IMPACT OF HPV IMMUNIZATION STRATEGIES & POTENTIAL FOR CERVICAL CANCER ELIMINATION

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SAGE meeting
October 24, 2018
Geneva
Questions

A. What is the potential for Cervical Cancer elimination with HPV immunization?

B. What is the population-level effectiveness and cost-effectiveness of different HPV immunization schedules and strategies?
POTENTIAL FOR CERVICAL CANCER ELIMINATION:
A COMPARATIVE MODELING STUDY

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Université Laval, Canada; Harvard T.H. Chan School of Public Health, USA; Cancer Council NSW, Australia; University of Massachusetts Amherst, USA; CHU de Québec-Université Laval Research Center, Canada; Avenir Health, USA; Imperial College, UK; World Health Organization, Switzerland

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Call for action to eliminate cervical cancer

- In May, the WHO Director-General made a global call for action to eliminate cervical cancer as a public health problem.

- Elimination of cervical cancer as a public health problem is different to elimination of an infectious disease:
  - Not reduction to 0 incidence
  - Control of cervical cancer at a low disease incidence
  - Requires clear well defined threshold
  - Previously used for other diseases by WHO
    - Neonatal Tetanus (NT): 1 NT per 1000 live births per yr
    - Congenital syphilis: Case rate of ≤50 per 100 000 live births

*: WHO Director-General Speech - [http://www.who.int/reproductivehealth/DG_Call-to-Action.pdf](http://www.who.int/reproductivehealth/DG_Call-to-Action.pdf)
Call for action to eliminate cervical cancer

Key questions that must be addressed

• What is the definition of cervical cancer elimination as a public health problem?
  - What outcome? Cancer incidence? Mortality? % Reduction?
  - Same for every country?
  - Pragmatic? Optimistic?

• What combination of screening and vaccination strategies can lead to elimination (for different definitions)?

• When could elimination be reached, for different strategies and countries?

• What is the most efficient/cost-effective strategy to reach elimination?
Need for mathematical models

• Mathematical models provide a formal framework to examine key elimination questions
  - project long-term population-level effects (e.g., herd immunity)
  - evaluate multiple strategies under varying assumptions

• However, models require many simplifications & assumptions which leads to uncertainty in the validity of predictions
  - can create uncertainty for decision makers

• WHO initiated a model comparison to help provide guidance for cervical cancer elimination
  - the Cervical cancer elimination modeling consortium was created
Systematic comparative modeling approach

- **Model Selection**
  - Dynamic model
  - Model includes vaccination & screening
  - Independent model that has been peer reviewed/published

- **Policy 1 Model**
  - Lead: Karen Canfell
  - Team: Kate Simms, Adam Keane, Megan Smith
  - Institution: Cancer Council NSW, Australia

- **Harvard Model**
  - Lead: Jane Kim
  - Team: Emily Burger, Stephen Sy, Catherine Regan
  - Institution: Harvard, USA

- **HPV-ADVISE Model**
  - Lead: Marc Brisson
  - Team: Mélanie Drolet, JF Laprise, Dave Martin, Élodie Bénard, Guillaume Gingras, Iacopo Baussano, Marie-Claude Boily, Mark Jit
  - Institution: U Laval, Canada; Imperial College, UK; LSHTM, UK; IARC, France

- **Spectrum Model**
  - Leads: Chaitra Gopalappa & Carel Pretorius
  - Institution: U Massachusetts & Avenir Health, USA
Global predictions

78 Low & Lower Middle Income Countries

2 vaccination/screening scenarios
Vaccination & Screening scenarios

- **S1 - Scenario 1:**
  - Girls-only vaccination (90% coverage, 9-14 yr old)
  - No change in Screening

- **S2 - Scenario 2:**
  - Girls-only vaccination (90% coverage, 9-14 yr old)
  - 2 lifetime screens at 35 and 45 yrs old
  - High Screening ramp-up (45%, 70%, 90% in 2023, 2030, 2045, respectively)

- **All scenarios:**
  - Screening: HPV testing, 100% treatment efficacy, 10% Lost to follow-up
  - Vaccine: Lifelong duration, 100% efficacy, HPV16/18/31/33/45/52/58
Dynamics of elimination  

Consistency in model predictions

High vaccination coverage & Screening Ramp-up

- No further change
- Vaccination only (S1)

Cervical cancer incidence (per 100,000)

Years

Low income countries

Lower middle income countries

HPV-ADVISE
Harvard
Policy1

Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58
Dynamics of elimination Impact over time
Low (LIC) & Lower Middle Income Countries (LMIC), High vaccination coverage & Screening Ramp-up

&. Mean predictions; Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58, HPV testing
Dynamics of elimination  
Impact over time - under 45 year olds
Low (LIC) & Lower Middle Income Countries (LMIC), High vaccination coverage & Screening Ramp-up

Cervical cancer incidence (per 100,000)

Vaccination only (S1)

Vaccination, 2 lifetime screens (S2)

Mean prediction of models; Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58, HPV testing
Dynamics of elimination \textbf{Incremental benefits of strategies}

High vaccination coverage & Screening Ramp-up

- No further change
- Vaccination only
- Vaccination, 2 lifetime screens

Cases averted$^\text{a}$ (vs no change)

<table>
<thead>
<tr>
<th></th>
<th>LIC</th>
<th>LMIC</th>
<th>LIC</th>
<th>LMIC</th>
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<tr>
<td>No further change</td>
<td>3.5 M</td>
<td>11.5 M</td>
<td>3.5 M</td>
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<td>4.3 M</td>
<td>14.2 M</td>
<td>0.8 M</td>
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$^\text{a}$ Mean prediction over 100 years; Adjusted cases averted for 2015 population; Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58, HPV testing
Country specific predictions
Low income & Lower Middle income countries
Vaccination only (S1)

2020

- Median prediction; Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58
Country specific predictions
Low income & Lower Middle income countries by region
Vaccination only (S1)

2120

Low income
Lower middle income

East Asia & Pacific
Europe & Central Asia
Latin America & Caribbean
Middle East & North Africa
South Asia
Sub-Saharan Africa

Time of elimination in all countries in region (lower & upper threshold)

Cervical Cancer Incidence [per 100,000]

0-4 4-10 10-15 15-30 30-80 80+

&. Median prediction; Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58
Country specific predictions
Low income & Lower Middle income countries
Vaccination, 2 lifetime screens (S2)

2020

- Median prediction; Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58, HPV test
Country specific predictions

Low income & Lower Middle income countries by region
Vaccination, 2 lifetime screens (S2)

Time of elimination in all countries in region (lower & upper threshold)

Median prediction; Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58, HPV test
Country specific elimination predictions

Impact of starting cervical cancer (CC) incidence
Low & Lower middle income countries, Vaccination only (S1)

Harvard & HPV-ADVISE; High vaccination coverage and screening ramp-up, Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58, HPV test
Country specific predictions
Absolute Reductions (AR) in Cervical cancer (CC) & Elimination
Low & Lower middle income countries, Vaccination only (S1)

&. Harvard & HPV-ADVISE; High vaccination coverage and screening ramp-up, Girls-only vaccination, Vaccine protection=HPV16/18/31/33/45/52/58, HPV test
Summary
Global analysis: 3 optimistic vaccination & screening coverage scenarios

What strategies lead to elimination?

- **Girls-only vaccination** leads to incidence <10/100,000 w-yrs without screening in most countries/regions
  - <15/100,000 w-yrs in Sub-Saharan Africa

- **Girls-only vaccination & 2 lifetime screens** leads to incidence <4/100,000 w-yrs in most countries/regions
  - <10/100,000 w-yrs in Sub-Saharan Africa

When does elimination occur?

- Average within LIC/LMIC: 2045-2060
  - UMIC/HIC: elimination occurs earlier
- 100% of countries: 2085-2105
- Depends on the strategy & threshold

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&. Low (LIC), Lower Middle Income (LMIC), Upper Middle Income (UMIC), High Income Countries (HIC), Vaccine protection=HPV16/18/31/33/45/52/58, HPV test
Sensitivity Analysis

What is the impact of:
Vaccination Strategies & Coverage?
Number of Screens?
Vaccine characteristics?
Dynamics of elimination  Impact of vaccination
No change in screening

- **No further change**
- **90% Girls-only vaccination**
- **80% Girls-only vaccination**
- **80% Girls & Boys vaccination**
- **80% Girls & Boys vaccination, Catch-up**

### Vietnam

- **Cervical cancer incidence (per 100,000)**

### Uganda

- **Mean predictions; Vietnam: Policy-1/HPV-ADVISE; Uganda: Harvard/HPV-ADVISE; Vaccine duration=lifelong; VE=100%**
Dynamics of elimination  **Impact of number of HPV types protected**

80% Girls-only vaccination, high screening ramp-up, 2 screens

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**Vietnam**

- No further change
- Efficacy against HPV16/18 only
- Efficacy against HPV16/18/31/33/45/52/58

**Uganda**

- No further change
- Efficacy against HPV16/18 only
- Efficacy against HPV16/18/31/33/45/52/58

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**Time to**

\[
\begin{array}{cccc}
\text{<10/100,000} & \text{<4/100,000} \\
\text{VN} & \text{UG} & \text{VN} & \text{UG} \\
2054 & 2073 & 2077 & 2097 \\
2054 & 2082 & 2089 & X \\
\end{array}
\]

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**Mean predictions; Vietnam:** Policy-1/HPV-ADVISE; **Uganda:** Harvard/HPV-ADVISE; Vaccine duration=lifelong; VE=100%
Dynamics of elimination Impact of duration of vaccine protected
80% Girls-only vaccination, high screening ramp-up, 2 screens

- No further change
- Vaccine Duration = lifelong
- Vaccine Duration = 20 years

Time to

<table>
<thead>
<tr>
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<th>&lt;10/100,000</th>
<th>&lt;4/100,000</th>
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<tbody>
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<td>2054</td>
<td>2077</td>
</tr>
<tr>
<td>Uganda</td>
<td>2073</td>
<td>2097</td>
</tr>
</tbody>
</table>

Mean predictions; Vietnam: Policy-1/HPV-ADVISE; Uganda: Harvard/HPV-ADVISE; Vaccine duration=lifelong; VE=100%
Sensitivity analysis
40 scenarios, 12 countries

- Greatest additional benefits (cancers cases averted over time):
  - Vaccination of Girls-only with high coverage (vs no vaccination)
  - 2 lifetime screens (vs current screening)
  - Multi-cohort vaccination (vs single-cohort vaccination) - No impact on elimination

- Screening or multi-cohort vaccination accelerates elimination (5-15 yrs)

- Smallest additional impact
  - Vaccinating boys (vs Girls-only) if Girls-only coverage is high

- Long-term duration of vaccine protection is required for elimination
SUMMARY

• Models produced consistent findings

• Countries with cervical cancer incidence < 30/100,000 w-yrs
  - >80% Girls-only vaccination coverage could lead to elimination without changes to screening

• Countries with cervical cancer incidence ≥ 30/100,000 w-yrs
  - elimination is highly dependent on the threshold used
  - high screening & vaccination coverage, and a broad spectrum vaccine is required
  - hardest to eliminate but have greatest absolute reductions in incidence
  - countries with incidence ≥ 70/100,000 w-yrs may not reach elimination

• Long-term vaccine protection is needed (>20 years)
  - particularly for higher cervical cancer incidence countries
SUMMARY

• Greatest additional benefits:
  - Vaccination of Girls-only (vs no vaccination)
  - 2 lifetime screens (vs no screening)
  - Multi-cohort vaccination (vs single-cohort vaccination)
  - Screening at least once in a lifetime & multi-cohort vaccination accelerates elimination by about 10 years

• Results are most sensitive to:
  - Definition of elimination - Threshold
  - Starting cervical cancer incidence

• Future work:
  - Examine the cost and cost-effectiveness of elimination
  - Identify the most efficient strategies for elimination
IMPACT OF DIFFERENT HPV IMMUNIZATION SCHEDULES AND STRATEGIES

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Objective

• Examine the population-level effectiveness and cost-effectiveness of HPV immunization of different schedules and strategies in Low and Lower Middle Income Countries, using:
  - Predictions from Mathematical Models

Schedules/strategies

• Girls-only HPV immunization (HPV2 or HPV4 vs HPV9)
• Gender-neutral HPV immunization (vs Girls-only)
• Multiple age cohort HPV immunization (vs single age cohort)
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, Benin, Nigeria and Uganda²
  - Demographic and sexual behaviour
  - HPV prevalence and cervical cancer incidence (age and type-specific)
  - Data from international databases and original studies²

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 (see back-up slides for references & model fit)
Question: Girls-only immunization

• 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

• HPV9 vaccine Girls-only vaccination (vs HPV2 or HPV4)
  • Likely cost-effective (vs HPV2 or HPV4) in HIC & LMIC unless
    • very strong cross-protection from HPV2 or HPV4 is expected
    • HPV9 priced too high
  • Main drivers: Cross-protection from HPV2/4 and vaccine price

REF: HPV-ADVISE, SAGE WG Meeting 2018; Ng, Vaccine 2018; Jit, Lancet Global Health 2015; Fesenfeld, Vaccine 2013
Question: Gender-neutral immunization

- 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

- HIC: Small additional benefits of vaccinating boys (even at low coverage)
- LMIC: Greater added benefit of vaccinating boys than in HIC
- HIC & LMIC: 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: May be cost-effective even if coverage in girls is high
- LMIC: More cost-effective to increase coverage in girls when coverage is low

Main drivers

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

REF: HPV-ADVISE, SAGE WG Meeting 2018; Ng, Vaccine 2018; Brisson, Lancet Public Health
Question

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

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Thank you!