IMPACT OF HPV IMMUNIZATION STRATEGIES IN THE CONTEXT OF SUPPLY CONSTRAINT

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Optimal HPV immunization strategies in the context of limited resources & vaccine supply

Brisson M¹,², Jit M³,⁴, Bénard É², Martin D², Drolet M², Laprise JF², Boily MC⁵, Alary M¹,², Gingras G², Pérez N², Hutubessy R⁷

Specific objectives

Using mathematical models:

• To estimate the population-level effectiveness and cost-effectiveness of various HPV vaccination strategies targeting 9 to 14 year old girls

• To identify optimal HPV vaccination strategies that maximize the number of cervical cancers averted under vaccine supply constraints
Why focus on vaccination of 9 to 14 year old girls?

In previous analyses presented to SAGE®, we showed that:

- Vaccinating girls between 9 & 14 years old was the most efficient and cost-effective strategy:
  - low Number Needed to Vaccinate (NNV) to prevent 1 cervical cancer case
  - very low incremental cost-effectiveness ratios

- Vaccinating boys & older women were much less efficient and cost-effective versus vaccinating girls between 9 & 14 years old

®: Brisson, SAGE (2017-2018); Brisson, SAGE Working Group Meeting (2019)
Population-level Effectiveness

What strategies maximize cancer prevention?
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 India, Vietnam, Nigeria and Uganda²
  - Demographic and sexual behaviour
  - HPV prevalence and cervical cancer incidence (age and type-specific)
  - Data from international databases and original studies³

REF: 1. Brisson, JNCI 2015; ²: 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
Vaccination Scenarios Investigated

Routine strategies **without** Multi-Age Cohort (MAC) or Catch-up vaccination

- Routine 9 yrs old (2 doses); No MAC *(S2)*
- Routine 9 years old 5-year extended interval (1+1 doses); No catch-up *(S5)*
- Routine 14 years old (2 doses); No MAC *(S8)*

Routine strategies **with** MAC or Catch-up

- Routine 9 years old (2 doses); with MAC 9-14 years old *(S1)*
- Routine 9 years old 5-year extended interval (1+1 doses); Catch-up at 14 years old *(S6)*
- Routine 14 years old (2 doses); Later switch to 9 years old *(S7)*
Vaccination Scenarios Investigated

Routine strategies without MAC or Catch-up vaccination

Routine 9 years old; No MACs

Routine 9 years old 5-year extended interval; No MACs

Routine 14 years old; No MACs

Routine strategies with MAC or Catch-up

Routine 9 years old; with MAC 9-14 years old

Routine 9 years old 5-year extended interval; 14-year-old catch-up

Routine 14 years old; Later switch to 9 years old
Example: Routine 9 years old (2 doses); No MAC

Strategy 2
Example: Routine 9 years old (2 doses); No MAC

Strategy 2

Girls are vaccinated at 9 years old in the 1st year of the program.
Example: Routine 9 years old (2 doses); No MAC

Strategy 2

Girls vaccinated at 9 years old in the 1st year of the program (dark blue)

are 10 years old in the 2nd year of the program and they are protected (light blue)

A new cohort of 9-year-old girls are vaccinated in the 2nd year of the program (dark blue)
Example: Routine 9 years old (2 doses); No MAC

Strategy 2

Routine 9 years old

Girls vaccinated at 9 years old in the 1st and 2nd year of the program (dark blue)

Are respectively 11 and 10 years old in the 3rd year of the program and they are protected (light blue)

A new cohort of 9-year-old girls is vaccinated in the 3rd year of the program (dark blue)
Example: Routine 9 years old (2 doses); No MAC

Strategy 2

As the number of years of vaccination increases, the number of cohorts vaccinated and protected increases.

Vaccinated Cohorts age protected (light blue)
Example: Routine 9 years old (2 doses); MAC 9-14 yrs

Adding Multi-Age Cohort vaccination:

Increases the number of vaccine doses 5-fold in the first year
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Increases the number of vaccine doses 5-fold in the first year

Example: Routine 9 years old (2 doses); MAC 9-14 yrs
Example: Routine 9 years old (2 doses); MAC 9-14 yrs

Strategy 1

Age

Years since start of vaccination

Example: Routine 9 years old (2 doses); MAC 9-14 yrs

Strategy 1

Added cohorts Protected
Impact of routine strategies

(no MAC or Catch-up)
Routine (2 doses) vs 5-year Extended interval (1+1 doses)
No MAC, 9 years old

Routine 9 years old (2 doses); No MAC

Routine 9 years old Extended 5-year interval (1+1 doses); No MAC

Years since start of vaccination

Protected

Age

(S2)

(S5)
Routine (2 doses) vs 5-year Extended interval (1+1 doses)
No MAC, 9 years old, Girls-only, 80% coverage

Mean of the model predictions; Base case: coverage=80%, 9valent, Efficacy=100%, Duration=Life
Routine (2 doses) vs 5-year Extended interval (1+1 doses)  
No MAC, 9 years old

**Extended (1+1 doses) = Routine (2 doses)**

- If efficacy same for 1 and 2 doses OR
- If coverage same at 9 and 14 years old

**Years since start of vaccination**

**Age**

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**Routine 9 years old (2 doses); No MAC**

**Years since start of vaccination**

**Age**

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**Routine 9 years old Extended 5-year interval (1+1 doses); No MAC**

**Years since start of vaccination**

**Age**

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VE 1 dose?

Coverage at 14 yrs?
Routine 9 years old vs Routine 14 years old, No MAC
2 doses
Routine 9 years vs Routine 14 years old, No MAC
2 doses, Girls-only, assumes 80% coverage at 9 & 14 years old

Mean of the model predictions; Base case: coverage=80%, 9valent, Efficacy=100%, Duration=Life
Routine 9 years old vs Routine 14 years old, No MAC

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<thead>
<tr>
<th>Years since start of vaccination</th>
<th>Routine 9 years old (2 doses); No MAC</th>
<th>Routine 14 years old (2 doses); No MAC</th>
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- **Routine at 14 years old**
  - Accelerates benefits

- Higher equilibrium if high risk girls start sex early
- Risk of lower effectiveness due to possible lower coverage

Routine at 14 years old (2 doses); No MAC

2 doses
Routine 9 years old vs Routine 14 years old, No MAC

2 doses

Routine at 14 years old
- Accelerates benefits
- Less benefits in long term if high risk girls start sex earlier than 14 years old
- Risk of lower effectiveness due to possible lower coverage
Routine 9 years old vaccination is similar to waiting 5 years before starting a routine 14 year old program.

Assuming:

- same coverage and
- low % of girls sexually active at 14 years old
Impact of adding
MAC and Catch-up vaccination
Multiple age-cohort (MAC) & Catch-up Girls-only 2 doses

Routine 9 years old (2 doses);
MAC 9-14 yrs old

Routine 9 years old 5-year extended interval
(1+1 doses); 14-year-old catch-up

Routine 14 years old (2 doses), later switch to 9 years old
(reverse catch-up)

All 3 strategies vaccinate 14 year olds at the start &
Have 9 year old vaccination in the long term
Impact of adding MAC or Catch-up vaccination

80% coverage

Mean of the model predictions; Base case: coverage=80%, 9-valent, Efficacy=100%, Duration=Life

---

**INDIA**

- No vaccination
- Routine 9 yrs; No MAC (S2)
- Routine 9 yrs & MAC 9-14 yrs (S1)
- Extended 5-years & Catch-up 14 yrs (S6)
- Routine 14 yrs, Later switch to 9 yrs (S7)

**VIETNAM**

**UGANDA**

**NIGERIA**

- 5
- 33
- 69
- 23
- 4
- 14
- 50
- 11
Impact of adding MAC or Catch-up vaccination

80% coverage

**INDIA**
- No vaccination
- Routine 9 yrs; No MAC (S2)
- Routine 9 yrs & MAC 9-14 yrs (S1)
- Extended 5-years & Catch-up 14 yrs (S6)
- Routine 14 yrs, Later switch to 9 yrs (S7)

**VIETNAM**
- Catch-up & MAC
  - Accelerates benefits
  - Additional cases prevented
  - Same long term benefit

**UGANDA**

**NIGERIA**

Mean of the model predictions; Base case: coverage=80%, 9valent, Efficacy=100%, Duration=Life
Routine only vs Routine with Catch-up or MAC

Routine 9 years old (2 doses); No MACs

Routine 9 years old (2 doses); with MACs 9-14 years old

More cohorts protected (grey area)

Grey Area: Cohorts that would have been missed with routine only

Routine 9 years old 5-year extended interval (1+1 doses); 14-year-old catch-up

Routine 14 years old (2 doses); Later switch to 9 years old

Years since start of vaccination

Age

Years since start of vaccination

Age

Years since start of vaccination

Age

Years since start of vaccination

Age
Routine only vs Routine with Catch-up or MAC

Adding MAC 9-14 years or Catch-up
- Takes the advantage of routine vaccination at 9 and 14 years

Routine 9 years old (2 doses); No MACs

Routine 9 years old; with 14-year-old catch-up

Routine 9 years old 5-year extended interval (1+1 doses); 14-year-old catch-up

Routine 9 years old (2 doses); with MACs 9-14 years old

Later switch to 9 years old
Summary Effectiveness

- Girls-only vaccination predicted to substantially reduce cervical cancer

- Age of routine vaccination:
  - Routine 9 years old: Lower long term incidence
    - If it allows Higher coverage
    - If high proportion of girls start sexual activity before 14 years old
  - Routine 14 years old: Accelerates decline in cervical cancer
    - Closer to sexual debut

- Adding MAC or CATCH-UP to routine vaccination
  - Benefits of both routine at 9 and 14 years old
  - Accelerates decline in cervical cancer
Number Needed to Vaccine (NNV) & Cost-effectiveness

What strategies are most efficient?

What are the strategies with the best return on investment?
Methods

Main outcomes

• Efficiency
  • Number needed to vaccinate (NNV) per dose
    • Number of cervical cancer prevented ÷ Number of doses given

• Cost-effectiveness
  • Cost/DALY averted
Efficiency (NNV) and cost-effectiveness (ICER)  
9-14 year-old vaccination strategies, Girls-only

- The most efficient strategies in terms of NNV & cost-effectiveness are:

| Years since start of vaccination | Age 1 | Age 2 | Age 3 | Age 4 | Age 5 | Age 6 | Age 7 | Age 8 | Age 9 | Age 10 | Age 11 | Age 12 | Age 13 | Age 14 | Age 15 | Age 16 | Age 17 | Age 18 | Age 19 | Age 20 | Age 21 | Age 22 | Age 23 |
|---------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Routine 9 years old             | (S6)  |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |

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<td>ICER</td>
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<td>379</td>
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| Routine 14 years old (2 doses); later switch to routine 9 years old | (S7) |

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<td>275</td>
<td>396</td>
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NNV: Number of doses needed to prevent 1 cervical cancer
ICER: Incremental cost-effectiveness ratio (Cost per DALY averted)
Base case: high-valency vaccine, VE=100%, duration=lifelong, coverage=80%; MAC: Multiple-age cohorts
Vaccine cost per dose: $4.60;
Efficiency (NNV) and cost-effectiveness (ICER)  
9-14 year-old vaccination strategies, Girls-only

- The most efficient strategies in terms of NNV & cost-effectiveness are:

  **Routine 9 years old**
  5-year extended interval (1+1 doses);
  14-year-old catch-up

  **Routine 14 years old (2 doses);**
  later switch to routine 9 years old

But: All strategies targeting girls between 9 & 14 years, with or without MAC, produce very low NNV
and incremental cost-effectiveness ratios

### Comparison of NNV & ICER

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Base case: high-valency vaccine, VE=100%, duration=lifelong, coverage=80%; MAC: Multiple-age cohorts

Vaccine cost per dose: $4.60;

See extra slides for all NNV & ICER results
Optimal strategy in the context of limited vaccine supply
Methods

- Estimated the cumulative cervical cancer cases averted over 100 years:
  - For different vaccination strategies
  - for 92 LMIC, which have yet to introduce vaccination
  - using yearly vaccine supply scenarios provided by WHO
  - using HPV-ADVISE predictions
Maximizing cervical cancer cases prevented
Time horizon = 100 years, supply scenario = base case

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Description</th>
<th>Cumulative number of countries (10 years)</th>
<th>Nb cases averted (Million)</th>
<th>Diff. cases averted (Million)</th>
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<td>S7</td>
<td>Routine 14 yrs old (2 doses), later switch to 9 yrs old</td>
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<td>100%</td>
<td>50.9</td>
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<td>S6</td>
<td>Routine 9 yrs old 5-yr extended interval (1+1 doses); with 14-yr-old catch-up</td>
<td></td>
<td>100%</td>
<td>50.6</td>
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<td>S1</td>
<td>Routine 9 yrs old (2 doses); MAC 9-14 yrs old</td>
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<td>100%</td>
<td>49.7</td>
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<tr>
<td>S8</td>
<td>Routine 14 yrs old (2 doses); No MACs</td>
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<td>100%</td>
<td>49.3</td>
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<tr>
<td>S5</td>
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<td>100%</td>
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<tr>
<td>S2</td>
<td>Routine 9 yrs old (2 doses); No MACs</td>
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<tr>
<td>S3</td>
<td>Routine 9 yrs old (1 dose); MACs 9-14 yrs old (Vaccine Efficacy=85%)</td>
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<td>100%</td>
<td>43.4</td>
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<tr>
<td>S3</td>
<td>Routine 9 yrs old (1 dose); MACs 9-14 yrs old (Vaccine Duration = 20yrs)</td>
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Maximizing cervical cancer cases prevented
Time horizon = 100 years, supply scenario = base case

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<td>Routine 9 yrs old (1 dose); MACs 9-14 yrs old (Vaccine Duration = 20yrs)</td>
<td>25%</td>
<td>100%</td>
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Maximizing cervical cancer cases prevented

Time horizon = 100 years, supply scenario = lower range

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Optimal strategy in the context of limited supply & projected demands

Kiesha Prem
Mark Jit
No conflicts of interest to declare

Contributors:
E Nickels, T Cernuschi, S Malvolti, R Hutubessy, M Brisson
Methods

- Estimated the cumulative cervical cancer cases averted over 90 years:
  - for different vaccination strategies
  - using yearly vaccine supply scenarios & projected market dynamics provided by WHO\(^1\)
  - using PRIME\(^2\) predictions

\(^1\) CERNUSHI presentation; \(^2\) JIT. Lancet Glob Health 2014; 2: e406-14.
Impact of vaccination under 7 scenarios
Supply constrained environment & projected market dynamics

- S1. Routine 2 doses 9 yo; with MACs 9-14 yo
- S2. Routine 2 doses 9 yo; No MACs
- S3. Routine 1 dose 9 yo; with MACs 9-14 yo
- S4. Routine 1 dose 9 yo; No MACs
- S5. Routine 2 doses 9 yo 3-y extended interval; No MACs
- S6. Routine 2 doses 9 yo 5-y extended interval; 14 yo catch-up
- S7. Routine 2 doses 14 yo; Later switch to 9 yo
Optimal vaccination scenarios
Supply constrained environment & projected market dynamics

Top 3 Ranked Scenarios:

S6: Routine 2 doses 9 years old 5-year extended interval; 14-year-old catch-up

S7: Routine 2 doses 14 years old; Later switch to 9 years old

S3: Routine 1 doses 9 years old; MAC*

* Assumes 100% vaccine efficacy of 1 dose
Summary Optimal strategies in context of supply constraints

- The strategies that optimized cervical cancer prevention were:
  - Routine 9 years old
    - 5-year extended interval (1+1 doses);
    - 14-year-old catch-up
  - Routine 14 years old (2 doses);
    - later switch to routine 9 years old

- Conclusions were robust to variations in supply constraints
Conclusion

- Two strategies are predicted to be optimal from the 3 different perspectives:
  - Efficiency - Cancer prevention per dose (NNV)
  - Return on investment - Cost-effectiveness (ICER)
  - Optimal vaccine distribution - Global cancer prevention

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<th>Years since start of vaccination</th>
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Routine 9 years old
5-year extended interval (1+1 doses);
14-year-old catch-up

Routine 14 years old (2 doses);
later switch to routine 9 years old

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Cancers prevented 50.4M

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Cancers prevented 50.9M
Thank you!