different strains
- 30-40 strains are transmitted through sexual contact
Human papillomavirus

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- HPV causes:
Human papillomavirus

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- 30-40 strains are transmitted through sexual contact
- HPV causes:
  - 5% of all cancers
Human papillomavirus

- Over 100 different strains
- 30-40 strains are transmitted through sexual contact
- HPV causes:
  - 5% of all cancers
  - 10% of all cancers in women.
HPV infections

HPV infection results in

![Bar chart showing the annual number of cases worldwide for different body parts affected by HPV infections. The chart indicates that the cervix is the most affected, followed by the mouth and throat.]
HPV infections

HPV infection results in
• genital warts
HPV infections

HPV infection results in

- genital warts
- cervical cancer

![Bar graph showing annual number of cases worldwide for different body parts: Cervix, Anus, Vagina/Vulva, Penis, Mouth, and Throat. The Cervix shows a significantly higher number of HPV-induced cases compared to the total cases, while other body parts have much lower numbers.](image)
HPV infections

HPV infection results in:
- genital warts
- cervical cancer
- penile cancer
HPV infections

HPV infection results in

- genital warts
- cervical cancer
- penile cancer
- anal cancer
HPV infections

HPV infection results in
• genital warts
• cervical cancer
• penile cancer
• anal cancer
• respiratory papillomatosis
HPV infections

HPV infection results in

- genital warts
- cervical cancer
- penile cancer
- anal cancer
- respiratory papillomatosis
  (vertical transmission)
HPV infections

HPV infection results in

- genital warts
- cervical cancer
- penile cancer
- anal cancer
- respiratory papillomatosis (vertical transmission)

...requiring frequent surgery.
Prevalence in women

• Including harmless strains, estimates are:
Prevalence in women

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- 20 year old women: 20-40%
Prevalence in women

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  - College women: >40%
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  • Lifetime risk: 75%
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(detection relies upon the pap smear, which detects cellular abnormalities caused by HPV)
Prevalence in women

- Including harmless strains, estimates are:
  - 20 year old women: 20-40%
  - College women: >40%
  - Lifetime risk: 75%
    (detection relies upon the pap smear, which detects cellular abnormalities caused by HPV)
- Acquisition to malignancy takes >10 years
Prevalence in women

• Including harmless strains, estimates are:
  • 20 year old women: 20-40%
  • College women: >40%
  • Lifetime risk: 75%

(detection relies upon the pap smear, which detects cellular abnormalities caused by HPV)

• Acquisition to malignancy takes >10 years
• Cervical cancer is the second most common cause of death from cancer in women.
Infections in the US

- 6,200,000 infections per year
Infections in the US

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- 14,000 women diagnosed with cervical cancer each year, leading to...
Infections in the US

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- 3,900 deaths
Infections in the US

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(many fewer than would be caused by HPV, due to effective pap smear screening and precancer treatments).
HPV strains of interest

- Types 6 and 11 account for 90% of genital wart infections
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- Types 16, 18, 31 and 45 lead to cancer
HPV strains of interest

- Types 6 and 11 account for 90% of genital wart infections (as well as respiratory papillomatosis)
- Types 16, 18, 31 and 45 lead to cancer
- Types 16 and 18 are responsible for 65% of cervical cancer cases.
Prevention

- Without condom use, risk of transmission is close to 90%
Prevention

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• With condom use, risk is close to 40%
Prevention

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- No antivirals have been developed for HPV
Prevention

• Without condom use, risk of transmission is close to 90%
• With condom use, risk is close to 40%
• No antivirals have been developed for HPV
• Vaccines are estimated at 90–100% efficacy.
The vaccines

- Gardasil (Merck) protects against strains 6, 11, 16 and 18
The vaccines

• Gardasil (Merck) protects against strains 6, 11, 16 and 18
  (the four most common strains)
The vaccines

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- Cervarix (GSK) protects against strains 16 and 18
The vaccines

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  (the four most common strains)
- Cervarix (GSK) protects against strains 16 and 18
  (the two most common cancer-causing strains)
The vaccines

• Gardasil (Merck) protects against strains 6, 11, 16 and 18
  (the four most common strains)
• Cervarix (GSK) protects against strains 16 and 18
  (the two most common cancer-causing strains)
• Some evidence of cross-protection against strains 31 and 45 (the other cancer strains).
Gardasil

- Protects against both persistent and incident infections
Gardasil

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- No side effects
Gardasil

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• Three shots over six months, costing $US360
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- Highly immunogenic (98%)
Gardasil

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• No side effects
• Three shots over six months, costing $US360
• Recommended for women aged 9–26
• Highly immunogenic (98%)
• No evidence of waning (so far).
Men?

- The vaccine has recently been approved for men
Men?

- The vaccine has recently been approved for men
- However, uptake rates are low
Men?

- The vaccine has recently been approved for men
- However, uptake rates are low
- Thus, we’ll assume vaccinated men have a negligible effect on the outcome.
The rollout program

• Canadian provinces are now vaccinating girls aged 9–13
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  (ie before they become sexually active)
The rollout program

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- The vaccine is available to women aged 14–26, but is not covered by Canadian health plans
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- Some also give two doses instead of three
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  (ie before they become sexually active)
• The vaccine is available to women aged 14–26, but is not covered by Canadian health plans
• However, different provinces vaccinate at different ages
• Some also give two doses instead of three
  – piggybacking on other vaccination programs tends to result in greater uptake rates.
# Provincial vaccination strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Province(s)</th>
<th>Grade</th>
<th>Doses</th>
<th>Coverage Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NWT</td>
<td>4</td>
<td>3</td>
<td>unknown</td>
</tr>
<tr>
<td>2</td>
<td>QU</td>
<td>4, 9</td>
<td>2, 1(last)</td>
<td>81-86%</td>
</tr>
<tr>
<td>3</td>
<td>AB</td>
<td>5</td>
<td>3</td>
<td>50-60%</td>
</tr>
<tr>
<td>4</td>
<td>BC</td>
<td>6,9</td>
<td>2</td>
<td>62%</td>
</tr>
<tr>
<td>5</td>
<td>NL</td>
<td>6,9</td>
<td>3</td>
<td>85%</td>
</tr>
<tr>
<td>6</td>
<td>MB</td>
<td>6</td>
<td>3</td>
<td>52-61%</td>
</tr>
<tr>
<td>6</td>
<td>NU</td>
<td>6</td>
<td>3</td>
<td>unknown</td>
</tr>
<tr>
<td>6</td>
<td>PE</td>
<td>6</td>
<td>3</td>
<td>85%</td>
</tr>
<tr>
<td>6</td>
<td>SK</td>
<td>6</td>
<td>3</td>
<td>58-66%</td>
</tr>
<tr>
<td>6</td>
<td>YK</td>
<td>6</td>
<td>3</td>
<td>unknown</td>
</tr>
<tr>
<td>7</td>
<td>NS</td>
<td>7</td>
<td>3</td>
<td>85%</td>
</tr>
<tr>
<td>7</td>
<td>NB</td>
<td>7</td>
<td>3</td>
<td>unknown</td>
</tr>
<tr>
<td>8</td>
<td>ON</td>
<td>8</td>
<td>3</td>
<td>49-59%</td>
</tr>
</tbody>
</table>
Coverage levels

• Initial surveys suggested that the majority of parents (77%) would be receptive to their children being vaccinated, if suitably informed about HPV
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- In the first year, Ontario reported only 53% vaccination coverage
Coverage levels

• Initial surveys suggested that the majority of parents (77%) would be receptive to their children being vaccinated, if suitably informed about HPV
• In the first year, Ontario reported only 53% vaccination coverage
• This has not increased substantially over subsequent years.
Research questions

• Does the age at which girls are vaccinated significantly affect the outcome?
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  - we’ll use grade instead of age, in line with how the program is organised
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• What are the implications of two vs three doses?
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• Should we attempt to standardise across Canada?
Research questions

• Does the age at which girls are vaccinated significantly affect the outcome?
  – we’ll use grade instead of age, in line with how the program is organised

• What are the implications of two vs three doses?

• Should we attempt to standardise across Canada?
  – health is provincial, but the Public Health Agency of Canada, based in Ottawa, can make recommendations.
Baseline model

• Our first approximation considered a single childhood class
Baseline model

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- Children progress to adults
Baseline model

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- Children progress to adults
  (defined as sexually active individuals)
Baseline model

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• Either children or adults can be vaccinated
Baseline model

- Our first approximation considered a single childhood class
- Children progress to adults
  (defined as sexually active individuals)
- Either children or adults can be vaccinated
- We only study heterosexual transmission.
The model

\[ \pi \]

\[ 1 - \varepsilon p \]

\[ \varepsilon p \]
The model

\[ \pi \]

1 - \( \varepsilon_p \)

\[ \alpha \]

Girls <9

\[ \varepsilon_p \]
The model

Proportion vaccinated

$1 - \varepsilon p$

$\pi$

Girls <9

$\varepsilon p$
The model

Proportion vaccinated

1-εp

π

Girls <9

εp

Vaccine immunogenicity
The model

Proportion vaccinated

$1 - \varepsilon p$

$\pi$

Girls <9

$\varepsilon p$

Vaccine immunogenicity

$\mu_C$

$C_U$

$C_V$
The model

Proportion vaccinated

1-εp

π

Girls <9

εp

Vaccine immunogenicity

μC

Cu

CV

UNVACCINATED
The model

Proportion vaccinated

1-εp

π

Girls <9

εp

Vaccine immunogenicity

μC

C_U

C_V

VACCINATED

UNVACCINATED

Proportion vaccinated

1-εp

π

Girls <9

εp

Vaccine immunogenicity

μC

C_U

C_V

VACCINATED

UNVACCINATED
The model

Proportion vaccinated

1-εp

π

Girls <9

εp

Vaccine immunogenicity

Death rate

μC

C_U

C_V

μ_C

VACCINATED

UNVACCINATED
The model

Proportion vaccinated

1 - εp

π

Girls <9

εp

Vaccine immunogenicity

Death rate

μc

μ

α

UNVACCINATED

VACCINATED

C_U

A_U

C_V

A_V
The model

Proportion vaccinated

1 - \( \varepsilon p \) - Girls < 9

Vaccine immunogenicity

Maturation

\( \mu_c \) - \( \alpha \) - \( \mu \)

\( C_V \) - \( C_U \) - \( A_V \) - \( A_U \)

Death rate

Proportion vaccinated

UNVACCINATED

VACCINATED
The model

- Proportion vaccinated
- Maturation
- Leaving rate
- Vaccine immunogenicity
- Vaccine immunoactivity
- Girls <9
- Death rate

UNVACCINATED

VACCINATED
The model

Proportion vaccinated

1-\(\varepsilon p\)

\(\pi\)

Girls <9

Vaccine immunogenicity

\(\frac{\mu_C}{\alpha}\) Maturation

\(\frac{\mu}{\alpha}\) Leaving rate

\(f(\varepsilon p)\)

VACCINATED

UNVACCINATED

\(\frac{\mu_C}{\alpha}\) Death rate
The model

Proportion vaccinated → $C_U$ → $A_U$ → $I_U$ (UNVACCINATED)

Vaccine immunogenicity → $C_V$ → $A_V$ → $I_V$ (VACCINATED)

Death rate → $A_U$ → $I_U$

Leaving rate → $A_U$ → $I_U$

Maturation → $C_U$ → $A_U$

Girls <9 → $C_U$ → $A_U$

Proportion vaccinated → $1 - \varepsilon p$

Vaccine immunogenicity → $\varepsilon p$

Proportion vaccinated = $\pi$

Death rate → $\mu_C$

Leaving rate → $\mu$

Maturation → $\alpha$

Leaving rate → $\beta_N$

Leaving rate → $1 - \psi \beta_N$
The model

Proportion vaccinated

$\pi$

$1 - \epsilon p$

$\mu_C$

Maturation

$\alpha$

Leaving rate

$\beta_N$

Death rate

$\epsilon p$

Vaccine immunogenicity

$\mu_C$

Girls <9

$\beta_N$

Vaccine efficacy

VACCINATED

UNVACCINATED

Proportion vaccinated

$\pi$

$1 - \epsilon p$

$\mu_C$

Maturation

$\alpha$

Leaving rate

$\beta_N$

Death rate

$\epsilon p$

Vaccine immunogenicity

$\mu_C$

Girls <9

$\beta_N$

Vaccine efficacy

VACCINATED

UNVACCINATED
The model

Proportion vaccinated

1 - εp

π

Girls <9

Vaccine immunogenicity

1 - εp

Maturation

μC

α

Leaving rate

βN

Girls <9

f(εp)

Death rate

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The model

Proportion vaccinated

$\pi$ → $C_U$ → $A_U$ → $I_U$ (UNVACCINATED)

Girls <9

$1 - \varepsilon p$ → $C_U$

$\varepsilon p$ → $C_V$ → $A_V$ → $I_V$ (VACCINATED)

Vaccine immunogenicity

Maturation

$\alpha$ → $A_U$ → $N$ → $M$ → $A_V$ → $I_V$

Leaving rate

$\mu$ → $N$ → $M$ → $I_V$

$\beta_N$ → $N$ → $M$ → $I_V$

Vaccine efficacy

Transmissibility

$\beta_M$ → $N$ → $M$ → $I_V$

$\mu$ → $N$ → $M$ → $I_V$

$\mu$ → $N$ → $M$ → $I_V$

Proportion vaccinated

Girls <9

$1 - \varepsilon p$ → $C_U$

$\varepsilon p$ → $C_V$ → $A_V$

Death rate

$\mu_C$ → $C_V$ → $A_V$

$\mu_C$ → $C_U$ → $A_U$

Vaccine efficacy

$\alpha$ → $A_U$ → $N$ → $M$ → $A_V$ → $I_V$

Transmissibility

$\beta_N$ → $N$ → $M$ → $I_V$

$\beta_M$ → $N$ → $M$ → $I_V$

$\mu$ → $N$ → $M$ → $I_V$
The model

Proportion vaccinated

\[ C_U \]

1-εp

Girls <9

εp

Vaccine immunogenicity

Maturation

\[ \mu_C \]

\[ \alpha \]

Leaving rate

\[ \mu \]

\[ \beta_N \]

N

f(εp)

\[ \mu \]

Maturation

\[ \mu_C \]

\[ \alpha \]

Death rate

\[ \mu_C \]

Vaccine efficacy

\[ (1-\psi) \beta_N \]

Transmissibility

\[ I_U \]

UNVACCINATED

\[ I_V \]

VACCINATED

\[ M \]

MEN.
Full model

- We now extend the baseline model to multiple classes of children
Full model

• We now extend the baseline model to multiple classes of children
  – these represent different school grades
Full model

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  – vaccination occurs at a particular grade
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  – vaccination occurs at a particular grade
  – otherwise the vaccination rate is zero
Full model

• We now extend the baseline model to multiple classes of children
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Full model

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  – these represent different school grades
  – vaccination occurs at a particular grade
  – otherwise the vaccination rate is zero
• Some children may already be infected
  – eg childhood sexual abuse
• These individuals will proceed directly to the infected class
• We also include recovery of infected individuals.
Adult vaccination rate

- The rate of vaccination of adults is
Adult vaccination rate

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\[
f(\bar{e}\bar{p}) = \frac{c\bar{e}\bar{p}}{1 - \bar{e}\bar{p} + \gamma}
\]
Adult vaccination rate

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where \( c/\gamma \) is the maximum possible rate of vaccination, assuming perfect efficacy and immunogenicity.
Adult vaccination rate

- The rate of vaccination of adults is

$$f(\vec{ep}) = \frac{c\vec{e}p}{1 - \vec{e}p + \gamma}$$

where $c/\gamma$ is the maximum possible rate of vaccination, assuming perfect efficacy and immunogenicity.

- This rate is zero if nobody is vaccinated and high (but not infinite) if everybody is.
The model

Girls in grade 4 (approx. 9 years old) are described as

\[ \frac{dC_4}{dt} = \pi_W - (1 + \mu_C)C_4. \]

Girls in grade 5 (approx. 10 years old) are described as

\[ \frac{dC_{5U}}{dt} = (1 - \epsilon_p)C_4 - (1 + \mu_C)C_{5U} \]
\[ \frac{dC_{5V}}{dt} = \epsilon_p C_4 - (1 + \mu_C)C_{5V}. \]

Girls in grade 6 (approx. 11 years old) are described as

\[ \frac{dC_{6U}}{dt} = (1 - \epsilon_p)C_{5U} - (1 + \mu_C)C_{6U} \]
\[ \frac{dC_{6V}}{dt} = \epsilon_p C_{5U} + C_{5V} - (1 + \mu_C)C_{6V}. \]

Girls in grade 7 (approx. 12 years old) are described as

\[ \frac{dC_{7U}}{dt} = (1 - \epsilon_p)C_{6U} - (1 + \mu_C)C_{7U} \]
\[ \frac{dC_{7V}}{dt} = \epsilon_p C_{6U} + C_{6V} - (1 + \mu_C)C_{7V}. \]

Girls in grade 8 (approx. 13 years old) are described as

\[ \frac{dC_{8U}}{dt} = (1 - \epsilon_p)C_{7U} - (1 + \mu_C)C_{8U} \]
\[ \frac{dC_{8V}}{dt} = \epsilon_p C_{7U} + C_{7V} - (1 + \mu_C)C_{8V}. \]

Girls in grade 9 (approx. 14 years old) are described as

\[ \frac{dC_{9U}}{dt} = (1 - \epsilon_p)C_{8U} - (1 + \mu_C)C_{9U} \]
\[ \frac{dC_{9V}}{dt} = \epsilon_p C_{8U} + C_{8V} - (1 + \mu_C)C_{9V}. \]

Girls in grade 10 (approx. 15 years old) are described as

\[ \frac{dC_{10U}}{dt} = (1 - \epsilon_p)C_{9U} - (1 + \mu_C)C_{10U} \]
\[ \frac{dC_{10V}}{dt} = \epsilon_p C_{9U} + C_{9V} - (1 + \mu_C)C_{10V}. \]

Uninfected adult women are described as

\[ \frac{dA_U}{dt} = (1 - \phi_U)C_{10U} + \xi_U I_U - f(\epsilon_{pW})A_U - \frac{\beta_W A_U N}{\sigma} - \mu_A A_U \]
\[ \frac{dA_V}{dt} = (1 - \phi_V)C_{10V} + \xi_V I_V + f(\epsilon_{pW})A_U - \frac{(1 - \psi)\beta_W A_V N}{\sigma} - \mu_A A_V. \]

Infected adult women are described as

\[ \frac{dI_U}{dt} = \phi_U C_{10U} + \frac{\beta_W A_U N}{\sigma} - \xi_U I_U - \mu_A I_U \]
\[ \frac{dI_V}{dt} = \phi_V C_{10V} + \frac{(1 - \psi)\beta_W A_V N}{\sigma} - \xi_V I_V - \mu_A I_V. \]

Uninfected men are described as

\[ \frac{dM}{dt} = \pi_M + \xi_M N - \frac{\beta_M I_U M}{\phi} - \frac{\beta_M I_V M}{\phi} - \mu_A M. \]

Infected men are described as

\[ \frac{dN}{dt} = \beta_M I_U M + \beta_M I_V M - \xi_M N - \mu_A N. \]
♀ and ♂

- The denominators are the total numbers of women (including girls) and men:
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\[ \varphi = C_4 + C_{5U} + C_{5V} + C_{6U} + C_{6V} + C_{7U} + C_{7V} + C_{8U} + C_{8V} + C_{9U} + C_{9V} \\
+ C_{10U} + C_{10V} + A_U + A_V + I_U + I_V, \]
♀ and ♂

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♀ = C_4 + C_{5U} + C_{5V} + C_{6U} + C_{6V} + C_{7U} + C_{7V} + C_{8U} + C_{8V} + C_{9U} + C_{9V} + C_{10U} + C_{10V} + A_U + A_V + I_U + I_V,

♂ = M + N.

C_j = children
A_j = uninfected adults
I_j = infected adults
M, N = men
Disease-free equilibrium

- The DFE is
Disease-free equilibrium

• The DFE is

\[(C_4, C_{5U}, C_{5V}, C_{6U}, C_{6V}, C_{7U}, C_{7V}, C_{8U}, C_{8V}, C_{9U}, C_{9V}, C_{10U}, C_{10V}, A_U, A_V, I_U, I_V, M, N),\]

\(C_j=\text{children} \ A_j=\text{uninfected adults} \ l_j=\text{infected adults} \ M, N=\text{men} \ f=\text{adult uptake} \ \mu_j=\text{death rates} \ \pi_M=\text{male birth rate} \ \epsilon_j=\text{efficacy} \ p_j=\text{coverage} \ \Phi_j=\text{childhood infection} \)
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where

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Disease-free equilibrium

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\[
(\overline{C_4}, \overline{C_{5U}}, \overline{C_{5V}}, \overline{C_{6U}}, \overline{C_{6V}}, \overline{C_{7U}}, \overline{C_{7V}}, \overline{C_{8U}}, \overline{C_{8V}}, \overline{C_{9U}}, \overline{C_{9V}}, \overline{C_{10U}}, \overline{C_{10V}}, \overline{A_U}, \overline{A_V}, \overline{I_U}, \overline{I_V}, M, N),
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where

\[
\overline{C_{4U}} = \frac{\pi_W}{1 + \mu_C}
\]

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\[
C_{4U} = \frac{\pi_W}{1 + \mu_C}
\]

- For \(4 \leq i \leq 10\), we have

\[
\begin{align*}
C_{iU} &= \frac{(1 - \epsilon p_{(i-1)})C_{(i-1)U}}{1 + \mu_C} \\
A_U &= \frac{C_{10U}}{f(\epsilon_W p_W) + \mu_A} \\
I_U &= 0 \\
M &= \frac{\pi_M}{\mu_A}
\end{align*}
\]

\[
\begin{align*}
C_{iV} &= \frac{\epsilon p_{(i-1)}C_{(i-1)V} + C_{(i-1)V}}{1 + \mu_C} \\
A_V &= \frac{f(\epsilon_W p_W)A_U + (1 - \phi_V)C_{10V}}{\mu_A} \\
I_V &= 0 \\
N &= 0.
\end{align*}
\]

\(C_j=\text{children} \ A_j=\text{uninfected adults} \ I_j=\text{infected adults} \ M,N=\text{men} \ f=\text{adult uptake} \ \mu_j=\text{death rates} \ \pi_M=\text{male birth rate} \ \epsilon_j=\text{efficacy} \ p_j=\text{coverage} \ \Phi_j=\text{childhood infection} \)
Stability

- We found the Jacobian matrix and used the Routh–Hurwitz criterion to determine stability of the DFE
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• We expect this to occur.
Basic reproduction number

- The stability comes down to the sign of the constant term in the characteristic polynomial
Basic reproduction number

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• From this, we find
Basic reproduction number

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- From this, we find

\[ R_0 = \frac{\beta_W \beta_M ((1 - \psi)(\mu_A + \xi_U)A_V + (\mu_A + \xi_V)A_U)}{\phi \mu_A (\mu_A^2 + \mu_A (\xi_U + \xi_V + \xi_M) + (\xi_U \xi_V + \xi_V \xi_M + \xi_V \xi_M))} \]

\( A_j \)=uninfected adults  \( \mu_j \)=death rates  
\( \beta_j \)=transmissibilities  \( \varphi \)=total women  
\( \Psi \)=protection  \( \xi_j \)=duration of infection
Basic reproduction number

- The stability comes down to the sign of the constant term in the characteristic polynomial.
- From this, we find

\[ R_0 = \frac{\beta_W \beta_M ((1 - \psi)(\mu_A + \xi_U)A_V + (\mu_A + \xi_V)A_U)}{\varphi \mu_A (\mu_A^2 + \mu_A (\xi_U + \xi_V + \xi_M) + (\xi_U \xi_V + \xi_V \xi_M + \xi_V \xi_M))}, \]

where the \( A_U \) and \( A_V \) values are evaluated at the disease-free equilibrium.

\( A_j \) = uninfected adults  \( \mu_j \) = death rates  
\( \beta_j \) = transmissibilities  \( \varphi \) = total women  
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Reformulated equilibria

- Let $k^*$ be the grade of vaccination
Reformulated equilibria

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- Then for $4 \leq i \leq 10$, we have
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- Then for $4 \leq i \leq 10$, we have

\[
\begin{align*}
\bar{C}_{kU} &= \frac{\pi_W}{(1 + \mu_C)^{k-3}} \quad \text{for } k \leq k^* \\
\bar{C}_{kU} &= \frac{\pi_W(1 - \epsilon \rho_{k-1})}{(1 + \mu_C)^{k-3}} \quad \text{for } k > k^* \\
\bar{C}_{kV} &= 0 \quad \text{for } k \leq k^* \\
\bar{C}_{kV} &= \frac{\pi_W \epsilon}{(1 + \mu_C)^{k-3}} \quad \text{for } k > k^* \\
\bar{A}_U &= \frac{\pi_W}{(f(p_W \epsilon_W) + \mu_A)(1 - \mu_C)^7} \\
\bar{A}_V &= \frac{\pi_W f}{(f(p_W \epsilon_W) + \mu_A)(1 - \mu_C)^7}.
\end{align*}
\]

$C_j =$ children  $A_j =$ uninfected adults  
$f =$ adult uptake  $\mu_j =$ death rates  
$\pi_W =$ female birth rate  $\epsilon_j =$ efficacy  
$p_j =$ coverage  $\Phi_j =$ childhood infection
Critical childhood vaccine immunogenicity

- We can evaluate the critical vaccine immunogenicity for children $\epsilon^*$
Critical childhood vaccine immunogenicity

• We can evaluate the critical vaccine immunogenicity for children $\epsilon^*$
• We set $R_0=1$ and use our reformulated equilibrium values
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- We solve for $\epsilon^*$ by looking at childhood-only vaccination
  - we thus set $p_{\text{W}}=0$

- Then we have
  \[
  \epsilon^* = \frac{\varphi \mu_A^2 (1 - \mu_C)^7 (\mu_A^2 + \mu_A (\xi_U + \xi_V + \xi_M) + \xi_U \xi_V + \xi_U \xi_M + \xi_V \xi_M)}{\beta_W \beta_M \pi_W ((1 - \psi)(\mu_A + \xi_U) - (\mu_A + \xi_V))}.
  \]

$\mu_j$=death rates $\pi_{\text{W}}$=female birth rate
$\beta_i$=transmissibilities $\varphi$=total women
$\Psi$=protection $\xi_j$=duration of infection
Other critical values

• Similarly, we can find the critical adult immunogenicity:
Other critical values

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\[ \epsilon^*_W = \frac{\mu_A (1 + \gamma) (\beta_W \beta_M \pi_W \xi_V + \mu_A (1 + \mu_C)^7 D)}{\beta_W \beta_M \pi_W (c + \mu_A (\mu_A + \xi_U)) - \mu_A^2 (1 + \mu_C)^7 D^3} \]

- \( \mu_j \): death rates
- \( \pi_W \): female birth rate
- \( \beta_j \): transmissibilities
- \( \varphi \): total women
- \( \Psi \): protection
- \( \xi_j \): duration of infection
- \( c/y = \text{max possible vaccination} \)
Other critical values

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\]

where D is the denominator of R_0.

\[\mu_j=\text{death rates} \quad \pi_W=\text{female birth rate} \quad \beta_j=\text{transmissibilities} \quad \varphi=\text{total women} \quad \Psi=\text{protection} \quad \xi_j=\text{duration of infection} \quad c/y=\text{max possible vaccination}\]
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• Using a similar method, we can find the critical protection rate

\[ \mu_J = \text{death rates} \quad \pi_W = \text{female birth rate} \quad \beta_j = \text{transmissibilities} \quad \varpi = \text{total women} \quad \Psi = \text{protection} \quad \xi_j = \text{duration of infection} \quad c/y = \text{max possible vaccination} \]
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• Using a similar method, we can find the critical protection rate

\[ \psi^* = 1 + \frac{\beta_W \beta_M(\mu_A + \xi_U)A_{U} - D}{\beta_M \beta_M(\mu_A + \xi_V)A_{V}} \]

\[ \mu_j = \text{death rates} \quad \pi_W = \text{female birth rate} \quad \beta_j = \text{transmissibilities} \quad \varphi = \text{total women} \quad \Psi = \text{protection} \quad \xi_j = \text{duration of infection} \quad c/y = \text{max possible vaccination} \]
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where \( D \) is the denominator of \( R_0 \).

- Using a similar method, we can find the critical protection rate

\[ \psi^* = 1 + \frac{\beta_W \beta_M (\mu_A + \xi_U) A_U - D}{\beta_W \beta_M (\mu_A + \xi_V) A_V}, \]

- If the vaccine protection is lower than this value, then we can never have eradication.

\( \mu_j = \text{death rates} \)
\( \pi_W = \text{female birth rate} \)
\( \beta_j = \text{transmissibilities} \)
\( \varphi = \text{total women} \)
\( \Psi = \text{protection} \)
\( \xi_j = \text{duration of infection} \)
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Latin Hypercube Sampling

• We explored the sensitivity of $R_0$ to parameter variations using
Latin Hypercube Sampling

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Latin Hypercube Sampling
- samples parameters from a random grid
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  - resamples, but not from the same row or column
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    (a bit like tic tac toe)
Latin Hypercube Sampling

- We explored the sensitivity of $R_0$ to parameter variations using:
  - Latin Hypercube Sampling
  - Partial Rank Correlation Coefficients

- Latin Hypercube Sampling:
  - samples parameters from a random grid
  - resamples, but not from the same row or column
    (a bit like tic tac toe)
  - runs 1,000 simulations.
Example
**Example**

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Partial Rank Correlation Coefficients

• Partial Rank Correlation Coefficients (PRCCs)
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  - test individual parameters while holding all other parameters at median values
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- PRCCs > 0 will increase $R_0$ when they are increased
Partial Rank Correlation Coefficients (PRCCs)

- test individual parameters while holding all other parameters at median values
- rank parameters by the amount of effect on the outcome

- PRCCs > 0 will increase $R_0$ when they are increased
- PRCCs < 0 will decrease $R_0$ when they are increased.

$R_0$ = basic reproductive ratio
PRCCs

Rate of transmission, women to men
Rate of transmission, men to women
Probability of protection
Death rate, adults
Recovery rate, men
Recovery rate, unvaccinated women
Proportion of vaccinated girls, grade 4
Proportion of infected girls, vaccinated
Proportion of vaccinated girls, grade 8
Maximal rate of vaccination, women
Proportion of vaccinated girls, grade 6
Proportion of vaccinated girls, grade 9
Efficacy, women
Proportion of vaccinated girls, grade 5
Attenuation constant
Efficacy, girls
Proportion of vaccinated women
Proportion of vaccinated girls, grade 7
Proportion of infected girls, unvaccinated
Death rate, children
Birth rate, women
Birth rate, men
Recovery rate, vaccinated women

Degree of Correlation

-0.2 -0.1 0 0.1 0.2 0.3 0.4 0.5 0.6 0.7

0.657
0.627
0.0787
0.0542
0.034
0.0272
0.0137
0.00752
0.00727
0.00436
Monte Carlo simulations
Two doses vs three doses

A

B

Vaccination Grade
Mean $R_0$ values
Vaccination coverage rates
Timecourse of infection

- No Vaccination
- 70% Child Vaccination
- Two Doses
- Three Doses
- 70% Child Vaccination and 30% Adult Vaccination
Summary

• Three doses is more effective than two, but not greatly
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• The age of vaccination does not matter terribly much for childhood vaccination
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• What matters most is coverage levels
• Childhood vaccination needs to be supplemented by moderate adult vaccination.
Eradicating targeted HPV types

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Eradicating targeted HPV types

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- This could be done through condom distribution or through changes in sexual behaviour.
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• This is significantly lower than the 90-95% protection rates afforded by the vaccine
• This suggests that eradication is feasible.
Policy outcomes

• This research was undertaken as part of a MITACS internship by Carley Rogers, as part of her M.Sc. at the University of Ottawa
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- Carley worked at the Public Health Agency of Canada for four months
- The model was developed in collaboration with PHAC members
- As a result of this research, Quebec changed its HPV vaccination policy in August 2013 from three to two doses.
Mathematics and policy

• This shows that we can have a direct influence on policy
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• However, it has to be done collaboratively
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• This illustrates the cycle of modelling.
Using math to solve real problems

Biological problem
Using math to solve real problems

- Biological problem
- Mathematical model
Using math to solve real problems

Biological problem → Mathematical model → Mathematical analysis
Using math to solve real problems

1. Biological problem
2. Mathematical model
3. Mathematical analysis
4. Mathematical conclusion
Using math to solve real problems

Biological problem

Mathematical model

Mathematical analysis

Biological conclusion

Mathematical conclusion
Using math to solve real problems

1. Biological problem
2. Compare with data
3. Biological conclusion
4. Mathematical model
5. Mathematical analysis
6. Mathematical conclusion
Conclusions

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• The age of vaccination is not a crucial parameter
• The number of doses barely affects the outcome, except to facilitate greater uptake rates
• Childhood vaccination should be supplemented by moderate adult vaccination
• This could be achieved by enhanced HPV awareness programs in colleges/universities.
Key references


http://mysite.science.uottawa.ca/rsmith43