Towards Cervical cancer elimination: the context of HPV vaccination

Paul Bloem
WHO IVB EPI

Antwerpen, 15 Nov 2019
Outline

• Cervical Cancer Elimination: HPV vaccine targets
• Global context of HPV vaccine introduction
• Performance of HPV programmes
• Global HPV vaccine supply situation
• SAGE recommendations to deal with supply constraints
• Key messages
Variability in Cervical Cancer Incidence Rates by World Region
Systematic Comparative Modeling Approach

• **Model Selection**
  – Dynamic model
  – Model includes vaccination, screening & treatment
  – 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
**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)
  - 1 lifetime screen at 35 yrs old
  - High Screening ramp-up (45%, 70%, 90% in 2023, 2030, 2045, respectively)

- **S3 - Scenario 3:**
  - 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
Variability in Model Predictions of the Impact of HPV Vaccination and Screening Strategies - LIC vs LMIC

Source: M. Brisson, J. Kim & K. Canfell et al. In publication
Dynamics of 78 LMICs Cervical Cancer Incidence After Vaccination and Screening

Source: M. Brisson, J. Kim & K. Canfell et al. In publication
**Impact of Vaccinating boys**

HPV9, 2 screens, High ramp-up, No catch-up

### INDIA

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

### VIETNAM

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

### NIGERIA

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

### UGANDA

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

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8: HPV-ADVISE, Mean of the model predictions
Impact of Catch-up vaccination to 25 years old
80% Girls & Boys vaccination, HPV9

Impact of Catch-up vaccination to 25 years old
80% Girls & Boys vaccination, HPV9

- HPV-ADVISE, Mean of the model predictions
Global Strategy towards the Elimination of Cervical Cancer

VISION: A world without cervical cancer

THRESHOLD: All countries to reach < 4 cases 100,000 women years

2030 CONTROL TARGETS

- **90%** of girls fully vaccinated with HPV vaccine by 15 years of age
- **70%** of women screened with an high precision test at 35 and 45 years of age
- **90%** of women identified with cervical disease receive treatment and care

SDG 2030: Target 3.4 – 30% reduction in mortality from cervical cancer

Timeline
Submitted to EB 2020 (Oct 2019) for discussion at WHA May 2020
Factors affecting introductions and performance

Global Strategy towards the Elimination of Cervical Cancer

1. **Supply**: Limited supply of the HPV vaccine

2. **Costs**: Vaccine price
   - High delivery cost

3. **Quality of Introduction Planning and Management**:
   - Choice and sustainability of delivery strategy
   - Insufficient communication
   - Addressing hesitancy related factors
Countries with HPV vaccine in the National Immunization Programme

- 50% of countries
- ~30% of girls 9-14yr

Globally

- Introduced (Includes partial introduction) to date (100 countries or 52%)
- Not Available, Not Introduced/No Plans (94 countries or 48%)
- Not applicable
Proportion of Countries that have introduced HPV vaccine by WHO region and WB Income level

Source: IVB Database, 2 Oct 2019
ESTIMATES: HPV vaccine PROGRAM COVERAGE, FEMALES, 2018

Source: IVB Database, 15 July 2019
SUPPLY SHORTAGE

- Ongoing programmes generally receive vaccine supply they require - some stockouts, and supplier related challenges reported in PAHO

- Insufficient supply for overall GAVI countries demand - however all planned* 2019 GAVI supported HPV vaccine introductions are moving ahead with routine cohorts
  - Majority of planned Multi Age Cohort (MAC) postponed

  * 11 countries planned, 10 received the final go-ahead for 2019, 4 of which with supply for MAC (smaller countries)

- 5 MICs have introduced in 2019 but at least one MIC has had to postpone introduction this year due to lack of supply
Supply to slowly grow in the short term, followed by steep ramp up from year 4-5

Available supply for commercialization may vary by +/-50% driven by manufacturers decisions and success in development/scale-up
Routine 2-dose scenarios (current recommendation)

**Assumptions:**
- All countries introduce by 2029
- Gender neutral only in countries with existing recommendations
- *These apply to all scenarios, 1-7*

**Results:**
- Programmatic dose requirement reaches and stabilizes at ~120M doses in 2025
- MACs have been distributed across years, but remain an important contributor to dose requirement in the next 5 years
Comparing dose requirement across 7 scenarios

Results:

- Scenarios w/ MACs have the highest short-term programmatic dose requirement
- 3y extended interval results in lowest doses in the short-term
- One dose greatly reduces dose required in mid and long run
- 14yo with later switch to 9yo increases requirements considerably in the long run
## Dynamic supply-demand balance

### Demand Scenarios

<table>
<thead>
<tr>
<th>Demand Scenarios</th>
<th>Short-Term (1-3)</th>
<th>Mid-Term (4-6)</th>
<th>Long-Term (6-9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 2-dose + MACs</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>#2 2-dose No MACs</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>#3 1-dose + MACs</td>
<td>Red</td>
<td>Green</td>
<td>Red</td>
</tr>
<tr>
<td>#4 1-dose No MACs</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>#5 3y Extended Interval</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
</tr>
<tr>
<td>#6 5y Ext. Int. + 14yo</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>#7 14yo, Later 9yo</td>
<td>Red</td>
<td>Green</td>
<td>Red</td>
</tr>
</tbody>
</table>

### Base Supply

- Some countries delayed: Supply <1.1X Demand
- No countries delayed: Supply <1.3X Demand
- No countries delayed: Supply >1.3X Demand

### Low Supply

- Some countries delayed: Supply <1.1X Demand
- No countries delayed: Supply >1.3X Demand

As a result of persistent shortages in past years, demand has been influenced (e.g. MACs postponement, program delayed)

More extensive implementation of commercially attractive gender neutral and adult catch-up policies will influence balance

Refusal of specific products (based on valency or country of origin) constituting relevant share of supply would influence balance
Base Supply Detailed Results: Scenarios w/ MACs/catch-up

MACs and catch-up scenarios intensify supply constraints in the short term, with more introductions postponed.

<table>
<thead>
<tr>
<th>Lives Not Saved due to supply constraints in specific countries not served</th>
<th>Short-Term (1-3)</th>
<th>Mid-Term (4-6)</th>
<th>Long-Term (6-9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1: 2-dose w/ MACs</td>
<td>143K (27 countries)</td>
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<tr>
<td>#3: 1-dose w/ MACs</td>
<td>103K (23 countries)</td>
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</tr>
<tr>
<td>#6: 5y Ext. Int. + 14y catch-up</td>
<td>45K (10 countries)</td>
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<td></td>
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<tr>
<td>#7 14yo, Later Switch to 9yo</td>
<td>56K (21 countries)</td>
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</tbody>
</table>

Of all alternative strategies, adoption of (#6) a 5 years extended interval between 1st and 2nd dose and (#7) intro in 14 yo with later switch to 9yo have the best outlook.
Base Supply Detailed Results: no MACs/catch up scenarios

Scenarios with no MACs/catch up contribute most to relieving supply constraints, allowing more countries to introduce sooner

<table>
<thead>
<tr>
<th>Lives Not Saved due to supply constraints in specific countries not served</th>
<th>Short-Term (1-3)</th>
<th>Mid-Term (4-6)</th>
<th>Long-Term (6-9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#2: 2-dose No MACs</td>
<td>20K (9 countries)</td>
<td></td>
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<tr>
<td>#4: 1-dose No MACs</td>
<td>20K (9 countries)</td>
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<tr>
<td>#5: 3y Extended Interval</td>
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Adoption of a 3-years interval between 1st and 2nd doses from 2020 by all Gavi and PAHO RF countries further contributes to the improvement of the supply-demand balance freeing supply in the 2020-2021 critical period.
Impact of vaccinating boys for girls in low income/high burden settings

2019 demand for use in boys is ~9M doses (18% of global demand)

Alternative use of doses: 9 low- and middle-income countries forecasted to have a delayed routine introductions in short term would be able to introduce

Other HICs adding boys would require additional ~4M doses (1/3 Gavi demand)

Implications: In short run, planned introductions would be delayed in 12 low- and middle-income countries.
Questions considered by the HPV vaccines SAGE Working Group

1. What is the current HPV vaccine uptake and what are the main barriers for access to HPV vaccines?

2. What does current evidence show on the immunogenicity and efficacy of a single dose of HPV vaccine; different intervals between the first and second doses of HPV vaccine and immunogenicity and efficacy of 2 vs 3 dose in 15-18 yr olds?

3. What are the potential demand scenarios and the supply of HPV vaccines (short and mid-term outlook) and what could one enhance HPV vaccine supply allocation?
Summary one dose efficacy/effectiveness

Current evidence for most outcomes was of low to very low certainty due to limitations in study design and imprecision.

Evidence suggests that one dose results in higher GMTs than no vaccine, but lower than two or three doses.

There was inconclusive evidence for one dose on CIN 1, 2, and 3 compared to no vaccine, two doses, or three doses.

One dose may result in fewer HPV 16/18 infections than no vaccine, and little to no difference to two doses.

Removing sources of bias suggest there is little to no difference between one dose and two doses for the younger age groups (<16 years) for genital warts and CIN2+.

Cochrane reviews: https://www.who.int/immunization/sage/meetings/2019/october/presentations_background_docs/en/
<table>
<thead>
<tr>
<th>Study name (country)</th>
<th>Evidence type</th>
<th>Vaccine(s)</th>
<th>Brief description</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
<th>2023</th>
<th>2024</th>
<th>2025</th>
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<tr>
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<td>Q4</td>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
<td>Q1</td>
<td>Q2</td>
</tr>
<tr>
<td><strong>KEN SHE</strong> Kenya</td>
<td>Efficacy</td>
<td>HPV2 vs HPV9 vs MenACWY (delay HPV)</td>
<td>Girls 15-20 yo randomized to 1 dose of HPV2, HPV9, or MenACWY; n=750 each arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18 months</td>
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<tr>
<td><strong>ESCUDDO</strong> Costa Rica</td>
<td>Efficacy</td>
<td>HPV2 and HPV9</td>
<td>Girls 12-16 yo randomized to 1 or 2 doses of HPV2 or HPV9; n=5000 each arm</td>
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<tr>
<td><strong>DoRIS</strong> Tanzania</td>
<td>Immunogenicity</td>
<td>HPV2 and HPV9</td>
<td>Girls 9-14 yo randomized to 1, 2, or 3 doses of HPV2 or HPV9; n=155 each arm</td>
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<td>24 months</td>
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<tr>
<td><strong>Primavera</strong> Costa Rica</td>
<td>Immunogenicity</td>
<td>HPV2 and HPV4</td>
<td>Girls 10-13 yo 1-dose HPV2 immunobridge to women 18-25 yo 3-doses HPV4; n=520 each</td>
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<td>24 months</td>
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<tr>
<td><strong>HANDS</strong> The Gambia</td>
<td>Immunogenicity</td>
<td>HPV9</td>
<td>Girls 4-8 yo and 9-14 yo randomized to 1 or 2 doses; girls 15-26 yo given 3 doses; n=344 each arm</td>
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<td>24 months</td>
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<tr>
<td><strong>India IARC</strong> India</td>
<td>Efficacy</td>
<td>HPV4</td>
<td>Girls 10-18 yo received 1, 2, 3 doses of HPV4; n=17586, 1-dose n=4980</td>
<td>10 yr f/u</td>
<td>11 yr f/u</td>
<td></td>
<td></td>
<td>Persistent infection endpoint from 3000+ 1-dose recipients</td>
<td>CIN 2+ endpoint from 10,000+ women screened</td>
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<tr>
<td><strong>CVT</strong> Costa Rica</td>
<td>Efficacy / Immunogenicity</td>
<td>HPV2 vs control</td>
<td>Women 18-25 yo received 1, 2, or 3 doses of HPV2; n=3727, 1-dose n=196</td>
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<td></td>
<td></td>
<td></td>
<td>13 yr f/u</td>
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<tr>
<td><strong>Thailand impact study</strong> Thailand</td>
<td>Effectiveness</td>
<td>HPV4</td>
<td>Girls in grade 8 given 1 or 2 doses; n=~8000 each arm; prevalence surveys of girls grades 10, 12; n=2,400 each grade x 2 provinces</td>
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<tr>
<td><strong>HOPE</strong> South Africa</td>
<td>Effectiveness</td>
<td>HPV2</td>
<td>Girls 17-18 yo serial prevalence surveys: unvaccinated (17-18 yo), 1-dose catch up (15-16 yo), and 2-dose routine (9 yo) cohorts; n=3260</td>
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- **RCTs**: Randomized controlled trials
- **Non-randomized RCTs**: Non-randomized randomized controlled trials
- **Impact effectiveness studies**: Impact effectiveness studies

- ★ Interim results
- ★ Final results

**Notes:**
- Year 2
- Year 3
- Year 4
1. For the prevention of cervical cancer, the WG reaffirms the (2017) WHO recommendations for the use of HPV vaccines:

- Primary target: 9-14 years old girls, 2-dose schedule, Interval minimum 6months, no maximum suggest 12-15m for programmatic reasons.

- HIV+ and females ≥15 years: 3-dose schedule

2. All three licensed HPV vaccines have excellent safety, efficacy, immunogenicity and effectiveness profiles, and are comparable for the prevention of cervical cancer.
3. SAGE is deeply concerned that the current HPV vaccine shortage could result in failure to introduce or sustain HPV vaccine programmes in some countries, particularly those with a high burden of cervical cancer. In this context of limited supply of HPV vaccine, SAGE recommends the following additional strategies:

Countries should temporarily postpone implementation of gender-neutral, older age group (>15 years) and multi-age cohort HPV vaccination strategies until all countries have access to HPV vaccine. This will significantly relieve supply constraints in the short term and enable allocation of doses to high-burden countries currently planning to introduce this vaccine.

NNV for any HPV-related cancer
- Girls in Uganda = 78
- Girls Canada = 560
- Boys Canada = 5,480
- Middle age adults US = 8,500+
4. Countries may, in consultation with their national immunization technical advisory groups (NITAGs), consider alternative strategies to ensure that girls receive two doses of HPV vaccine before the age of sexual activity, as appropriate to the individual national context.

The following alternative strategies, which require careful consideration of the programmatic challenges and clear, well-planned communication, are recommended:

A. To retain the accelerated impact of vaccinating multi-age cohorts (MACs), countries could target an older cohort of girls (e.g., 13 or 14 years old girls or in an equivalent school grade), who are close to initiating sexual activity and thus of high risk of exposure and in whom a high 2-dose coverage can be achieved.

Once the vaccine supply situation has improved, countries could then consider: (i) Continuing with this strategy (i.e., targeting older girls) if high 2-dose coverage is being achieved; or (ii) Shifting to a strategy of targeting younger girls (9 or 10 year old or lower school grade) if vaccinating older girls results in low coverage rates or high drop-out rates between doses 1 and 2 or if vaccination is occurring after the age of sexual activity.
4. …the following alternative strategies are recommended: (Continued)

B. To temporarily reduce vaccine supply needs, countries could adopt a “1+1” schedule with an extended interval of 3-5 years between doses for younger girls (e.g., first dose provided at 9 or 10 years old or lower school grade) and taking measures to ensure that the girls receive two doses each. This strategy constitutes an off-label use of the vaccine. This off-label use is justified considering evidence that:
   - One dose is better than no vaccine. Some emerging evidence suggests likely protection after one dose.
   - A low risk of exposure between dose 1 and 2 is assumed in this young age group.
   - However, it requires careful consideration for programmatic challenges (capacity to trace girls later, registration, reminder systems) and risk considerations (age of onset of sexual activity)

5. SAGE calls upon WHO and its partners to urgently convene a dialogue on global access to HPV vaccine, engaging all relevant stakeholders including vaccine manufacturers.
Key Messages

- No change in WHO HPV Policy, 2-dose recommendation for all girls 9-14 yr old
- Urge to reach high coverage among girls and postpone or pause plans for vaccination males and adults (15+) until global supply has improved
- In case of supply challenges countries encourages to use 1+1 schedules or - in case of stock out - catch up any missed girls before reaching 15 yrs of age
- All countries that have not done so yet are encouraged to introduce HPV as soon as possible.

- Encourage programmes to monitor performance and intervene rapidly in case of decreases due to hesitancy & safety events.
- Low performing countries to develop redesign and HPV vaccine coverage improvement plans based on careful assessment
Thank You

World Health Organization

https://www.who.int/immunization/hpv/en/