One-Dose Human Papillomavirus (HPV) Vaccination: Overview of Current Evidence

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Division of Viral Diseases

Advisory Committee on Immunization Practices
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Objectives of this presentation

- Update ACIP on data regarding 1-dose HPV vaccination
- Review recently revised HPV vaccination recommendations of WHO’s Strategic Advisory Group of Experts (SAGE) on Immunization
Outline

▪ Background on data for initial licensure of HPV vaccines in 2006 and the change to a 2-dose schedule in 2016
▪ Evidence regarding 1-dose HPV vaccination
▪ SAGE HPV vaccination recommendations, April 2022
Efficacy and immunogenicity data for initial licensure of HPV vaccines, 3-dose schedules (0, 1-2, 6 months)

- **Randomized controlled efficacy trials in 15–26-year-old women**
  - Trial endpoints: cervical precancer lesions*
  - Efficacy against vaccine-type endpoints over 96% in per protocol analyses
  - Seroconversion one month after last dose close to 100%

- **Immunobridging trials in 9–15-year-olds**
  - Licensure in this age group based on non-inferior antibody response compared with women in the age group of the efficacy trials

Quadrivalent vaccine trials had other outcomes as well including, vulvar, vaginal precancers in females, genital warts
2-dose schedule for persons aged 9–14 years

- Interest stimulated by post hoc analyses of a 3-dose randomized trial
  - Not all individuals completed the 3-dose schedule
  - Efficacy against HPV16/18 infection similar after 3, 2, and 1 doses

Proof-of-Principle Evaluation of the Efficacy of Fewer Than Three Doses of a Bivalent HPV16/18 Vaccine


J Natl Cancer Inst 2011

- Immunobridging trials
  - 2-doses (0,6 or 0,12 months) in 9–14-year-olds vs 3-doses in 15–23-year-olds
  - Seroconversion and GMTs were non-inferior in 2-dose vs 3-dose group
9vHPV 2-dose immunobridging trial results

- Non-inferior GMTs at 1 month post last dose in 2-dose group (girls age 9–14 years) vs 3-dose group (women age 16–26 years)

<table>
<thead>
<tr>
<th>Fold difference (girls/women)</th>
<th>2.15</th>
<th>2.39</th>
<th>2.54</th>
<th>2.46</th>
<th>2.51</th>
<th>2.96</th>
<th>1.67</th>
<th>1.60</th>
<th>2.55</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI</td>
<td>(1.83, 2.53)</td>
<td>(2.03, 2.82)</td>
<td>(2.14, 3.00)</td>
<td>(2.05, 2.96)</td>
<td>(2.10, 3.00)</td>
<td>(2.50, 3.50)</td>
<td>(1.38, 2.03)</td>
<td>(1.36, 1.87)</td>
<td>(2.15, 3.01)</td>
</tr>
</tbody>
</table>

Iversen O-E, et al. JAMA 2016 and https://www.fda.gov/media/90064/download
4vHPV 2- vs 3-dose immunobridging trial

- GMTs in three groups through month 36
  - 2 doses (0,6 months) in 9–13-year-olds
  - 3 doses (0,2,6 months) in 9–13-year-olds
  - 3 doses (0,2,6 months) in 16–26-year-olds

- Antibody kinetics similar in all 3 groups

Adapted from: Dobson SR, et al. JAMA 2013
FDA licensure and ACIP recommendations for a 2-dose HPV vaccination schedule, 2016

- 9vHPV manufacturer submitted sBLA for a 2-dose schedule in 9–14-year-olds
- FDA approved application in Oct 2016
- ACIP recommended a 2-dose HPV vaccination series for persons starting vaccination at ages 9–14 years, Oct 2016
  - 3 doses recommended for persons with immunocompromising conditions

sBLA, Supplemental Biologics Licensure Application
Evidence on 1-dose HPV vaccination
Evaluation of 1-dose HPV vaccination

- Same studies that stimulated interest in 2-dose schedules led to interest in 1-dose vaccination

- **Immunobridging trials not possible because 1 dose results in lower antibody titers than 2 or 3 doses**

- Basis of protection after HPV vaccination thought to be neutralizing antibody
  - No established minimum antibody threshold for protection
  - Very low levels of antibody thought to be protective

- Efficacy trials needed to evaluate 1-dose HPV vaccination
**ESCUDDO**

- Randomized trial in Costa Rica to evaluate efficacy (U.S. National Cancer Institute)
- Objectives: 1) to evaluate non-inferiority of 1 versus 2 doses of bivalent and 9-valent vaccines for prevention of new cervical HPV16/18 infections that persist 6+ months, and 2) to evaluate 1 dose compared to unvaccinated

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**Trial**

**Girls 12-16 years old**

(n=20,300)

- **Bivalent**
  - (n=10,150)
  - M0: Randomized to vaccine
  - M6: Randomized to dosing schedule
  - 1 Dose | 2 Doses

- **9-valent**
  - (n=10,150)
  - M0: Randomized to vaccine
  - M6: Randomized to dosing schedule
  - 1 Dose | 2 Doses

**Active Follow-up**

Cervical cells, blood, urine at M12, M18, M24, M30, M36, M42, M48, M54, M60

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**Epidemiologic surveys of unvaccinated women**

HPV infection status

M0 and M6

HPV vaccine

First results expected 2024

Porras, et al. Vaccine 2022
Meanwhile, interest in 1-dose HPV vaccination increased

- Global HPV vaccine supply/demand imbalance recognized\(^1\)
- Global HPV vaccination coverage continued to be low\(^2\)
- Challenges implementing HPV vaccination programs
- Additional studies initiated to evaluate 1-dose HPV vaccination
- Studies that initially provided data on 1-dose vaccination had further follow-up data


\(^2\) Bruni L, et al. Preventive Medicine 2019
<table>
<thead>
<tr>
<th>Trial/country</th>
<th>Evidence</th>
<th>Vaccine</th>
<th>Age (yrs) at vaccination</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVT, Costa Rica</td>
<td>Efficacy/Immunogenicity</td>
<td>2vHPV</td>
<td>18–25</td>
<td>Post-hoc analyses: participants randomized to 3 doses or control, but analyzed as 1-, 2-, 3-dose groups</td>
</tr>
<tr>
<td>India IARC, India</td>
<td>Efficacy/Immunogenicity</td>
<td>4vHPV</td>
<td>10–18</td>
<td>Post-hoc analyses: participants randomized to 2 or 3 doses but analyzed as 1-, 2-, 3-dose groups</td>
</tr>
<tr>
<td>KEN SHE, Kenya</td>
<td>Efficacy</td>
<td>2vHPV</td>
<td>15–20</td>
<td>Randomized trial: 1 dose of 2vHPV, 9vHPV, meningococcal vaccine</td>
</tr>
<tr>
<td>DoRIS, Tanzania</td>
<td>Immunogenicity</td>
<td>2vHPV</td>
<td>9–14</td>
<td>Randomized trial: 1-, 2-, 3-dose groups</td>
</tr>
<tr>
<td>Thailand Impact</td>
<td>Impact/effectiveness</td>
<td>2vHPV</td>
<td>grade 8</td>
<td>Students in one province received 1 dose; in another 2 doses</td>
</tr>
</tbody>
</table>

CVT, Costa Rica Vaccine Trial; IARC, International Agency for Research on Cancer. All studies conducted among girls/women.
Costa Rica Vaccine Trial (CVT): protection after 1, 2 or 3 doses of 2vHPV through 11 years

- Post hoc analysis of RCT: women vaccinated at age 18–25 years
- Randomized to receive 3 doses of 2vHPV or control, but not all completed series

<table>
<thead>
<tr>
<th>Doses</th>
<th>Number</th>
<th>Prevalent 16/18 HPV % (95% CI)</th>
<th>Vaccine efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 doses</td>
<td>1365</td>
<td>2.0 (1.3–2.8)</td>
<td>80.0% (70.7–87.0)</td>
</tr>
<tr>
<td>2 doses</td>
<td>62</td>
<td>1.6 (0.1–7.7)</td>
<td>83.8% (19.5–99.2)</td>
</tr>
<tr>
<td>1 dose</td>
<td>112</td>
<td>1.8 (0.3–5.8)</td>
<td>82.1% (40.2–97.0)</td>
</tr>
<tr>
<td>Control</td>
<td>1783</td>
<td>10.0 (8.7–11.4)</td>
<td>Reference</td>
</tr>
</tbody>
</table>

Costa Rica Vaccine Trial (CVT): HPV 16 antibody after 1, 2 or 3 doses of 2vHPV through 11 years

- Stable HPV 16 antibody levels through 11 years post vaccination in all dose groups
- Levels at least 10-fold above those in unvaccinated

Antibody by VLP-based ELISA at the NCI HPV Immunology Laboratory
India IARC 4vHPV trial

Designed as a cluster randomized trial to compare 2 vs 3 doses of 4vHPV in 10–18 year-old unmarried girls, initiated Sept 2009

Ministry of Health order in April 2010 to stop HPV vaccination in research studies

- 2-dose Group (0,6 months)
- 3-dose Group (0,2,6 months)

Analyzed as observational cohort

1 dose
2 doses 0, 2 months
2 doses 0, ≥6 months
3 doses

IARC, International Agency for Research on Cancer
India IARC Trial: protection after 1, 2 or 3 doses of 4vHPV through 10 years

<table>
<thead>
<tr>
<th>Doses</th>
<th>Number</th>
<th>Persistent 16/18 HPV % (95% CI)</th>
<th>Vaccine efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 doses</td>
<td>1649</td>
<td>0.1 (0.0–0.4)</td>
<td>91.2% (75.3–98.7)</td>
</tr>
<tr>
<td>2 doses (0, 6 months)</td>
<td>1685</td>
<td>0.1 (0.0–0.4)</td>
<td>94.5% (82.4–99.8)</td>
</tr>
<tr>
<td>1 dose</td>
<td>2454</td>
<td>0.0 (0.0–0.3)</td>
<td>94.2% (83.7–99.1)</td>
</tr>
<tr>
<td>Control</td>
<td>1268</td>
<td>2.7 (1.9–3.7)</td>
<td>Reference</td>
</tr>
</tbody>
</table>

Post hoc analysis; women vaccinated at age 10-18 years, randomized to receive 3 or 2 4vHPV doses
Unvaccinated women age-matched to married vaccinated participants recruited as controls
Persistent infection defined as the same HPV type detected in consecutive samples at least 10 months apart
VE adjusted for background HPV infection, time between marriage and first cervical specimen collection, and number of cervical specimens per participant

KEN SHE, RCT of 1 dose of 9vHPV, 2vHPV or MCV

- 2250 Kenyan women aged 15–20 years
- 1458 evaluated for efficacy at month 18 in mITT HPV 16/18 cohort

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Number</th>
<th>Incident persistent HPV 16/18</th>
<th>Incidence/100 PY</th>
<th>Vaccine efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9vHPV</td>
<td>496</td>
<td>1</td>
<td>0.17</td>
<td>97.5% (81.7–99.7)</td>
</tr>
<tr>
<td>2vHPV</td>
<td>489</td>
<td>1</td>
<td>0.17</td>
<td>97.5% (81.6–99.7)</td>
</tr>
<tr>
<td>MCV</td>
<td>473</td>
<td>36</td>
<td>6.83</td>
<td>Reference</td>
</tr>
</tbody>
</table>

Enrollment criteria: 1-5 lifetime partners; HIV negative; enrollment between December 2018 and June 2021
MCV, meningococcal vaccine
mITT, modified intention to treat: HPV 16/18 HPV DNA negative (external genital and cervical swabs) at enrollment and month 3 (self-collected vaginal swab) and HPV antibody negative at enrollment
PY, person years

Barnabas R, et al. DOI 10.21203/rs.3.rs-1090565/v1; NEJM Evidence 2022
### mITT analysis for efficacy against HPV 16/18/31/33/45/52/58 efficacy

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<th>Vaccine</th>
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<tr>
<td>9vHPV</td>
<td>325</td>
<td>4</td>
<td>1.03</td>
<td>88.9% (68.5–96.1)</td>
</tr>
<tr>
<td>MCV</td>
<td>490</td>
<td>29</td>
<td>9.42</td>
<td>Reference</td>
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Enrollment criteria: 1-5 lifetime partners; HIV negative; enrollment between December 2018 and June 2021
MCV, meningococcal vaccine
mITT, modified intention to treat analysis
PY, person years

Barnabas R, et al. DOI 10.21203/rs.3.rs-1090565/v1; NEJM Evidence 2022
DoRIS

- **Dose Reduction Immunobridging & Safety Study**
- Randomized trial of 1, 2, 3 doses of 2vHPV or 9vHPV
- 930 Tanzanian girls aged 9–14 years

**Objectives:**
- Demonstrate non-inferiority of HPV 16/18 antibody response after 1 dose compared with 2 or 3 doses of same vaccine at month 24
- Demonstrate non-inferiority of HPV 16/18 GMCs comparing 1 dose in DoRIS with 1 dose in studies that evaluated efficacy

GMC, geometric mean concentration
## DoRIS: seroconversion results, month 24

<table>
<thead>
<tr>
<th></th>
<th>1 dose</th>
<th>2 doses</th>
<th>3 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Seropositive (%)</td>
<td>N</td>
</tr>
<tr>
<td><strong>2vHPV (Cervarix)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV-16</td>
<td>148</td>
<td>147 (99.3%)</td>
<td>141</td>
</tr>
<tr>
<td>HPV-18</td>
<td>141</td>
<td>139 (98.6%)</td>
<td>140</td>
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VLP-based ELISA at the NCI HPV Immunology Laboratory
DoRIS: seroconversion results, month 24

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<td>147 (99.3%)</td>
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<td>141 (100%)</td>
<td>141</td>
<td>141 (100%)</td>
</tr>
<tr>
<td>HPV-18</td>
<td>141</td>
<td>139 (98.6%)</td>
<td>140</td>
<td>140 (100%)</td>
<td>136</td>
<td>136 (100%)</td>
</tr>
<tr>
<td><strong>9vHPV (Gardasil-9)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV-16</td>
<td>145</td>
<td>144 (99.3%)</td>
<td>141</td>
<td>141 (100%)</td>
<td>140</td>
<td>140 (100%)</td>
</tr>
<tr>
<td>HPV-18</td>
<td>136</td>
<td>133 (97.8%)</td>
<td>136</td>
<td>136 (100%)</td>
<td>142</td>
<td>141 (99.3%)</td>
</tr>
</tbody>
</table>

- HPV 16: non-inferiority criteria met for 1 dose compared with 2 or 3, both vaccines
- HPV 18: non-inferiority criteria not met for 1 dose compared with 2 or 3 doses
DoRIS: geometric mean concentrations, 9vHPV

- 2-dose and 3-dose levels decline after peak at month 7
- 2-dose and 3 dose levels similar at month 24
- 1-dose levels lower than 2-dose or 3-dose levels; relatively stable from month 12 (plateau)

VLP-based ELISA at the NCI HPV Immunology Laboratory
DoRIS: other findings

- Avidity - no difference between dose groups or vaccines
- Immunobridging - seropositivity and GMCs were non-inferior in the 1 dose groups in DoRIS compared with those in 1-dose groups in trials where efficacy observed

Thailand Impact Study

- Observational study of 1 dose and 2 doses of 2vHPV given to Grade 8 girls (age <15 years) in two similar Thai provinces

- Primary objectives:
  - Demonstrate HPV vaccine effectiveness of 1 dose and 2 doses
    - Year 2 and Year 4 post-vaccination
    - Measured by comparing vaccine-type HPV prevalence* in years 2 and 4 vs unvaccinated same grade students in baseline survey
  - Evaluate if vaccine effectiveness of 1 dose is non-inferior to 2 doses
    - Year 4 post-vaccination

*Measured in urine, by COBAS
Modeling and health economic data

- Compared to no vaccination, 1-dose HPV vaccination yields substantial health benefits and is good value for money, even if efficacy is lower (80-85% vs 100%) and duration of protection is shorter (10-20 years vs lifelong) than with 2 doses.

- Impact and cost-effectiveness of adding a second dose is driven by duration of protection, and, possibly, the ability to achieve higher coverage or expand catch-up with 1-dose versus 2 or 3 doses.

- Projected impact and cost-effectiveness of 1-dose versus 2-dose 9vHPV vaccination in 192 countries using a comparative modeling approach (Public Health England, HPV-ADVISE, and Harvard models) has been conducted.

Burger E, et al. Health and economic benefits of single-dose HPV vaccination in a GAVI-eligible country. Vaccine 2018
“On the basis of the recent data on efficacy and effectiveness, SAGE endorsed the optimization of the HPV vaccine schedules. For 9–14-year-olds, national immunization programmes can use either a single-dose or a 2-dose vaccination schedule with an interval between doses of at least 6 months.”

“This off-label option for routine and multi-age cohort (MAC) catch-up vaccination is recommended from a public health perspective, on the basis of providing comparable levels of individual protection while being more cost-effective and efficient (fewer doses per cancer case prevented), providing more programme flexibility, and enabling the expansion of the MACs targeted.”
### 2017 WHO and 2022 SAGE recommendations regarding number of HPV vaccine doses

<table>
<thead>
<tr>
<th>2017 WHO recommendations (current)(^1)</th>
<th>2022 SAGE recommendations(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary age group</strong></td>
<td></td>
</tr>
<tr>
<td>Girls aged 9-14 years</td>
<td>Girls aged 9-14 years</td>
</tr>
<tr>
<td><strong>Vaccination Schedule</strong></td>
<td></td>
</tr>
<tr>
<td>9-14 years</td>
<td>2-dose schedule</td>
</tr>
<tr>
<td>Either a 1-dose* or a 2-dose schedule can be used</td>
<td></td>
</tr>
<tr>
<td>15-20 years</td>
<td>3-dose schedule</td>
</tr>
<tr>
<td>Either a 1-dose* or a 2-dose schedule can be used</td>
<td></td>
</tr>
<tr>
<td>≥21 years</td>
<td>3-dose schedule</td>
</tr>
<tr>
<td>2-dose schedule can be used</td>
<td></td>
</tr>
<tr>
<td>Immuno-compromised</td>
<td>3-dose schedule</td>
</tr>
<tr>
<td>at least 2 doses but ideally 3 doses, if programmatically feasible</td>
<td></td>
</tr>
</tbody>
</table>


2 Meeting of the Strategic Advisory Group of Experts on Immunization, April 2022: conclusions and recommendations. WER 2022;97:261–276

* For products for which efficacy data is available, or immunogenicity has been bridged to vaccines with proven single-dose efficacy.
### Selected other trials evaluating 1-dose HPV vaccination, data forthcoming

<table>
<thead>
<tr>
<th>Trial/country</th>
<th>Evidence</th>
<th>Vaccine</th>
<th>Age (yrs) at vaccination</th>
<th>Description</th>
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</thead>
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<tr>
<td>HOPE South Africa</td>
<td>Impact/Effectiveness</td>
<td>2vHPV</td>
<td>15–16</td>
<td>Students in one district received 1 dose as catch-up in grade 10. Baseline and post-vaccination cross sectional prevalence surveys; includes WLWH</td>
</tr>
<tr>
<td>HANDS The Gambia</td>
<td>Immunogenicity</td>
<td>9vHPV</td>
<td>4–8, 9–14, 15–26</td>
<td>Randomized to 1 or 2 doses 3 doses in 15–26-year-olds</td>
</tr>
<tr>
<td>ESCUDDO Costa Rica</td>
<td>Efficacy/Immunogenicity</td>
<td>2vHPV, 9vHPV</td>
<td>12–16</td>
<td>Randomized trial: 1 or 2 doses of 2vHPV or 9vHPV</td>
</tr>
</tbody>
</table>

WLWH, women living with HIV; RCT, randomized controlled trial. All studies conducted among girls/women.
Summary

- HPV vaccines were first studied and licensed in a 3-dose schedule in persons aged 9–26 years and later in a 2-dose schedule in persons aged 9–14 years.
- There are now data on 1-dose HPV vaccination, including efficacy data from a randomized controlled trial with 18-month follow-up.
- Long term follow-up from other studies suggest good duration of protection (>10 years) with 1 dose.
- SAGE recommends 1 or 2 doses in the primary target age groups; WHO will consider and revise recommendations later this year.
- No regulatory approval for 1-dose HPV vaccination in any age group or for 2-dose vaccination in age groups >14 years.
- HPV Team in the Division of Viral Diseases/NCIRD will continue to
  - Provide updates on these data and discuss with ACIP as requested
  - Collaborate with and provide assistance to international partners.
For more information, contact CDC
1-800-CDC-INFO (232-4636)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.