Cost-Effectiveness of extending HPV vaccination above age 26 years in the U.S.

Marc Brisson
Professor, Université Laval

Jean-François Laprise
CHU de Québec-Université Laval
Modeling Team

Université Laval
• Jean-François Laprise
• Mélanie Drolet
• Élodie Bénard
• Dave Martin

Imperial College
• Marie-Claude Boily

CDC
• Harrell Chesson
• Lauri Markowitz

Disclaimer

• The findings and conclusions expressed are those of the author and do not necessarily represent the official views of the Centers for Disease Control and Prevention (CDC) or the Department of Health and Human Services (DHHS)

Peer reviewed

• Follows Guidelines for economic analyses to be presented to the ACIP
Conflicts of interest statements

- Brisson, Laprise, Drolet, Martin, Bénard, Boily, Chesson & Markowitz
  - No known conflicts of interest

Funding
Study Question

• From the health care sector perspective, what is the additional impact and cost-effectiveness of extending the established HPV vaccine program in the U.S. to females aged 27-45 years and males aged 22-45 years?

Objective

• To evaluate the:
  – additional population-level effectiveness, and
  – incremental cost-effectiveness
of vaccinating females and males up to 45 years of age in the U.S. against HPV (vs current recommendation)
Methods
Model Overview – HPV-ADVISE

• **Model type:** Individual-based transmission-dynamic model

• **Components:**
  - Demographic
  - Sexual behaviour & HPV transmission
  - Natural history of disease
  - Vaccination
  - Screening & Treatment
  - Economic

• **Population:** Open-Stable, 10 to 100 years of age

• **HPV infections:** 18 genotypes, including 6/11/16/18/31/33/45/52/58

• **Diseases:**
  - Anogenital warts (AGW)
  - Cervical cancer (squamous cell carcinoma (SCC) & adenocarcinoma)
  - Cancers of the anus, oropharynx, penis, vagina & vulva

&: Brisson *JNCI* 2016; Laprise *JID* 2016; Van de Velde *JNCI* 2012; Description of model components in extra slides
Parameter overview

Fitting process

Step 1: Uniform prior distributions are defined for each model parameter
  • min-max values for each parameter derived from the literature

Step 2: Hundreds of thousands of different combinations of parameter values are drawn from the prior distributions

Step 3: Multiple parameter sets are identified, which fit U.S. data:
  • Sexual & screening behaviour (stratified by gender and age)
  • HPV prevalence (stratified by HPV type, gender, age and sexual activity)
  • Incidence of anogenital warts, cervical lesions, cervical cancer and other HPV-related cancers (stratified by HPV type, gender, and age)
  • Total of 776 data points fitted

&: Description of data used for fit and references available in extra slides
Model Fit

- ≈ 200,000 different combinations of parameters sampled from the prior parameter distributions
- 50 parameter sets produced acceptable fit to the 776 pre-specified data target points
Model Fit - sexual behaviour

Ex: Number of partners in the past 12 months in women

Data: Haderxhanaj STD 2014 (using NFSG (2006-2010))
Model Fit - HPV prevalence in women

Ex: HPV-16/18 prevalence by age

Data: NHANES (2005-2006)
Model Fit - anogenital warts (AGW)

Ex: Incidence of AGW diagnoses

Data: Hoy *Curr Med Res Opin* 2009; Data adjusted to account for the % of AGW caused by HPV-6/11
Model Fit - squamous cell carcinoma (SCC)

Ex: Incidence of SCC

Model validation

Model predictions vs. Post-vaccination U.S. data

Change in prevalence over time is shown as % change versus pre-vaccination values (2003-2006). Predictions: Mean & min/max of HPV-ADVISE predictions; Data: NHANES
Intervention: HPV vaccination

- **2007**: 4-valent, 3 doses for females 9-26 years of age.
- **2011**: 4-valent, 3 doses for females.
- **2015**: 9-valent, 3 doses for males 9-21 years of age.
- **2016**: 9-valent, 2 doses <15 yrs, 3 doses 15+yrs for females.

Decision:
- Extended catch-up in mid-adults.
- No changes (Current recommendation) for 9-valent.
Vaccination coverage - Current recommendation

Base case

**Girls & Boys age 18 years or less**
- Data from National Immunization Survey-Teen (age 13-17 years)
- 2007-16: Observed uptake rates
  - 18 year-olds: Assume same uptake rates as 17 year-olds
- 2017+: Assume uptake rates constant at 2016 levels

**Women & Men above 18 years of age**
- Uptake rates based on Chesson et al. *Vaccine* 2018
  - Females 19-26 years: 2.6% per year
  - Males 19-21 years: 1.9% per year
Vaccination coverage - Current recommendation  
Base case, Fit to data

- Model reproduces data from National Immunization Survey-Teen

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Girls</th>
<th>Boys</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 &amp;</td>
<td>43%</td>
<td>38%</td>
</tr>
<tr>
<td>14</td>
<td>49%</td>
<td>45%</td>
</tr>
<tr>
<td>15</td>
<td>57%</td>
<td>52%</td>
</tr>
<tr>
<td>16</td>
<td>61%</td>
<td>56%</td>
</tr>
<tr>
<td>17</td>
<td>67%</td>
<td>62%</td>
</tr>
<tr>
<td>13 to 17</td>
<td>55%</td>
<td>51%</td>
</tr>
</tbody>
</table>

&: For simplicity, vaccination at age 13 years in our model incorporates vaccination series that occur from ages 9 through 13 years. Vaccination coverage increases until 2021 due to age and time cohort effects.
Base case vaccination scenarios

- **Mid-adult vaccination scenarios - Females and Males**
  - ≤26 years of age (harmonization)
  - ≤30 years
  - ≤40 years
  - ≤45 years

- **Vaccination uptake**
  - Females: 2.6% per year
  - Males: 1.9% per year
Economic analysis

- **Perspective:** Health care sector
- **Costs:** All direct medical costs
- **Outcome Measure:** Cost per QALY gained
- **Discounting:** 3% for costs and benefits
- **Time Horizon:** 100 years (from onset of program)
- **9-valent vaccination cost/dose (min-max)**
  - $\leq 18$ years, $205 (176-235)$
  - $\geq 19$ years, $225 (176-235)$

QALY=Quality-Adjusted Life-Year

&: Description of parameters and references available in extra slides
£: Cost per dose, personal communication Harrell Chesson
## Economic analysis

### Health care costs (2018 USD)

| Disease/Procedure               | Base case | Maximum Cost | Standardized Cost\*
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital warts[1]</td>
<td>680</td>
<td>770</td>
<td>860</td>
</tr>
<tr>
<td>Screening &amp; treatment[2]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine test</td>
<td>129</td>
<td>164</td>
<td>129</td>
</tr>
<tr>
<td>Colposcopy/biopsy</td>
<td>583</td>
<td>862</td>
<td>583</td>
</tr>
<tr>
<td>CIN 2/3 treatment</td>
<td>3,095</td>
<td>4,872</td>
<td>3,095</td>
</tr>
<tr>
<td>Cancers[1]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>64,800</td>
<td>81,000</td>
<td>72,800</td>
</tr>
<tr>
<td>Vulvar</td>
<td>41,300</td>
<td>58,700</td>
<td>51,400</td>
</tr>
<tr>
<td>Vaginal</td>
<td>111,400</td>
<td>142,400</td>
<td>116,500</td>
</tr>
<tr>
<td>Anal</td>
<td>52,600</td>
<td>78,300</td>
<td>93,600</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>141,800</td>
<td>166,600</td>
<td>126,500</td>
</tr>
<tr>
<td>Penile</td>
<td>22,100</td>
<td>43,300</td>
<td>22,200</td>
</tr>
</tbody>
</table>

\*: Standardized costs for model comparison. \[1\] Chesson personal communication; \[2\] Brisson JNCI & Laprise JID 2016
Results: Effectiveness
Effectiveness Extended to 45 years vs. Current recommendation

Base case

CIN2/3

- Current recommendation
- Females & Males ≤45 years

Anogenital Warts

- 13 million Cases prevented
- 56,000 additional Cases prevented
- 32 million Cases prevented
- 124,000 additional Cases prevented

Cervical Cancer

- 653,000 Cases prevented
- 3,000 additional Cases prevented

Non-Cervical HPV-associated Cancers

- 769,000 cases prevented
- 4,000 additional Cases prevented

CIN=Cervical Intraepithelial Neoplasia; Predictions: Median estimate generated by the 50 best fitting parameter sets
Why is Mid-adult vaccination predicted to produce small additional reductions in burden?

Number of people vaccinated:
- Number of additional people vaccinated by extending vaccination to mid-adults is small compared to the current program

Herd effects:
- Current vaccination program is predicted to provide substantial herd effects among unvaccinated adults older than 26 years
  - Incidence of infection and cancer among unvaccinated adults 26-45 years old will decline substantially (due to herd effects)

Age of causal infection:
- Large proportion of cervical cancers are predicted to be caused by an HPV infection acquired before 26 years of age
Cumulative proportion of the age of acquisition of HPV infection that causes cervical cancer

No Vaccination or Screening, HPV-16/18/31/33/45/52/58

Predictions: The solid blue line represents the mean and the shaded area the minimum and maximum of model predictions generated by the 50 best fitting parameter sets. Burger (CID 2017) predict a median age of 20 years.
Results: Cost-effectiveness
## Cost-effectiveness Mid-adult vs. Current recommendation

### Base case

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Scenario Comparison</th>
<th>Cost-effectiveness ratio - Median ($/QALY-gained)</th>
<th>Cost-effectiveness ratio - 90% UI ($/QALY-gained)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0) No vaccination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Current recommendation</td>
<td>1 vs. 0</td>
<td>CS</td>
<td>(CS; 5,000)</td>
</tr>
<tr>
<td>(2) Females &amp; Males ≤26 yrs</td>
<td>2 vs. 1</td>
<td>-*</td>
<td>(40,000; -)</td>
</tr>
<tr>
<td>(3) Females &amp; Males ≤30 yrs</td>
<td>3 vs. 1</td>
<td>830,000</td>
<td>(104,000; -)</td>
</tr>
<tr>
<td>(4) Females &amp; Males ≤40 yrs</td>
<td>4 vs. 1</td>
<td>1,843,000</td>
<td>(339,000; -)</td>
</tr>
<tr>
<td>(5) Females &amp; Males ≤45 yrs¶</td>
<td>5 vs. 1</td>
<td>1,471,000</td>
<td>(360,000; -)</td>
</tr>
</tbody>
</table>

QALY=Quality-Adjusted Life-Year; UI=Uncertainty Interval; CS=Cost Saving; Predictions: Median, and 5<sup>th</sup> to 95<sup>th</sup> percentiles (90% UI) of predictions generated with the 50 best fitting parameter sets; Base case: 9-valent cost/dose=$205 in ≤18 year-olds and $225 in 19-45 year-olds

*: A dash ‘-’ means that no significant gains in QALY could be measured

¶: Dominance of scenario (5) over scenario (4) is likely due to the much greater herd effects of the current vaccination strategy among individuals aged 30-40 years compared to those aged >40 years. Lower herd effects among older mid-adults result in greater potential for benefits.
## Cost-effectiveness: Mid-adult vs. Current recommendation

**Base case - Stratified by natural history parameters**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Scenario Comparison</th>
<th>All parameter sets (N=50) ($/QALY-gained)</th>
<th>Faster progression &amp; lower natural immunity (n=22) ($/QALY-gained)</th>
<th>Slower progression &amp; higher natural immunity (n=28) ($/QALY-gained)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0) No vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Current recommendation</td>
<td>1 vs. 0</td>
<td>CS</td>
<td>CS</td>
<td>CS</td>
</tr>
<tr>
<td>(2) Females &amp; Males ≤26 yrs</td>
<td>2 vs. 1</td>
<td>-*</td>
<td>178,000</td>
<td>-</td>
</tr>
<tr>
<td>(3) Females &amp; Males ≤30 yrs</td>
<td>3 vs. 1</td>
<td>830,000</td>
<td>404,000</td>
<td>2,308,000</td>
</tr>
<tr>
<td>(4) Females &amp; Males ≤40 yrs</td>
<td>4 vs. 1</td>
<td>1,843,000</td>
<td>973,000</td>
<td>2,909,000</td>
</tr>
<tr>
<td>(5) Females &amp; Males ≤45 yrs</td>
<td>5 vs. 1</td>
<td>1,471,000</td>
<td>1,047,000</td>
<td>1,592,000</td>
</tr>
</tbody>
</table>

CE=cost-effectiveness; QALY=Quality-Adjusted Life-Year; Predictions: Median of predictions; Base case: 9-valent cost/dose=$205 in ≤18 year-olds and $225 in 19-45 year-olds

&: Parameter sets that have lower probability of natural immunity following clearance in females (≤ 35% vs > 35%) and faster progression to CIN2/3 (26 months vs 30 months)

*: A dash ‘-’ means no significant gains in QALY could be measured
**Sensitivity Analysis**  
Cost-effectiveness through age 30 years

**Mid-adult vs. Current recommendation - Vaccination parameters**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>All parameter sets (N=50) ($/QALY-gained)</th>
<th>Fast progression &amp; low natural immunity (n=22) ($/QALY-gained)</th>
<th>Slower progression &amp; higher natural immunity (n=28) ($/QALY-gained)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>830,000</td>
<td>404,000</td>
<td>2,308,000</td>
</tr>
<tr>
<td>High catch-up coverage</td>
<td>747,000</td>
<td>507,000</td>
<td>1,487,000</td>
</tr>
<tr>
<td>Low historical vaccination coverage£</td>
<td>336,000</td>
<td>318,000</td>
<td>410,000</td>
</tr>
<tr>
<td>Stopping mid-adult catch-up after 40 years</td>
<td>616,000</td>
<td>296,000</td>
<td>1,697,000</td>
</tr>
<tr>
<td>Low vaccine efficacy¶</td>
<td>481,000</td>
<td>366,000</td>
<td>835,000</td>
</tr>
</tbody>
</table>

QALY=Quality-Adjusted Life-Year; **Predictions**: Median result; **Base case**: 9-valent cost/dose=$225 in 19-45 year-olds; 
°: Parameter sets that have lower probability of natural immunity following clearance in females and faster progression to CIN1/2/3; £: 75% of base case vaccination uptake rates for historical coverage; ¶: Vaccine efficacy is assumed to be 85% against persistent infections for all HPV types included in the vaccine. Lower vaccine efficacy produces lower cost-effectiveness ratios for mid-adult vaccination (vs current recommendations) because it results in fewer benefits and less herd effects under the current recommendations, thus allowing for greater mid-adult vaccination benefits.
## Sensitivity Analysis Cost-effectiveness through age 30 years

**Mid-adult vs. Current recommendation - Economic parameters**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>All parameter sets (N=50) ($/QALY-gained)</th>
<th>Faster progression &amp; lower natural immunity (n=22) ($/QALY-gained)</th>
<th>Slower progression &amp; higher natural immunity (n=28) ($/QALY-gained)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>830,000</td>
<td>404,000</td>
<td>2,308,000</td>
</tr>
<tr>
<td>Vaccine cost/dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• $176</td>
<td>644,000</td>
<td>310,000</td>
<td>1,775,000</td>
</tr>
<tr>
<td>• $235</td>
<td>867,000</td>
<td>423,000</td>
<td>2,417,000</td>
</tr>
<tr>
<td>Max health care costs§</td>
<td>821,000</td>
<td>395,000</td>
<td>2,253,000</td>
</tr>
<tr>
<td>Max Burden of disease§</td>
<td>753,000</td>
<td>317,000</td>
<td>1,211,000</td>
</tr>
<tr>
<td>Disutility in cervical cancer survivors*</td>
<td>499,000</td>
<td>276,000</td>
<td>658,000</td>
</tr>
<tr>
<td>Standardized economic parameters</td>
<td>829,000</td>
<td>402,000</td>
<td>2,302,000</td>
</tr>
</tbody>
</table>

QALY=Quality-Adjusted Life-Year; **Predictions**: Median result; **Base case**: 9-valent cost/dose=$225 in 19-45 year-olds; **a**: Parameter sets that have lower probability of natural immunity following clearance in females and faster progression to CIN1/2/3; **§**: Maximum estimates from the US literature; ***: We assume a permanent 0.24 yearly disutility for cervical cancer survivors in this scenario (0 disutility after 5 yrs in the base case)
Discussion: Strengths & Limitations
Strengths

- HPV-ADVISE calibrated to highly stratified U.S. data
  - HPV-ADVISE is calibrated to represent country-specific sexual behaviour, HPV epidemiology, health care resource use and cervical cancer screening

- HPV-ADVISE validated with post-vaccination U.S. data
  - Predictions are consistent with age-specific post-vaccination HPV infection and Anogenital warts diagnosis prevalence data from the U.S.[1]
  - HPV-ADVISE has also been validated to post-vaccination data in Australia[2]

- Predictions are made using 50 parameter sets
  - Captures uncertainty in the natural history of HPV infection and related diseases, and variability in sexual behaviour data
  - Results in wide uncertainty intervals, reflecting that results are highly sensitive to natural history assumptions and lack of data among mid-adults

- Sensitivity analyses were performed on key parameters

[1]: Drolet IPVC 2018, [2]: Drolet JID 2018
Limitations of examining mid-adult vaccination

- Long term herd effects of vaccinating younger age cohorts on mid-adult women and men remain uncertain
  - If HPV-ADVISE overestimates herd effects of current program, our results may overestimate the cost-effectiveness ratios of vaccinating mid-adult men and women
  - However, our model reproduces short term post-vaccination herd effects

- Time to lesions & level of natural immunity after infection remains uncertain
  - Model predictions are very sensitive to these natural history parameters

- Relative progression of a re-infection or new infection in mid-adults (vs younger adults) is unknown
  - HPV-ADVISE assumes that progression is independent of age
  - However, it has been suggested that a proportion of re-detection is due to deposition\(^{[1]}\), and that new infections later in life have a smaller risk of progressing to cervical cancer\(^{[2,3]}\)
  - If this is the case, mid-adult vaccination would produce lower benefits and higher cost-effectiveness ratios

- Screening recommendations are changing in the U.S.
  - If changes to screening result in more effective cervical cancer prevention, mid-adult vaccination would produce lower benefits and higher cost-effectiveness ratios

\(^{[1]}\): Malagon *JID* 2017; \(^{[2]}\): Plummer *Int J Cancer* 2012; \(^{[3]}\): Rodriguez *JNCI* 2010
Summary  Effectiveness & Cost-effectiveness predictions

• Current HPV vaccination program:
  – Predicted to reduce the HPV-burden of disease substantially
    • E.g., 82% reduction in anogenital wart diagnoses and 59% of cervical cancer cases over 100 years
  – Likely cost-saving (vs. no vaccination)

• Extending vaccination to 45 year old females and males:
  – Predicted to produce small additional reductions in HPV burden of disease
    • E.g., additional 0.2-0.4 percentage point reduction in anogenital warts diagnoses and cervical cancer cases
  – Results in cost-effectiveness ratios ≥ $360,000 per QALY-gained in 95% of model simulations under base case assumptions (median=$1.5 million) &

• The cost-effectiveness of mid-adult vaccination is highly sensitive to:
  – Level of natural immunity after infection & rate of progression to cervical lesions
  – Historical vaccination coverage

&: median cost per QALY-gained of extending vaccination to 30 year olds = $830,000; 95% of simulations ≥ $104,000 per QALY-gained
Thank you!