Observed and Modeled impact of different HPV immunization schedules and strategies

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1.Université Laval, 2. Centre de recherche du CHU de Québec, 3. Imperial College, 4. London School of Hygiene & Tropical Medicine, 5. Public Health England, 6. International Agency for Research on Cancer (IARC)

Meeting of the Strategic Advisory Group of Experts on Immunization (SAGE)
October 20, 2016
Geneva
Objective

• Summarize existing evidence about the population-level effectiveness and cost-effectiveness of HPV immunization of different schedules and strategies, using:
  - Observational post-vaccination data
  - Predictions from Mathematical Models

Schedules/strategies

• Girls-only HPV immunization (2- or 4- vs 9-valent)
• Gender-neutral HPV immunization (vs Girls-only)
• Multiple age cohort HPV immunization (vs single age cohort)
Observed population-level effectiveness

Systematic review & meta-analysis
Methods
Systematic reviews - Population-level effectiveness & herd effects

- We conducted two systematic reviews
  - Initial review: Studies published between Jan 2007 & Feb 2014
  - Updated review: Studies published between Feb 2014 & July 2016
  - Used same methodology

- Search strategy
  - Medline and Embase, and main HPV conference abstracts

- Eligibility
  - Comparisons between pre- and post-vaccination periods
  - Incidence/prevalence of HPV infection, anogenital warts, or CIN2+

- Analysis (initial review only)
  - Stratified by age & sex
  - Pooled relative risk (RR) derived from random-effects models

Results of review\textsuperscript{1} Girls-only immunization

High Income Countries with \textit{≥ 50% vaccination coverage} of girls

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<td></td>
<td></td>
</tr>
<tr>
<td>HPV 16/18 (n=1) *</td>
<td></td>
<td>0.50 [0.34; 0.74]</td>
</tr>
<tr>
<td>AGW (n=6)</td>
<td></td>
<td>0.86 [0.79; 0.94]</td>
</tr>
<tr>
<td>CIN2+ (n=2)</td>
<td></td>
<td>New data from US: Significant decrease in CIN2+ lesions 2-3</td>
</tr>
</tbody>
</table>

**Women 20-39 years old**

| HPV 16/18 (n=4) †       |                                     | 0.96 [0.77; 1.18]                     |
| AGW (n=6)               |                                     | 1.02 [0.90; 1.16]                     |
| Cin2+ (n=1)             |                                     | 0.97 [0.92; 1.02]                     |

**Boys 15-19 years old**

| HPV 16/18 (n=0)         |                                     | NA                                    |
| AGW (n=6)               |                                     | 1.07 [0.93; 1.22]                     |

**Men 20-39 years old**

| HPV 16/18 (n=0)         |                                     | NA                                    |
| AGW (n=6)               |                                     | 1.13 [0.95; 1.33]                     |

**Favours vaccination**

RR=prevalence ratio (post-vaccination ÷ pre-vaccination prevalence); * 13-19 year age group; † 20-24 years age group

Results  Gender-neutral & multiple age cohort immunization

- Gender-neutral immunization
  - 2 countries with population-level data after Gender-neutral immunization (Australia, the USA)\(^1-6\)
  - Too early to measure the additional impact of Gender-neutral vaccination
    - Max follow-up available is 1-2 years after the switch from girls-only to gender-neutral vaccination

- Multiple age cohort immunization
  - Many countries vaccinated many age cohorts (Australia, Canada, Denmark, Greece, New-Zealand, Norway, Sweden, the UK and the US)
  - Too few countries without Multiple age cohort immunization to isolate the additional population-level impact of this strategy (vs a single cohort)

Need for mathematical models

- Compelling population-level evidence suggest that **Girls-only HPV immunization programs**:
  - Reduce HPV-16/18 infection, anogenital warts and CIN2+ lesions
  - Provide herd effects
  - Magnitude of impact strongly depend on vaccination coverage

- Remaining questions: What will be the long term-population level effectiveness, and expected cost-effectiveness of:
  - Girls-only HPV immunization with 2- or 4-valent vs 9-valent
  - Gender-neutral vs Girls-only HPV immunization
  - Multiple vs single age cohort HPV immunization

- Mathematical models provide a formal framework to examine these questions
Predicted population-level effectiveness, herd effects & cost-effectiveness

Model-based analysis
Methods

Modeling - Population-level effectiveness & herd effects

HPV-ADVISE (Agent-based Dynamic model for Vaccination & Screening Evaluation)\(^1\)

- Transmission-dynamic model of HPV infection and disease (includes herd immunity)

- Models 18 HPV types:
  - Types included in the 9-valent vaccine (HPV-6/11/16/18/31/33/45/52/58)
  - 9 other high risk types

- Fit HPV-ADVISE to Canada, India, Vietnam, and Uganda\(^\&\):
  - Demographic and sexual behaviour
  - HPV prevalence and cervical cancer incidence (age and type-specific)
  - Data from international databases and original studies\(^\&\)

\(^{\text{REF}}\): 1. Brisson, *JNCI* 2015; &: Demographic and Health Surveys, Multiple Indicator Survey, ICO information Centre on HPV and Cancer, United Nations Statistics Division, HIV and AIDS HUB for Asia Pacific-Evidence to action, WHO Global Health Observatory data repository, literature reviews, and original studies from IARC and Dr. M Alary (see back-up slides for references & model fit)
High risk HPV prevalence, women data for model fit

REF: Literature review (see back-up slides)
Sexual behavior & Cervical cancer data for model fit

Lifetime partners

Mean number

Women

Canada*
Vietnam
India
Uganda

Men

Had sex < 15 yrs old

Partner > 10 yrs older, 15-19 yr-old girls

Cervical cancer

Cervical cancer Incidence (per 100,000 w-yr)

Age (yrs)

15-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75+

Start sex

Proportion (%)

Canada Lifetime partners estimated from USA data

REF: Sexual activity:
Demographic and Health Surveys, Multiple Indicator Survey, HIV and AIDS HUB for Asia Pacific-Evidence to action, National Health and Nutrition Examination Survey, National Survey of Family Growth
Cervical cancer:
GLOBOCAN 2012 (extrapolated from cervical cancer incidence by age)

* Canada Lifetime partners estimated from USA data

12
Methods

Modeling - Cost-effectiveness

Systematic Review:\(^1\):

- Cost-effectiveness studies published up to July 2016

PRIME (Papillomavirus Rapid Interface for Modelling and Economics)\(^2\)

- Developed by scientists from U Laval and London School of Hygiene and Tropical Medicine, in collaboration with WHO (www.PRIMEtool.org)

- Static model (no herd effects)

- Reproduces country-specific cervical cancer incidence and mortality, % of cervical cancer due to the vaccine types, vaccine costs

- Model predictions for 179 countries

REF: 1. Chaiyakunapruk (SAGE background documents); 2. Jit, *Lancet Global Health* 2014 (see back-up slides for PRIME description)
Vaccinating Girls-only
(vs no vaccination)

Model predictions
Effectiveness & Cost-effectiveness
Effectiveness: Women HPV-16/18

Girls-only vaccination (age=10yrs old), Vaccine duration=Lifelong, Vaccine Efficacy=95%

% Reduction in HPV-16/18 prevalence

Years since start of Vaccination

&: HPV-ADVISE, Median (line), and 10 and 90th percentiles (area) of the model predictions
Effectiveness: Cervical cancer

**Girls-only & 9-valent** (age=10yrs), Coverage=80%, Vacc duration=Lifelong, Vacc efficacy=95%

- **Canada:** 84%
- **Vietnam:** 69%
- **India:** 72%
- **Uganda:** 81%

&: HPV-ADVISE, Median (line), and 10th and 90th percentiles (area) of the model predictions
Absolute reduction in Cervical cancer

Girls-only & 9-valent (age=10yrs), Coverage=80%, Vacc duration=Lifelong, Vacc efficacy=95%

CANADA

INDIA

VIETNAM

UGANDA

Change in cervical cancer incidence (per 100,000)

Years since start of Vaccination

*: HPV-ADVISE, Median of the model predictions; Incidence of squamous cell carcinoma
Cost-effectiveness: Girls-only vaccination

• Models from HIC\textsuperscript{1-4} & LMIC\textsuperscript{5} produce consistent conclusions

• Girls-only immunization is cost-effective (vs no vaccination)\textsuperscript{1,3,4}
  - at current prices of the 2- and 4-valent vaccines
  - irrespective of the vaccine used
  - even when assuming no cross-protection or herd effects

• For example, Girls-only immunization is cost-effective in 173/179 countries in a global analysis using PRIME\textsuperscript{5}
  - including only the direct impact on vaccinated women
  - including only cervical cancer as an outcome
  - using different cost-effectiveness thresholds

• Main driver: Prevention of HPV-16/18 related cervical cancer

Vaccinating Girls-only

9-valent vaccine (vs 2/4-valent)

Model predictions
Effectiveness & Cost-effectiveness
Contribution of HPV-types to cervical cancer

Potential for cancer prevention through HPV vaccination, data for model fit

Contribution of HPV-types to cervical cancer
Potential for cancer prevention through HPV vaccination, data for model fit

2- or 4-valent vaccine: Cervical cancer

Girls-only (age=10 yrs), Coverage=80%, Vacc duration=Lifelong, Vacc Efficacy=95%

---

\&: HPV-ADVISE, Median (line) of model predictions, High Cross protection 2-valent (CP)=Max CP in Malagon LID 2013
9-valent vs 2- or 4-valent vaccine: Cervical cancer

Girls-only (age=10 yrs), Coverage=80%, Vacc duration=Lifelong, Vacc Efficacy=95%

% Reduction in Cervical Cancer

- No cross-protection
- High cross-protection
- 9-valent vaccine

Years since start of Vaccination

&: HPV-ADVISE, Median (line) of model predictions, High Cross protection 2-valent (CP)=Max CP in Malagon LID 2013
Cost-effectiveness: 9-valent vaccine
vs 2-valent or 4-valent vaccine

• **HIC**: 9-valent immunization is cost-effective in Canada, Austria, and cost saving in the US\textsuperscript{1-6}
  - when additional cost/dose of the 9-valent was 10-15\% greater than the 4-valent

• **LMIC**: Girls-only 9-valent immunization is cost-effective in LMIC, in a global analysis using PRIME\textsuperscript{7}
  - assuming 2-dose vaccination & cost/dose of the 9-valent in the same range as the 2- and 4-valent vaccines
  - 9-valent was not cost-effective (vs 2-valent), under assumptions of maximum cross-protection for the 2-valent vaccine

---

Gender-neutral vaccination

Model predictions

Effectiveness & Cost-effectiveness
Long term effectiveness: HPV-16/18

**Girls-only vaccination** (age=10yrs old), Vaccine duration=Lifelong, Vaccine efficacy=95%

&: HPV-ADVISE; Long term effectiveness after 70 yrs of vaccination; **NOTE**: Box plots represent the median, and 10, 25, 75, and 90th percentiles of the model predictions; CA=Canada, VN=Vietnam, IN=India, UG=Uganda
Long term effectiveness: Men/Herd Immunity

*Girls-only vaccination* (age=10yrs old), Vaccine duration=Lifelong, Vaccine efficacy=95%

Relative reduction (%), HPV-16/18 prevalence

---

©: HPV-ADVISE; Long term effectiveness after 70 yrs of vaccination; **NOTE**: Box plots represent the median, and 10, 25, 75, and 90th percentiles of the model predictions; CA=Canada, VN=Vietnam, IN=India, UG=Uganda
**Long term effectiveness: Men/Herd Immunity**

*Girls-only vaccination* (age=10yrs old), Vaccine duration=Lifelong, Vaccine efficacy=95%

---

**Relative reduction (%), HPV-16/18 prevalence**

- **Women**
  - CA: 54, VN: 38, IN: 43, UG: 53
  - 40% coverage: 91, 76, 80, 89
  - 80% coverage: 61, 65

- **Men**
  - CA: 83, VN: 61, IN: 65, UG: 82
  - 40% coverage: 42, 24, 30, 46
  - 80% coverage: 53, 89

---

*&: HPV-ADVISE; Long term effectiveness after 70 yrs of vaccination; NOTE: Box plots represent the median, and 10, 25, 75, and 90th percentiles of the model predictions; CA=Canada, VN=Vietnam, IN=India, UG=Uganda*
Long term effectiveness: HPV-16/18
Girls-only & **Girls&Boys vaccination**, Vaccine duration=Lifelong, Vaccine efficacy=95%

<table>
<thead>
<tr>
<th>Girls-only</th>
<th>Girls&amp;Boys</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA 40%</td>
<td>VN 40%</td>
</tr>
<tr>
<td>40% coverage</td>
<td>80% coverage</td>
</tr>
<tr>
<td>74</td>
<td>54</td>
</tr>
<tr>
<td>71</td>
<td>60</td>
</tr>
<tr>
<td>74</td>
<td>60</td>
</tr>
<tr>
<td>95</td>
<td>91</td>
</tr>
</tbody>
</table>

Note: HPV-ADVISE; Long term effectiveness after 70 yrs of vaccination; **NOTE:** Box plots represent the median, and 10, 25, 75, and 90\textsuperscript{th} percentiles of the model predictions; CA=Canada, VN=Vietnam, IN=India, UG=Uganda
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Effectiveness: Increasing coverage in Girls or Boys?

Girls-only & **Girls&Boys vaccination**, Vaccine duration=Lifelong, Vaccine efficacy=95%

---

**Women**

- 40% Girls & 40% Boys
- 80% Girls-only

**Men**

- 40% Girls & 40% Boys
- 80% Girls-only

---

Relative reduction (%), HPV-16/18 prevalence

---

&: HPV-ADVISE; Long term effectiveness after 70 yrs of vaccination; **NOTE**: Box plots represent the median, and 10, 25, 75, and 90th percentiles of the model predictions; CA=Canada, VN=Vietnam, IN=India, UG=Uganda
Effectiveness: Increasing coverage in Girls or Boys?

Girls-only & **Girls&Boys vaccination**, Vaccine duration=Lifelong, Vaccine efficacy=95%

**CA**=Canada, **VN**=Vietnam, **IN**=India, **UG**=Uganda

---

**NOTE:** Box plots represent the median, and 10, 25, 75, and 90th percentiles of the model predictions.

---

Relative reduction (%), HPV-16/18 prevalence

- **Women**
  - 40% Girls & 40% Boys
  - 80% Girls-only

- **Men**
  - 40% Girls & 40% Boys
  - 80% Girls-only

---

&: HPV-ADVISE; Long term effectiveness after 70 yrs of vaccination; **NOTE:** Box plots represent the median, and 10, 25, 75, and 90th percentiles of the model predictions; **CA**=Canada, **VN**=Vietnam, **IN**=India, **UG**=Uganda
Effectiveness: Increasing coverage in Girls or Boys?

Girls-only & Girls&Boys vaccination, Vaccine duration=Lifelong, Vaccine efficacy=95%

NOTE: Box plots represent the median, and 10, 25, 75, and 90th percentiles of the model predictions; CA=Canada, VN=Vietnam, IN=India, UG=Uganda

&: HPV-ADVISE; Long term effectiveness after 70 yrs of vaccination;
Cost-effectiveness: Gender-neutral vaccination

- Strong evidence suggests that Girls-only vaccination will provide substantial herd protection to boys/men\(^1,2\)
  - Added benefit of vaccinating boys is predicted to be limited\(^1\)

- Increasing coverage in girls provides greater impact than including boys

- **HIC**: Gender-neutral immunization (vs Girls-only) is:
  - Unlikely cost-effective IF vaccine coverage is high in girls\(^3\)
  - May be cost-effective IF vaccine coverage is less than 50% in girls\(^3\)

- **LMIC**: Cost-effectiveness studies of Gender-neutral immunization are largely lacking\(^3\)

- Considerations about Gender-neutral immunization should focus on:
  - Feasibility of increasing coverage in girls vs vaccinating boys\(^1\)
  - Equity for men who have sex with men
  - Vaccine price

---

Multiple age cohort HPV immunization

Model predictions
Effectiveness & Cost-effectiveness
Multiple age cohort immunization: HPV-16/18 &

Girls-only vaccination, Coverage=80%, Vaccine duration=Lifelong, Vaccine Efficacy=95%

&: HPV-ADVISE, Median (line) of model predictions
Multiple age cohort immunization: HPV-16/18 &

Girls-only vaccination, Coverage=80%, Vaccine duration=Lifelong, Vaccine Efficacy=95%

&: HPV-ADVISE, Median (line) of model predictions

Girls-only vaccination, Coverage=80%, Vaccine duration=Lifelong, Vaccine Efficacy=95%
Multiple age cohort immunization: HPV-16/18 &

Girls-only vaccination, Coverage=80%, Vaccine duration=Lifelong, Vaccine Efficacy=95%

&: HPV-ADVISE, Median (line) of model predictions
Multiple age cohort immunization: Cervical cancer

Girls-only & 9-valent, Coverage=80%, Vaccine duration=Lifelong, Vaccine Efficacy=95%

% Reduction in Cervical Cancer

Years since start of Vaccination

&: HPV-ADVISE, Median (line) of model predictions
Multiple age cohort immunization: Cervical cancer

Girls-only & 9-valent, Coverage=80%, Vaccine duration=Lifelong, Vaccine Efficacy=95%

- **Canada**
- **Vietnam**
- **India**
- **Uganda**

Years since start of Vaccination

% Reduction in Cervical Cancer

 HPV-ADVISE, Median (line) of model predictions
Multiple age cohort vs Gender-Neutral: HPV16/18

Coverage=80%, Vaccine duration=Lifelong, Vaccine Efficacy=95%

% Reduction in HPV-16/18 prevalence

Years since start of Vaccination

Canada

10 yr-old Girls-only
10 yr-old Girls&Boys
10-18 yr-old Girls-only

Mexico

0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

0 5 10 15 20 25 30 35

Vietnam

0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

0 5 10 15 20 25 30 35

India

0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

0 5 10 15 20 25 30 35

Uganda

0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

0 5 10 15 20 25 30 35

HPV-ADVISE, Median (line) of model predictions
Cost-effectiveness: Vaccinating multiple age cohorts vs single age cohort vaccination

- Vaccinating multiple age cohorts predicted to produce faster population-level impact
  - substantial impact in all countries modeled with HPV-ADVISE
  - magnitude of impact depends on country-specific distribution of age at sexual debut and remaining lifetime risk of infection

- **HIC:*** multiple age cohort vaccination of girls/women
  - likely to be cost-effective between 9-18 yrs
  - unlikely to be cost-effective between 19-24 yrs vs 9-18 yrs

- **LMIC:** In a global analysis using PRIME, vaccinating multiple age cohorts
  - girls 9-14 yrs old: cost-effective using 2 dose schedules
  - cohorts older than 15 yrs old: reduced incremental cost-effectiveness
    - requires 3-dose schedule
    - more girls/women will already have been infected

Question

• What is the incremental effectiveness and cost-effectiveness for cervical cancer prevention of different HPV vaccines based on Girls-only immunization?

Key modeling results

• Girls-only HPV vaccination (vs no vaccination)
  • High population-level effectiveness & strong herd effects
  • Highly cost-effective, irrespective of vaccine used
  • Main driver: Prevention of HPV-16/18 related cervical cancer
    • Cost-effective even when excluding herd immunity, cross-protection & benefit from reducing non-cervical diseases

• 9-valent Girls-only vaccination (vs 2- or 4-valent)
  • Further reduction of cervical cancer, little impact on non-cervical cancers
  • Likely cost-effective (vs 2 and 4-valent) in HIC & LMIC unless
    • very strong cross-protection from 2- or 4-valent is expected
    • 9-valent priced too high
  • Main drivers: Cross-protection from 2/4-valent / vaccine price
**Question**

- What is the incremental effectiveness and cost-effectiveness of adolescent Gender-neutral HPV immunization compared to Girls-only HPV immunization?

**Key modeling results**

**Incremental effectiveness**

- Strong herd effects from girls-only vaccination
- Added benefit of vaccinating boys is predicted to be limited
- Increasing coverage in girls provides greater impact than including boys

**Cost-effectiveness of vaccinating girls & boys (vs girls-only)**

- HIC: Unlikely cost-effective IF vaccine coverage is high in girls
- LMIC: Studies are largely lacking; Results will vary between countries depending on predicted herd effects

**Main drivers**

- Magnitude of herd effects by Girls-only vaccination / Burden of anogenital warts and HPV-related cancers
Question

• What is the incremental effectiveness and cost-effectiveness of multiple age cohort HPV immunization of females compared to single age cohort immunization of girls-only aged 9-13 years?

Key modeling results

Incremental effectiveness of multiple age cohort vaccination

• Rapid impact with stronger herd effects
• More cervical cancer cases averted over time

Cost-effectiveness of multiple age cohorts (vs single age cohort immunization)

• Catch-up up to age 14 years predicted to be at least as cost-effective as routine vaccination
• Catch-up after 15 years of age less cost-effective

Main drivers of incremental effectiveness & cost-effectiveness

• Timing of benefits & enhanced herd effects
• Age of start of sexual activity (age-specific proportion susceptible)
• 3 dose recommendation for 15+ year olds
Thank you!
Conflicts of interest statements

- Brisson: Past 3 years, Unrestricted grant, Merck (Zoster burden)
- Drolet: Consultation, GSK (Zoster vaccine)
- Jit, Laprise, Boily, Baussano, Franceschi, Alary, Martin, Bénard: no potential conflicts to declare

HPV related funding