International Federation of Gynecology and Obstetrics
HPV VACCINATION
Cervical cancer is a rare long-term outcome of persistent infection with one or more of high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82)
With these interventions, elimination of cervical cancer can be possible!

- Socio-economic development
- Women’s awareness / empowerment
- HPV vaccination
- Screening
- Early diagnosis and treatment
# Characteristics of HPV vaccines

<table>
<thead>
<tr>
<th></th>
<th><strong>Gardasil ®</strong> (Quadrivalent vaccine)</th>
<th><strong>Cervarix ®</strong> (Bivalent vaccine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Merck</td>
<td>GSK</td>
</tr>
<tr>
<td>VLP types</td>
<td>6/11/16/18</td>
<td>16/18</td>
</tr>
<tr>
<td>Dose L1 protein</td>
<td>20/40/40/20 µg</td>
<td>20/20 µg</td>
</tr>
<tr>
<td>Producer cells</td>
<td>Saccharomyces cerevisiae expressing L1</td>
<td>Trichoplusia ni (Hi 5) insect cell line infected with L1 recombinant baculovirus</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>225 µg Aluminum hydroxyphosphate sulfate</td>
<td>500 µg aluminum hydroxyde, 50 µg 3-O-deacylated-4'-monophosphoryl lipid A</td>
</tr>
<tr>
<td>Schedule</td>
<td>0, 2, 6 months</td>
<td>0, 1, 6 months</td>
</tr>
</tbody>
</table>
Global Phase III efficacy trials with disease endpoints

Quadrivalent vaccine
(Gardasil™, Merck Co.)
- HPV 6/11/16/18 vaccine vs. placebo (0, 2, 6 mo)
- Age range 16-26
- N=17,622
- Study start: 2002
- 4-year follow-up
- FUTURE I/II (Protocols 013, 015)

Bivalent vaccine
(Cervarix™, GlaxoSmithKline)
- HPV 16/18 vaccine vs. Havrix (0, 1, 6 mo)
- Age range 15-25
- N= 18,644
- Study start: 2004
- 4-year follow-up
- PATRICIA (HPV-008)

Europe*, Asia-Pacific, Latin America, North America (13 countries)  
Europe*, Asia-Pacific, Latin America, North America (14 countries)

*Predominantly Northern Europe

Courtesy: Dr Paavonen
Immunogenicity of the bivalent vaccine up to 8.4 y after vaccination: seropositivity rates and geometric mean titers for HPV 16

A

Anti-HPV-16 antibodies

Immunogenicity of the bivalent vaccine up to 8.4 y after vaccination: seropositivity rates and geometric mean titers for HPV 18

Persistence of *anti-HPV16* response following three-doses of quadrivalent vaccine or placebo and booster
Persistence of *anti-HPV18* response following three-dose of quadrivalent vaccine or placebo and booster

### Per-protocol efficacy for prevention of HPV-type disease outcomes among females in trials of the bivalent and quadrivalent HPV vaccines, end-of-study analyses

<table>
<thead>
<tr>
<th>Vaccine/Endpoint related type</th>
<th>Vaccine</th>
<th>Control</th>
<th>Vaccine efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Cases</td>
<td>No.</td>
</tr>
<tr>
<td><strong>Quadrivalent vaccine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN2/3 or AIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 6, 11, 16, 18</td>
<td>7,864</td>
<td>2</td>
<td>7,865</td>
</tr>
<tr>
<td>HPV 16</td>
<td>6,647</td>
<td>2</td>
<td>6,455</td>
</tr>
<tr>
<td>HPV 18</td>
<td>7,382</td>
<td>0</td>
<td>7,316</td>
</tr>
<tr>
<td>VIN/VaIN2/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 6, 11, 16, 18</td>
<td>7,900</td>
<td>0</td>
<td>7,902</td>
</tr>
<tr>
<td>HPV 16</td>
<td>6,654</td>
<td>0</td>
<td>6,467</td>
</tr>
<tr>
<td>HPV 18</td>
<td>7,414</td>
<td>0</td>
<td>7,343</td>
</tr>
<tr>
<td><strong>Genital warts</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 6 and/or 11</td>
<td>6,718</td>
<td>2</td>
<td>6,647</td>
</tr>
<tr>
<td><strong>Bivalent vaccine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN2/3 or AIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 16 and/or 18</td>
<td>7,338</td>
<td>5</td>
<td>7,305</td>
</tr>
<tr>
<td>HPV 16</td>
<td>6,296</td>
<td>2</td>
<td>6,160</td>
</tr>
<tr>
<td>HPV 18</td>
<td>6,789</td>
<td>3</td>
<td>6,739</td>
</tr>
</tbody>
</table>

Per-protocol efficacy of quadrivalent human papillomavirus vaccine for prevention of HPV 6-, 11-, 16-, and 18-related disease among males aged 16–26 years

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine</th>
<th>Control</th>
<th>Vaccine efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Cases</td>
<td>No.</td>
</tr>
<tr>
<td>Genital warts</td>
<td>1,397</td>
<td>3</td>
<td>1,408</td>
</tr>
<tr>
<td>PIN</td>
<td>1,397</td>
<td>0</td>
<td>1,408</td>
</tr>
<tr>
<td>AIN 1/2/3</td>
<td>194</td>
<td>5</td>
<td>208</td>
</tr>
<tr>
<td>AIN2/3</td>
<td>194</td>
<td>3</td>
<td>208</td>
</tr>
</tbody>
</table>
Kaplan–Meier curves of the estimated cumulative incidence of CIN3+ in the PATRICIA and FUTURE clinical trials

a) Women who were HPV PCR-negative at baseline and who received control or Cervarix® vaccines
b) The intention-to-treat cohort who received control or Cervarix® vaccines

Lehtinen et al, Nature Reviews Clinical Oncology 2013, 10:400-410
Kaplan–Meier curves of the estimated cumulative incidence of CIN3+ in the PATRICIA and FUTURE clinical trials

c) Women who were HPV6, HPV11, HPV16 and HPV18 PCR-negative at baseline and who received control or Gardasil® vaccines

d) The intention-to-treat cohort who received control or Gardasil® vaccines. All data points have 95% CI error bars marked

Lehtinen et al, Nature Reviews Clinical Oncology 2013, 10:400-410
Efficacy and safety of HPV vaccination

- 100% sero-conversion
- Sero-positivity remains > 98% at 9 years
- 100% protection of CIN 2/3 caused by HPV 16/18 for at least 6 years in HPV-naïve populations
- Some cross protection against CIN 2/3 caused by HPV 45 and HPV 31
- Vaccine-induced antibody levels maintained over 9 years (both vaccines) robust recall response (quadrivalent)
- Safe and well-tolerated
Mean MFI values for HPV 16, 18 L1 antibodies at different time points among girls who completed vaccination per protocol (vaccination at day 1, 60 and 180 (3-dose group) or day 1 and 180 (2-dose group)), and those who did not have their complete vaccine schedules (vaccination at day 1 and 60 or a single dose).
Randomised Trial of 2 versus 3 doses of HPV vaccination in India

Geometric mean MFI avidity index of HPV 16, 18, 6 and 11 L1 antibodies at 18 months after the first dose among girls who received vaccination per protocol, and those who did not have their complete vaccine schedules

Sankaranarayanan et al., Lancet Oncol. 2016;17(1):67-77

Supported by the Bill & Melinda Gates Foundation
Vaccines provided by Merck
Evaluation of less than 3 doses of HPV Vaccination in India:
Frequency of persistent HPV 16 and 18 infection in 1235 vaccinated women by dose regime and 738 unvaccinated women

- 3-Dose: 0/241
- 2-Dose (day 1-180): 0/224
- 2-Dose (day 1-60): 0/365
- 1-Dose: 0/405
- All vaccinated girls: 0/1235
- UNVACCINATED WOMEN: 6/738 (0.8%)
HPV vaccine efficacy of fewer than 3-doses in preventing HPV infections in Costa Rica

<table>
<thead>
<tr>
<th>Doses</th>
<th>Arm</th>
<th>Women No</th>
<th>Women with HPV infections (%)</th>
<th>HPV vaccine efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 doses</td>
<td>Control</td>
<td>3010</td>
<td>133 (4.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>2957</td>
<td>25 (0.9%)</td>
<td>80.9%</td>
</tr>
<tr>
<td>2 doses</td>
<td>Control</td>
<td>380</td>
<td>17 (4.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>422</td>
<td>3 (0.7%)</td>
<td>84.1%</td>
</tr>
<tr>
<td>1 dose</td>
<td>Control</td>
<td>188</td>
<td>10 (5.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>196</td>
<td>0</td>
<td>100%</td>
</tr>
</tbody>
</table>

Kreimer A et al, JNCI 2011;103:1-8
WHO’s Strategic Advisory Group of Experts (SAGE) on 2-dose and 3-dose HPV vaccination, February 2014

• SAGE recommends 2-dose vaccination, 6-months or 1-year apart between the two doses, if vaccination is initiated prior to 15 years of age,

• 3-dose schedule is necessary if vaccination is initiated after 15\textsuperscript{th} birth day.

• 3-dose schedule is recommended for immuno-compromised individuals, including HIV infected persons.

HPV vaccine safety

- The GACVS has systematically investigated HPV vaccine safety concerns
- To date, GACVS has not found any safety issue that would alter its recommendations
HPV vaccine safety

- More than 250 million doses of HPV vaccines have been administered since 2007
- No serious adverse event has been directly linked to HPV vaccination
- The frequency of anaphylaxis ~ 1/200,000 doses (similar to other vaccines)
Global map showing HPV vaccination experience in Gavi eligible and non-eligible countries

Hanson et al., Vaccine. 2015;3:408-419
HPV vaccination as part of National immunization programs

• HPV vaccination as part of National Immunization Programs (NIP) or pilot demonstration programs in 83 countries

• Australia, UK, USA and Canada were the among the first countries to implement HPV vaccination

• In Europe, the countries implementing HPV vaccination as part of NIP increased from 3 in 2007 to 29 in 2015

• Bhutan, Panama and Rwanda were among the first LMICs to implement HPV vaccination in NIP

Bhutan: pilot program followed by national scale-up

- Pilot phase (Oct 2009-Apr 2010)
  - ACCF/GAP program donation of 9,600 doses
  - School-based (22), 3,167 girls aged 11-13 years targeted
  - 94% 3rd dose coverage
- National scale-up (May-Nov 2010)
  - GAP donation of 184,000 doses
  - Schools, 47,888 girls 12-18 year old eligible
  - 96% 3rd dose coverage
- National program (2011)
  - Health clinics based delivery, 12 year old (2012,2013) (3rd dose coverage 69%)
  - School based delivery (2014), 90% 3rd dose coverage
- The Bhutan HPV vaccine program is a model for other developing countries that aspire to implement national HPV vaccination programs

Dorji et al., Vaccine. 2015;33(31):3726-30
HPV vaccination programme in Malaysia

- Introduced in mid-2010
- Primarily school-based delivery
  - community health centres for missed girls or out-of-school girls
- Extensive communications preparation: electronic media, radio, newspapers, posters, pamphlets
- Strong monitoring system
- HPV vaccination well accepted by communities and parents
- Eligible population: 236,000 (13 year old girls)
Malaysia HPV vaccination performance
2010 - 2014

<table>
<thead>
<tr>
<th>Year</th>
<th>Acceptance</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Completed 3 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>95.9</td>
<td>99.5</td>
<td>98.9</td>
<td>98.4</td>
</tr>
<tr>
<td>2011</td>
<td>97.6</td>
<td>99.0</td>
<td>99.6</td>
<td>98.3</td>
</tr>
<tr>
<td>2012</td>
<td>98.2</td>
<td>99.8</td>
<td>99.1</td>
<td>98.7</td>
</tr>
<tr>
<td>2013</td>
<td>98.4</td>
<td>99.9</td>
<td>99.8</td>
<td>99.4</td>
</tr>
<tr>
<td>2014</td>
<td>98.5</td>
<td>99.0</td>
<td>99.8</td>
<td>99.6</td>
</tr>
</tbody>
</table>

AEFI REPORTED TO PHARMACEUTICAL BUREAU BETWEEN 2010 AND 2014

<table>
<thead>
<tr>
<th>Year</th>
<th>Total doses of vaccine delivered</th>
<th>Number AEFI report received</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>687,735</td>
<td>403</td>
</tr>
<tr>
<td>2011</td>
<td>678,897</td>
<td>3023</td>
</tr>
<tr>
<td>2012</td>
<td>693,905</td>
<td>1757</td>
</tr>
<tr>
<td>2013</td>
<td>727,518</td>
<td>960</td>
</tr>
</tbody>
</table>

0.06% | 0.45% | 0.25% | 0.13%

NATIONAL HPV SCHOOL BASED HPV VACCINATION PERFORMANCE FOR 12 - 13 YEARS OLD GIRLS: AUSTRALIA, ENGLAND, SCOTLAND AND MALAYSIA SCORE CARD

AUSTRALIA (12 -13), 2011: Dose 1 81, Dose 3 71
ENGLAND (12 -13), 2012/13: Dose 1 90.9, Dose 3 86.1
SCOTLAND (12-13), 2008/09: Dose 1 94.4, Dose 3 91.4
MALAYSIA (12-13), 2010: Dose 1 99.5, Dose 3 97.9

Courtesy slide from: Saidatul Norbaya Buang and Rohani Jahis for Asia Dengue Summit
## HPV vaccination coverage in Rwanda, 2011

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls vaccinated in school (No.)</td>
<td>91 752</td>
<td>89 704</td>
<td>88 927</td>
</tr>
<tr>
<td>Girls vaccinated outside school (No.)</td>
<td>2 136</td>
<td>3 066</td>
<td>3 180</td>
</tr>
<tr>
<td>Total number of girls vaccinated (No.)</td>
<td>93 888</td>
<td>92 770</td>
<td>92 107</td>
</tr>
<tr>
<td><strong>Cumulative coverage</strong></td>
<td><strong>95%</strong></td>
<td><strong>94%</strong></td>
<td><strong>93%</strong></td>
</tr>
</tbody>
</table>

National HPV vaccination program in Panama

- Initiated in 2008
- Delivered in schools and clinics for 10 year old girls
- In 2009, 1 dose coverage was 89% and 3-dose coverage was 46%
- In 2010, 3-dose coverage was 67%
- In 2011, 3-dose coverage improved to 81%
Impact of HPV vaccination in real world settings

- Over the last decade, impact of HPV vaccination in real-world settings is increasingly evident, especially among girls vaccinated before HPV exposure in countries with high vaccine uptake.

- Maximal reductions of ~90% for HPV 6/11/16/18 infection, ~90% for genital warts, ~60% for low-grade cytological cervical abnormalities, and ~90% for high-grade histologically-proven cervical abnormalities have been reported.

- The full public health potential of HPV vaccination not yet realized. HPV-related disease remains a significant source of morbidity and mortality in developing and developed nations, underscoring need for HPV vaccination programs with high coverage.

Garland et al., Clin Infect Dis. 2016. pii: ciw354. [Epub ahead of print]
Global impact of HPV vaccination and herd effects

- A pooled analysis of 20 studies in 9 high income countries with >50% coverage
- 140 million person years of follow-up
- HPV16 and HPV 18 infections declined by 68% (RR 0.32, 95% CI: 0.19-0.52) in girls aged 13-19 years
- Anogenital warts declined by 61% (RR: 0.39, 95% CI: 0.22-0.71) in 13-19 year old girls
- HPV types 31,33, 45 declined by 28% (RR: 0.72, 95% CI:0.54-0.96)
- Anogenital warts declined by 34% (RR: 0.66, 95% CI: 0.47-0.91) in boys <20 years age
- Anogenital warts declined by 32% (RR: 0.68, 95% CI: 0.51-0.89) in women <30 years age

Drolet et al., Lancet Infect Dis. 2015;15:565-80
Global impact of HPV vaccination and herd effects in countries with <50% coverage

- HPV16 and HPV 18 infections declined by 50% (RR 0.50, 95% CI: 0.34-0.74) in girls aged 13-19 years
- Anogenital warts declined by 14% (RR: 0.86, 95% CI: 0.79-0.94) in 13-19 year old girls
- No indication of cross-protection or herd effects
- Long-term population-level effects of HPV vaccination programmes are promising
- Continued monitoring is essential to identify any waning efficacy or type-replacement.

Drolet et al., Lancet Infect Dis. 2015;15:565-80
Impact and effectiveness of HPV vaccination on cervical cytological and histological abnormalities

Australia: Victoria

Australia: Queensland

Garland et al., Clin Infect Dis. 2016. pii: ciw354. [Epub ahead of print]
Impact and effectiveness of HPV vaccination on cervical cytological and histological abnormalities

Canada

Denmark

Garland et al., Clin Infect Dis. 2016. pii: ciw354. [Epub ahead of print]
Impact and effectiveness of HPV vaccination on cervical cytological and histological abnormalities

**Sweden**

- **CIN2+**
  - <17 yr (n=33): 75%
  - 17-19 yr (n=139): 46%
  - 20-29 yr (n=124): 22%
  - <17 yr (n=52): 57%
  - 17-19 yr (n=8): 25%

- **CIN3+**
  - <17 yr (n=33): 100%
  - 17-19 yr (n=139): 84%
  - 20-29 yr (n=124): 57%
  - <17 yr (n=52): 72%
  - 17-19 yr (n=8): 25%

**United States**

- **CIN2+**
  - 13-24 mo (n=149): 9%
  - 25-36 mo (n=109): 21%
  - >36 mo (n=85): 49%
  - 13-24 mo (n=41): 72%
  - 25-36 mo (n=32): 38%
  - >36 mo (n=10): 45%

- **CIN3/AIS**
  - 13-24 mo (n=149): 8%
  - 25-36 mo (n=109): 8%
  - >36 mo (n=85): *%
  - 13-24 mo (n=41): *%
  - 25-36 mo (n=32): *%
  - >36 mo (n=10): *%

---

n=number of vaccinated women with lesion in each age group.

n=number of vaccinated women with lesion in each time category.

Garland et al., Clin Infect Dis. 2016. pii: ciw354. [Epub ahead of print]
We know it's effective. So why is there opposition to the HPV vaccine?

David Robert Grimes

Over 90% of cervical cancers are caused by HPV. But squeamishness about sex and unsupported safety fears are threatening vaccination programmes.
Slides prepared by

R. Sankaranarayanan MD
Special Advisor on Cancer Control & Head, Screening Group
International Agency for Research on Cancer, Lyon, France

On behalf of the
FIGO Committee on Gynecologic Oncology