Incremental Cost-Effectiveness of the 9-valent vs. the 4-valent HPV vaccine in the U.S.

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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 (past 3 years): Unrestricted grant from Merck Frosst (Zoster vaccine, none ongoing)
- Drolet (past 3 years): Consulted for GSK (Zoster vaccine)
- Boily, Laprise, Chesson & Markowitz
  - No known conflicts of interest

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Université Laval
Imperial College London
Study Question

• From the societal perspective, what is the additional impact and cost-effectiveness of the 9-valent compared to 4-valent (quadrivalent) HPV vaccine in the context of an established 4-valent HPV vaccine program in the U.S.?

Objective

• To evaluate the:
  – additional population-level effectiveness, and
  – incremental cost-effectiveness

of switching from the 4-valent to the 9-valent HPV vaccine in the U.S.
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
  - Cervical cancer (SCC & adenocarcinoma)
  - Cancers of the anus, oropharynx, penis, vagina & vulva

&: Van de Velde et al. JNCI 2012 104(22):1712-23; 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 AGW, cervical lesions, cervical cancer and other HPV-related cancers (stratified by HPV type, gender, and age)
  • Total of 826 data points fitted

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

- ≈ 200,000 different combinations of parameters sampled from the prior parameter distributions
- 50 parameter sets produced acceptable fit to the 826 pre-specified data target points
Model Fit - sexual behaviour

Ex: Proportion sexually active women

- Data
- Box plots represent the min, max and median of model predictions

Other examples of model fit in extra slides; Data: NHANES
Model Fit - HPV Prevalence in women

Ex: HPV-16/18 prevalence by age and level of sexual activity

Data: NHANES

Box plots represent the min, max and median of model predictions

&: Other examples of model fit in extra slides; Data: NHANES
Model Fit - Screening

Ex: Incidence of HSIL

Data

Box plots represent the min, max and median of model predictions

Incidence of HSIL per 100,000 people-year

Age (years)

Data: Other examples of model fit in extra slides; Data: Insinga 2004
Model Fit - Squamous cell carcinoma (SCC)

Ex: Incidence of SCC

Incidence of SCC per 100,000w-y

Age group (years)

Data

Box plots represent medians, and 5, 25, 75, and 95th percentiles

Other examples of model fit in extra slides; Data: US Cancer Statistics (NPCR/SEER)
Vaccine efficacy (VE) parameters

VE among susceptible females & males

<table>
<thead>
<tr>
<th>HPV-type</th>
<th>Base case</th>
<th>4-valent (no cross protection)</th>
<th>4-valent* (cross protection)</th>
<th>9-valent£</th>
</tr>
</thead>
<tbody>
<tr>
<td>16/18</td>
<td>95.0</td>
<td>95.0</td>
<td>95.0</td>
<td>95.0</td>
</tr>
<tr>
<td>6/11</td>
<td>95.0</td>
<td>95.0</td>
<td>95.0</td>
<td>95.0</td>
</tr>
<tr>
<td>31</td>
<td>0.0</td>
<td>46.2</td>
<td>95.0</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>0.0</td>
<td>28.7</td>
<td>95.0</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>0.0</td>
<td>7.8</td>
<td>95.0</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>0.0</td>
<td>18.4</td>
<td>95.0</td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>0.0</td>
<td>5.5</td>
<td>95.0</td>
<td></td>
</tr>
<tr>
<td>Other HR-types</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

* Malagón, *Lancet Infectious Disease* 2012

£ We assume that VE against HPV-16/18 is equal for the 4- and 9-valent vaccines (based on immunogenicity presented at Eurogin 2013)
Economic analysis

- **Perspective:** Societal
- **Costs:** All direct medical costs
- **Outcome Measure:** Cost per QALY gained
- **Discounting:** 3% for costs and benefits
- **Time Horizon:** 70 years
- **Vaccine Cost:**
  - 4-valent: $145/dose (with administration)
  - 9-valent: $158/dose

QALY=quality-adjusted life-year

&: Description of parameters and references available in extra slides

†: Cost from Merck presentation at the 29th International Papillomavirus Conference, 2014
Intervention  HPV vaccination 2007-2014


Decision

4-valent  4-valent

3-dose vaccination
Intervention HPV vaccination 2015+


Decision

4-valent 4-valent 4-valent

16
Intervention  HPV vaccination 2015+


Decision

4-valent  4-valent  9-valent  4-valent

9-valent  4-valent
3-dose Vaccination Coverage

- Data: National Immunization Survey
- Used age-specific 3-dose uptake rates:
  - Annual % vaccinated with 3\textsuperscript{rd} dose among those who had not previously received a 3\textsuperscript{rd} dose
- 2007-13: Observed uptake rates
- 2014+: Assumed uptake rates constant at 2013 levels
- Overall vaccination coverage increases until 2017 due to age and time cohort effects

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Girls</th>
<th>Boys</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>26%</td>
<td>12%</td>
</tr>
<tr>
<td>14</td>
<td>38%</td>
<td>18%</td>
</tr>
<tr>
<td>15</td>
<td>48%</td>
<td>27%</td>
</tr>
<tr>
<td>16</td>
<td>55%</td>
<td>31%</td>
</tr>
<tr>
<td>17</td>
<td>62%</td>
<td>38%</td>
</tr>
<tr>
<td>13 to 17</td>
<td>46%</td>
<td>25%</td>
</tr>
</tbody>
</table>
Results: Health Outcomes
9-valent HPV vaccine
Potential for additional cancer prevention

[Graph showing HPV-type specific positivity in women and men across different body parts.]

1) Saraiya, JNCI (under review)
9-valent HPV vaccine

Potential for additional cancer prevention in the U.S.

Number of cases per year

<table>
<thead>
<tr>
<th>Disease</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>10,000</td>
<td>0</td>
</tr>
<tr>
<td>Vulva</td>
<td>3,000</td>
<td>0</td>
</tr>
<tr>
<td>Vagina</td>
<td>1,000</td>
<td>0</td>
</tr>
<tr>
<td>Anus</td>
<td>500</td>
<td>0</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>200</td>
<td>0</td>
</tr>
<tr>
<td>Penis</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Anus</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>30</td>
<td>0</td>
</tr>
</tbody>
</table>

Ref: 1) Jemal JNCI 2013; 2) Saraiya, JNCI (under review)
Effectiveness 4-valent vs. 9-valent Girls & Boys

Base case, **No Cross Protection for 4-valent**

**Effectiveness**

- 4-valent vs. 9-valent Girls & Boys
- Base case, **No Cross Protection for 4-valent**

**Predictions:** Mean estimate generated by the 50 best fitting parameter sets

**CIN2/3**

- % Change in incidence
- Years since start of vaccination

**Cervical Cancer**

- % Change in incidence
- Years since start of vaccination

**Base case:** vaccine-type efficacy=95%, duration=Lifelong

**Predictions:** Mean estimate generated by the 50 best fitting parameter sets
Effectiveness 4-valent vs. 9-valent Girls & Boys

Base case, with & without Cross Protection for 4-valent

CIN2/3

Cervical Cancer

% Change in incidence

Years since start of vaccination

Base case: vaccine-type efficacy=95%, duration=Lifelong
Predictions: Mean estimate generated by the 50 best fitting parameter sets
Effectiveness 9-valent Girls & Boys vs. 9-valent Girls & 4-valent Boys
Base case, No Cross Protection for 4-valent

CIN2/3

Cervical Cancer

% Change in incidence

Years since start of vaccination

Base case: vaccine-type efficacy=95%, duration=Lifelong
Predictions: Mean estimate generated by the 50 best fitting parameter sets
Effectiveness

Base case, **No Cross Protection for 4-valent**

Oropharyngeal Cancer

Anogenital warts

% Change in incidence

Years since start of vaccination

Base case: vaccine-type efficacy=95%, duration=Lifelong
Predictions: Mean estimate generated by the 50 best fitting parameter sets
Health Outcomes Prevented over 70 years

Base case

- 4-valent Girls & Boys (No Cross Protection)
- 4-valent Girls & Boys (Cross Protection)
- 9-valent Girls & 4-valent Boys (No Cross Protection)
- 9-valent Girls & Boys

Base case: vaccine-type efficacy=95%, duration=Lifelong
Predictions: Mean estimate generated by the 50 best fitting parameter sets
Health Outcomes Prevented over 70 years

Base case, No Cross Protection for 4-valent

**NNV\(^\alpha\)=1,100**

87K

**NNV=4,500**

26K

**All Cancers**

**Deaths**

- 4-valent Girls & Boys (No Cross Protection)
- 4-valent Girls & Boys (Cross Protection)
- 9-valent Girls & 4-valent Boys (No Cross Protection)
- 9-valent Girls & Boys

\(\alpha\): NNV=(# females vaccinated with 9-valent)\+(	ext{Additional events prevented by vaccinating females with 9-valent}); Base case: vaccine-type efficacy=95%, duration=Lifelong; Predictions: Mean estimate generated by the 50 best fitting parameter sets
Health Outcomes Prevented over 70 years

Base case, with Cross Protection for 4-valent

<table>
<thead>
<tr>
<th>Vaccination Type</th>
<th>Number of Prevented Events (Thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-valent Girls &amp; Boys (No Cross Protection)</td>
<td>47K</td>
</tr>
<tr>
<td>4-valent Girls &amp; Boys (Cross Protection)</td>
<td>6K</td>
</tr>
<tr>
<td>9-valent Girls &amp; 4-valent Boys (No Cross Protection)</td>
<td>14K</td>
</tr>
<tr>
<td>9-valent Girls &amp; Boys</td>
<td>28K</td>
</tr>
</tbody>
</table>

\[ \text{NNV} = \frac{\text{Additional events prevented by vaccinating females with 9-valent}}{\text{Number of females vaccinated with 9-valent}} \]

Base case: vaccine-type efficacy=95%, duration=Lifelong; Predictions: Mean estimate generated by the 50 best fitting parameter sets
Health Outcomes Prevented over 70 years

Base case, 9-valent Girls & Boys vs. 9-valent Girls & 4-valent Boys

\[ NNV = 13,700 \]

\[ NNV = 32,100 \]

\&: NNV=(\# boys vaccinated with 9-valent) + (Additional events prevented by vaccinating boys with 9-valent); Base case: vaccine-type efficacy=95%, duration=Lifelong; Predictions: Mean estimate generated by the 50 best fitting parameter sets
Results: Cost-effectiveness
**Incremental QALYs-gained**

Discounted over 70 years

- **No Cross Protection, 4-valent**
  - 4-valent Girls & Boys [1 vs No vacc]
  - 9-valent Girls [1 vs No vacc]
  - 9-valent Girls & Boys [3 vs 2]

- **Cross Protection, 4-valent**
  - 4-valent Girls & Boys [1 vs No vacc]
  - 9-valent Girls [2 vs 1]
  - 9-valent Girls & Boys [3 vs 2]

- 4-valent Girls & Boys
- 9-valent Girls, 4-valent Boys
- 9-valent Girls & Boys

**Incremental QALY-gained** (1,000)

- AGW consultations
- Other cancers
- Cervical lesions
- Cervical cancer

**Base case:** vaccine-type efficacy=95%, duration=Lifelong

**Predictions:** Mean estimate generated by the 50 best fitting parameter sets
Incremental Healthcare costs saved
Discounted over 70 years

Base case: vaccine-type efficacy=95%, duration=Lifelong; 4-valent cost/dose=$145; 9-valent cost/dose=$158
Predictions: Mean estimate generated by the 50 best fitting parameter sets
## Cost-effectiveness

**Base Case, No Cross Protection for 4-valent**

<table>
<thead>
<tr>
<th></th>
<th>Change in costs ($ million)</th>
<th>Change in QALY-gained (1,000 QALY)</th>
<th>ICER ($/QALY-gained)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0) No Vaccination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) 4-valent Girls &amp; Boys</td>
<td>6,866</td>
<td>1,068</td>
<td>6,400 [3,500; 10,100]</td>
</tr>
<tr>
<td>(2) 9-valent Girls &amp; Boys</td>
<td>-2,149</td>
<td>131</td>
<td>Cost saving [CS; CS]</td>
</tr>
<tr>
<td></td>
<td>421</td>
<td>13</td>
<td>31,200 [1,900; &gt;1million]</td>
</tr>
<tr>
<td></td>
<td>-2,209</td>
<td>145</td>
<td>Cost saving [CS; CS]</td>
</tr>
</tbody>
</table>

ICER: Incremental Cost-Effectiveness Ratio; QALY=quality-adjusted life-year

**Base case:** Vaccine-type efficacy=95%, duration=Lifelong; 4-valent cost/dose=$145; 9-valent cost/dose=$158

**Predictions:** Mean result of the 50 best fitting parameter sets (25 runs per parameter set)

**Uncertainty intervals:** 10th and 90th percentiles of model results based on the 50 best fitting parameter sets, reflects uncertainty in the natural history parameters
## Cost-effectiveness

**Base Case, with Cross Protection for 4-valent**

<table>
<thead>
<tr>
<th></th>
<th>Change in costs ($ million)</th>
<th>Change in QALY-gained (1,000 QALY)</th>
<th>ICER ($/QALY-gained)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0) No Vaccination</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(1) 4-valent Girls &amp; Boys</td>
<td>1 vs. 0</td>
<td>5,379</td>
<td>1,131</td>
</tr>
<tr>
<td>(2) 9-valent Girls</td>
<td>2 vs. 1</td>
<td>-1,009</td>
<td>90</td>
</tr>
<tr>
<td>4-valent Boys</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) 9-valent Girls &amp; Boys</td>
<td>3 vs. 2</td>
<td>575</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>3 vs. 1</td>
<td>-434</td>
<td>94</td>
</tr>
</tbody>
</table>

ICER: Incremental Cost-Effectiveness Ratio; QALY=quality-adjusted life-year

**Base case:** Vaccine-type efficacy=95%, duration=Lifelong; 4-valent cost/dose=$145; 9-valent cost/dose=$158

**Predictions:** Mean result of the 50 best fitting parameter sets (25 runs per parameter set)

**Uncertainty intervals:** 10th and 90th percentiles of model results based on the 50 best fitting parameter sets, reflects uncertainty in the natural history parameters
Results: Sensitivity Analysis
Influential Variables
## Sensitivity Analysis

Incremental cost-effectiveness ($/QALY-gained), **No Cross Protection** for 4-valent

<table>
<thead>
<tr>
<th></th>
<th>4-valent (Girls &amp; Boys) vs. No vaccination</th>
<th>9-valent (Girls &amp; Boys) vs 4-valent (Girls &amp; Boys)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base case</strong></td>
<td>6,400</td>
<td>Cost saving</td>
</tr>
<tr>
<td><strong>Duration of Protection=20yrs</strong></td>
<td>8,300</td>
<td>Cost saving</td>
</tr>
<tr>
<td><strong>Vaccine Coverage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• All doses at 13 yrs of age</td>
<td>8,000</td>
<td>Cost saving</td>
</tr>
<tr>
<td>• Girls=75%, Boys=69%</td>
<td>12,000</td>
<td>Cost saving</td>
</tr>
<tr>
<td><strong>Min Health Care Costs</strong></td>
<td>13,300</td>
<td>Cost saving</td>
</tr>
<tr>
<td><strong>Min Burden of Disease</strong></td>
<td>10,500</td>
<td>Cost saving</td>
</tr>
<tr>
<td><strong>Cervical screening - Co-testing</strong></td>
<td>-</td>
<td>Cost saving</td>
</tr>
</tbody>
</table>

**ICER:** Incremental Cost-Effectiveness Ratio; QALY=quality-adjusted life-year

**Base case:** Vaccine-type efficacy=95%, duration of protection =Lifelong; 4-valent cost/dose=$145; 9-valent cost/dose=$158

**Min:** Minimum estimates from the U.S. literature; *All doses given at 13 yrs of age:* Vaccination coverage Girls=62%, Boys=38%

**HPV Co-testing:** HPV co-testing every 5 years (30-65 year old women)

**Predictions:** Mean result of the 50 best fitting parameter sets (20 runs per parameter set)
## Sensitivity Analysis

Incremental cost-effectiveness ($/QALY-gained), with Cross Protection for 4-valent

<table>
<thead>
<tr>
<th></th>
<th>4-valent (Girls &amp; Boys) vs. No vaccination</th>
<th>9-valent (Girls &amp; Boys) vs 4-valent (Girls &amp; Boys)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base case</strong></td>
<td>4,800</td>
<td>Cost saving</td>
</tr>
<tr>
<td><strong>Duration of Protection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 9- &amp; 4-valent=20yrs</td>
<td>6,500</td>
<td>Cost saving</td>
</tr>
<tr>
<td>• Cross-protection=20yrs</td>
<td>4,900</td>
<td>Cost saving</td>
</tr>
<tr>
<td><strong>Vaccination Coverage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• All doses at 13 yrs of age</td>
<td>6,700</td>
<td>Cost saving</td>
</tr>
<tr>
<td>• Girls=75%, Boys=69%</td>
<td>9,900</td>
<td></td>
</tr>
<tr>
<td><strong>Min Health Care Costs</strong></td>
<td>11,700</td>
<td>4,500</td>
</tr>
<tr>
<td><strong>Min Burden of Disease</strong></td>
<td>8,000</td>
<td>Cost saving</td>
</tr>
</tbody>
</table>

ICER: Incremental Cost-Effectiveness Ratio; QALY=quality-adjusted life-year

**Base case:** Vaccine-type efficacy=95%, duration of protection =Lifelong; 4-valent cost/dose=$145; 9-valent cost/dose=$158

**Min:** Minimum estimates from the U.S. literature; All doses given at 13 yrs of age: Vaccination coverage Girls=62%, Boys=32%

**Predictions:** Mean result of the 50 best fitting parameter sets (20 runs per parameter set)
**Sensitivity Analysis**

**Additional Cost/dose of the 9-valent (vs. 4-valent)**

QALY = quality-adjusted life-year;

**Base case**: Vaccine-type efficacy = 95%, duration of protection = Lifelong; 4-valent cost/dose = $145; 9-valent cost/dose = $158

**Predictions**: Mean, and 10\(^{th}\) and 90\(^{th}\) percentile of model results based on the 50 best fitting parameter sets (20 runs per parameter set). 10\(^{th}\) and 90\(^{th}\) percentiles reflect the uncertainty in the natural history parameters.
Discussion: Limitations
Limitations

• Duration of 4- and 9-valent vaccine efficacy and future vaccination coverage remains unknown:
  – Varied duration of protection and vaccination coverage
  – Duration of protection and coverage had no impact on conclusions

• Modeled both cytology-based screening and HPV co-testing:
  – Screening may change in the coming years
  – If the changes to screening result in less costly and/or more effective cervical cancer prevention the 9-valent may be less cost-effective

• Did not present cost-effectiveness 9-valent vs 2-valent
  – In Canada, the 2-valent vaccine was less cost-effective than the 9- and 4-valent
Summary
Summary  Population-level effectiveness predictions

• Current U.S. 4-valent Girls & Boys strategy is expected to substantially reduce HPV-related diseases
  – 61% and 65% reduction in CIN2/3 and Cervical cancer, respectively, after 70 years (assuming no cross protection)
  – 1 HPV-related cancer would be prevented for every 250 vaccinated individuals

• Switching to a 9-valent Girls & Boys is expected to further reduce precancerous lesions and cervical cancer, with less impact on other HPV-related outcomes
  – 19% and 14% additional reduction in CIN2/3 and Cervical cancer, respectively, after 70 years (assuming no cross protection)
  – 1 additional HPV-related cancer prevented for every 1,000 vaccinated individuals with the 9-valent instead of the 4-valent

• Vaccinating girls with the 9-valent provides the great majority of benefits of a 9-valent Girls & Boys program
Summary Cost-effectiveness predictions

• Current U.S. 4-valent Girls & Boys HPV vaccination program is highly cost-effective

• Switching to a 9-valent Girls & Boys program is likely cost-effective (and cost saving)
  – Vaccinating girls with the 9-valent provides the majority of cost savings and QALYs-gained of a 9-valent Girls & Boys program

• Results are robust across a range of plausible assumptions
  – with or without cross protection
  – price, duration of protection, health care costs, burden of illness
Thank you!