Thank you for joining the webinar! We will begin momentarily. Please note that all attendees are automatically muted.
Single-dose HPV vaccination evidence

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Anne Schuind, PATH
Background

- Cervical cancer is a leading cause of cancer death among women in low- and lower-middle-income countries (LMIC)
- More than 604,000 cases and 341,000 deaths occur annually, with more than 90% of deaths occurring in LMIC
- HPV is present in virtually all cervical cancers and is a necessary cause of cervical cancer
- In November 2020, WHO launched the global strategy to accelerate the elimination of cervical cancer as a public health problem with the following 2030 targets:

90% of girls fully vaccinated with HPV vaccine by age 15 years.

70% of women are screened with a high-performance test by 35 years of age and again by 45 years of age.

90% of women identified with cervical disease receive treatment (90% of women with precancer treated, and 90% of women with invasive cancer managed).


https://www.who.int/publications/i/item/9789240014107
Background

• Current HPV vaccines are prophylactic, i.e., to be administered prior to exposure with HPV, optimally before sexual debut

• HPV vaccines were first introduced in 2006 on a three-dose schedule

• In 2014, the WHO reduced the schedule from three doses to two, following an evidence review by the Strategic Advisory Group of Experts (SAGE) on Immunization

• There is accumulating evidence that a single-dose of HPV vaccine may elicit an immune response that can protect against HPV infection
HPV vaccination schedules

Current WHO recommendations:
• 2 doses for girls 9 - 14 yoa, with dosing flexibility for dose 2 as early as 5 months after dose 1
• 3 doses for girls $\geq 15$ yoa and immune-compromised girls (including HIV infected) - original dosage recommendation

During the current supply constraint, SAGE recommended that countries who have introduced the HPV vaccine:
• Pause vaccinations in boys, older girls ($>15$ years), and multi-age cohorts
• Adopt an extended interval of 3-5 years between doses
### Table 1. Summary of available HPV vaccines

<table>
<thead>
<tr>
<th></th>
<th>Cervarix™&lt;sup&gt;a&lt;/sup&gt;</th>
<th>GARDASIL®&lt;sup&gt;b&lt;/sup&gt;</th>
<th>GARDASIL&lt;sup&gt;®&lt;sub&gt;b&lt;/sub&gt;&lt;/sup&gt;</th>
<th>Cecolin&lt;sup&gt;®&lt;sub&gt;c&lt;/sub&gt;&lt;/sup&gt;</th>
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<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>GlaxoSmithKline</td>
<td>Merck &amp; Co., Inc.</td>
<td>Merck &amp; Co., Inc.</td>
<td>Xiamen Innovax Biotech Co. Limited</td>
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<td><strong>HPV VLPs included</strong></td>
<td>16, 18</td>
<td>6, 11, 16, 18</td>
<td>6, 11, 16, 18, 31, 33, 45, 52, 58</td>
<td>16, 18</td>
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<td><strong>Injection Schedule</strong>&lt;sup&gt;d&lt;/sup&gt; (2 doses)</td>
<td>0, 6–12 months</td>
<td>0, 6–12 months</td>
<td>0, 6–12 months</td>
<td>0, 6 months</td>
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<tr>
<td><strong>Injection Schedule</strong>&lt;sup&gt;d&lt;/sup&gt; (3 doses)</td>
<td>0, 1, 6 months</td>
<td>0, 2, 6 months</td>
<td>0, 2, 6 months</td>
<td>0, 1, 6 months</td>
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</table>

*Note: HPV, human papillomavirus; VLP, virus-like particle.*

<sup>a</sup> Cervarix is a trademark of GlaxoSmithKline Biologicals, Belgium.

<sup>b</sup> Gardasil and Gardasil-9 are registered trademarks of Merck Sharp & Dohme Corp., United States.

<sup>c</sup> Cecolin is a registered trademark of Xiamen Innovax Biotech Co. Limited, China. Cecolin is licensed and used only in China and is currently under review for WHO prequalification (expected 2021).

<sup>d</sup> In some countries, the vaccines are also licensed and recommended for boys, in the same dosing schedules as for girls.
Global HPV vaccine introductions by burden of disease
Expanding access to HPV vaccines

If demonstrated to be effective, single-dose HPV vaccination could:

• accelerate introduction for countries that have yet to introduce the vaccine

• facilitate new options for current national programs by simplifying delivery costs and lowering program costs

• reduce the potential for supply shortages and delivery challenges, such as those faced during the COVID-19 pandemic
Impact of supply shortage and COVID-19 pandemic

Several countries have had to adapt their HPV vaccination programs due to:

Supply shortages:

- Some countries (e.g., Kenya, Ethiopia, Tanzania) only vaccinate one age cohort instead of the recommended multi-age cohort (9-14 years old) at introduction following with routine immunization (9 years old).

COVID-19 pandemic:

- Countries have delayed introducing the HPV vaccine (e.g., Mauritania, Sao Tome and Principe).
- When schools closed due to lockdown, programs had to shift from school-based to facility-based (e.g., Uganda).
- Second doses were delayed for months, and concerns arose about the girls aging out of the cohort (e.g., Ethiopia).
The Single-Dose HPV Vaccine Evaluation Consortium encompasses eight leading health and research institutions working together to collate and synthesize existing evidence and evaluate new data on the potential for single-dose HPV vaccination.

- Harvard University
- London School of Hygiene & Tropical Medicine
- PATH
- Université Laval
- University of British Columbia
- US Centers for Disease Control and Prevention
- US National Cancer Institute
- Wits Reproductive Health and HIV Institute
Evidence review

• Summarizes existing evidence from trials, non-trials, and impact and economic modeling work into one paper

• Third edition is now available, and fourth edition will be available in 2022

• Each edition accompanied by a synthesis and summary (available in English, French, and Spanish)
Single-dose HPV vaccination evidence from clinical trials and observational studies
Rationale for Single Dose HPV vaccination strategy

- Current HPV vaccines (multidose regimens) are highly efficacious in preventing persistent infections and cervical lesions associated with vaccine genotypes
  - HPV-16 and 18 account for ~ 70% of cervical cancers worldwide
- Vaccines elicit a strong and durable neutralizing antibody response
  - Stability of antibody responses observed ≥ 10 years after vaccination
  - In healthy young women, seroconversion rates are virtually 100%
- After a single dose of vaccine
  - The durability of the antibody response remains
  - The quantity of neutralizing antibodies is lower, but the quality is similar to multidose vaccination

Clinical trials – Efficacy and immunogenicity

A systematic review was conducted on the efficacy and immunogenicity of a single HPV vaccine dose compared to multidose schedules (or no HPV vaccination)

**Seven articles identified (additional 2 published early 2020**) reporting on results from four studies**

Except for 1 study, data originated from randomized controlled trials participants having failed to complete their allocated 2 or 3-dose schedule

- HPV 16 and 18 infections were extremely low in all efficacy trial participants who received any HPV vaccine, and significantly lower than in unvaccinated participants or control vaccine recipients
- HPV 16 and 18 efficacy was comparable following 1-dose and 2- or 3-dose in healthy young females up to eleven years post-vaccination
- High proportion of participants seroconverting to HPV 16 and 18 in all HPV vaccine dosing regimens

*Two in India [International Agency for Research on Cancer (IARC) India HPV Trial], five in Costa Rica [Costa Rica Vaccine Trial (CVT)]**, one in the United States of America, and one multinational study [PApilloma TRIal against Cancer In young Adults (PATRICIA)].
Protection against HPV-16/18 infections after a single dose of 2vHPV - Combined analysis of Costa Rica Vaccine and PATRICIA Trials

Dose-stratified vaccine efficacy against HPV-16/18 infections

Durability of the immune response after a single dose of 2vHPV Costa Rica Vaccine Trial

**HPV-16 antibody levels (ELISA) over time by number of doses received**

Results for HPV-18 ELISA show a similar kinetics response

Stable antibody levels for HPV16 and HPV-18 antibodies up to 11 years post vaccination with different dosing schedules of 2vHPV at least 10 fold above natural immunity.

Observational studies - Immunogenicity

Eleven articles were identified reporting on immunogenicity with results from 9 studies*:
Participants receiving only one HPV dose resulted from noncompletion of an intended multidose schedule

• A single-dose HPV vaccination results in high rates of seroconversion and sustained seropositivity
  • one study presenting data up to eight years after vaccination
• Antibody titers were lower with 1-dose than with 2- or 3-doses
  • Titers in 1-dose arms remained stable
  • Titers are considerably higher than with natural infection
• Some adolescents demonstrated higher antibody titers after a single-dose than those observed in 3-dose clinical efficacy trials conducted in adult women (using the same laboratory methods)

*one each from Uganda, the Netherlands, and Mongolia; two from the United States; and three each from Canada and Fiji.
A systematic review provided evidence of HPV vaccine effectiveness by number of doses.

**Results from 32 studies: HPV infections [8]; anogenital warts [9]; cervical abnormalities [15]**

- Most of the studies found highest effectiveness with 3 doses, followed by 2 doses, and then 1 dose
- Biases in many studies; most that would result in apparent lower effectiveness with fewer doses
- Half of the studies found significant vaccine effectiveness for single dose HPV vaccination in some or all analyses
- Higher effectiveness estimates was found with younger age at vaccination
- More recent studies with younger vaccine recipients, or with analyses stratified by age at vaccination, have found high effectiveness with one dose or similar effectiveness for one, two, and three doses
Protection against High grade cervical lesions after single dose of 4vHPV National cohort analysis - Australia

One dose had comparable effectiveness as two or three doses in preventing high grade cervical lesions in women vaccinated ≤15 yo.

Brotherton JM, Papillomavirus Res 2019

Cumulative failure probability plot for CIN2/AIS+ among 250,648 screening women

Hazard ratio for 1 dose compared to 3 doses: 1.01 (95%CI 0.81–1.26)
Single-dose HPV Vaccination Modeling Evidence
# Modeling - Overview

<table>
<thead>
<tr>
<th>Data for fit</th>
<th>Harvard Models</th>
<th>U Laval Model</th>
<th>LSHTM Model</th>
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<tr>
<td></td>
<td>Demographic a&lt;br&gt;Sexual behavior a&lt;br&gt;HPV prevalence a&lt;br&gt;Cancer Incidence Type distribution in Cancers</td>
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<td>Countries</td>
<td>US&lt;br&gt;India&lt;br&gt;Uganda, South Africa&lt;br&gt;Costa Rica, El Salvador, Nicaragua</td>
<td>Canada, US&lt;br&gt;India, Vietnam&lt;br&gt;Benin, Uganda &amp; Nigeria&lt;br&gt;Colombia</td>
<td>All countries</td>
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<td>Outcomes</td>
<td>Health outcomes (cancers, deaths, life-years)&lt;br&gt;Costs&lt;br&gt;Cost/LY-gained&lt;br&gt;Cost/QALY-gained&lt;br&gt;Cost/DALY-averted</td>
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^: Demographic (Life tables, Population size); Sexual behaviour (start sex, number/age of partners, mixing); HPV prevalence (by age and HPV-type)
Harvard Model Schematic

**Agent-Based Model**
- HPV Transmission
- Partnership Formation
- HPV incidence

**Microsimulation Model**
- Disease Progression
- Cervical Cancer
- CIN 2
- CIN 3
- HPV Infection
- No HPV Infection

**Scale-Up Model**
- Global Population

**SINGLE-DOSE HPV VACCINE EVALUATION CONSORTIUM**

### Harvard Model Schematic

- **Agent-Based Model**
  - HPV Transmission
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- **Scale-Up Model**
  - Global Population

HPV-16 Prevalence in Females (Ages 12-59)

- No Waning

**Prevalence**

- 1-dose (eff 80%), cov 70%
- 2-dose (eff 100%), cov 70%

**Years after vaccination**

- No vaccination
HPV-16 Prevalence in Females (Ages 12-59)

No Waning

No vaccination

1-dose (eff 80%), cov 70%

2-dose (eff 100%), cov 70%

1-dose (eff 80%), cov 90%

years after vaccination

prevalence

0.00 0.01 0.02 0.03 0.04 0.05 0.06

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35
HPV-16 Prevalence in Females (Ages 12-59)

Wane begins at 15 years

![Graph showing HPV-16 prevalence in females over years after vaccination with different vaccination scenarios: no vaccination, 1-dose (eff 80%), 2-dose (eff 100%), each with 70% coverage.](image)
HPV-16 Prevalence in Females (Ages 12-59)

Wane begins at 15 years

prevalence

0.06

0.05

0.04

0.03

0.02

0.01

0.00

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35

years after vaccination

1-dose (eff 80%), cov 70%

1-dose (eff 80%), cov 90%

2-dose (eff 100%), cov 70%

No vaccination
Looking ahead
Gaps, research priorities, and forthcoming evidence

- More evidence on single-dose HPV vaccine is needed. Several clinical studies are underway to address the durability of protection, efficacy, effectiveness, immunogenicity of a single dose, and the standardization of laboratory assays will also be important.

- An updated systematic review will include any newly published studies on efficacy and immunogenicity; single-dose effectiveness of HPV vaccination from observational studies; and new quality assessments of the evidence.

- Evidence generated by future modeling work will focus on integrating new trial, non-trial, and effectiveness data into existing models, as well as conducting model-based analyses in LMICs with different sexual behavior and epidemiological profiles.

- In South Africa and other countries with high prevalence of HIV infection, it will be critical to generate more evidence on the health and economic impacts of reduced-dose HPV vaccination in HIV-positive individuals.
<table>
<thead>
<tr>
<th>Study name (country)</th>
<th>Efficacy (or Immunogenicity)</th>
<th>Vaccine(s)</th>
<th>Brief description</th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
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<tbody>
<tr>
<td>DoRIS 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=1655 each arm</td>
<td>Q4</td>
<td>Q1</td>
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<td>Q3</td>
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<td>KEN SHE Kenya</td>
<td>Efficacy (virological EP)</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; delayed dose 2 planned</td>
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<tr>
<td>HANDS The Gambia</td>
<td>Immunogenicity</td>
<td>HPV9</td>
<td>Girls 4-6 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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<tr>
<td>Primavera 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>ESCUDDO Costa Rica</td>
<td>Efficacy (virological EP)</td>
<td>HPV2 and HPV9</td>
<td>Girls 12-16 yo randomized to 1 or 2 doses of HPV2 or HPV9; n=3000 each arm</td>
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<tr>
<td>India IARC India</td>
<td>Efficacy (virological and histological EP)</td>
<td>HPV4</td>
<td>Girls 10-18 yo received 1, 2, 3 doses of HPV4; n=17,886, 1-dose n=4,890</td>
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<tr>
<td>CVT Costa Rica</td>
<td>Efficacy till YII / Immunogenicity</td>
<td>HPV2 vs control</td>
<td>Women 10-25 yo received 1, 2, or 3 doses of HPV2; n=3727, 1-dose n=196</td>
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<tr>
<td>Thailand impact study</td>
<td>Effectiveness (virological EP)</td>
<td>HPV2</td>
<td>Girls in grade 8 given 1 or 2 doses; n=8,000 each arm; prevalence surveys of girls grades 10, 12; n=2,400 each grade x 2 provinces</td>
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<tr>
<td>HOPE South Africa</td>
<td>Effectiveness (virological EP)</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 (19 yo) cohorts; n=3260</td>
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Available Resources

• Fact sheet
• Evidence Review
• Technical Synthesis
• General Summary
• Consensus statement

• Website: path.org/singledosehpv
• HPVFlash newsletter: path.org/hpvflash
Questions
For more information

The consortium, coordinated by PATH, includes Harvard University, London School of Hygiene & Tropical Medicine, Université Laval, University of British Columbia, US Centers for Disease Control and Prevention, US National Cancer Institute, and Wits Reproductive Health and HIV Institute.

In addition to the consortium members, representatives from the following institutions serve as advisors: the World Health Organization, International Agency for Research on Cancer; Medical Research Council Unit The Gambia at the London School of Hygiene & Tropical Medicine; Instituto Nacional de Salud Pública de Mexico; Quebec Institut National de Santé Publique; Victorian Cytology Service, Australia; University of Washington, USA; and International Vaccine Institute, South Korea.

Inquiries about this project can be directed to Evan Simpson, esimpson@path.org.
Question & Answer