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

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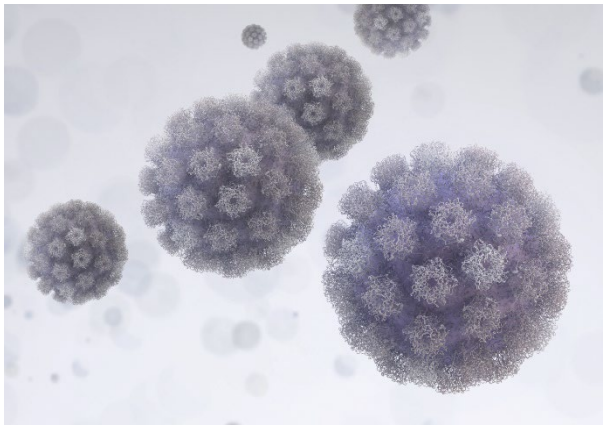
Advisory Committee on Immunization Practices
June 23, 2022



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

SAGE, Strategic Advisory Group of Experts on Immunization

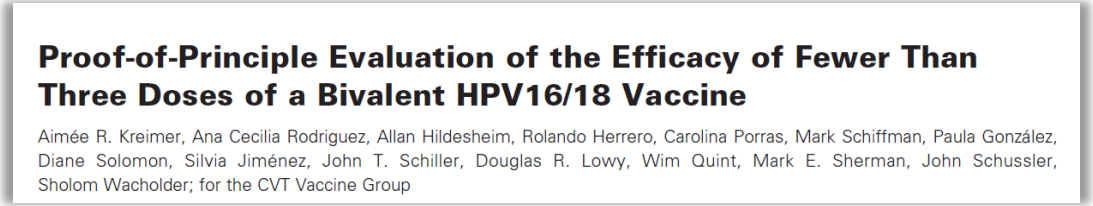
Efficacy and immunogenicity data for initial licensure of HPV vaccines, 3-dose schedules (0, 1-2, 6 months)

- **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

*Future II Study Group, NEJM 2007; Garland S, et al. NEJM 2007; Paavonen J, et al. Lancet 2007
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

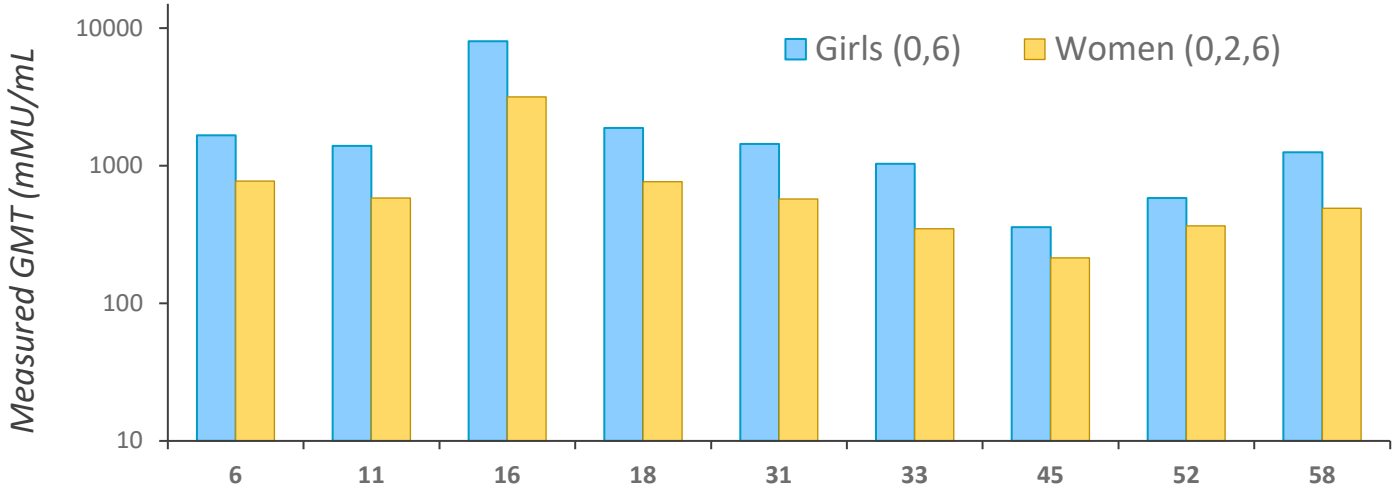
Aimée R. Kreimer, Ana Cecilia Rodriguez, Allan Hildesheim, Rolando Herrero, Carolina Porras, Mark Schiffman, Paula González, Diane Solomon, Silvia Jiménez, John T. Schiller, Douglas R. Lowy, Wim Quint, Mark E. Sherman, John Schussler, Sholom Wacholder; for the CVT Vaccine Group

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)

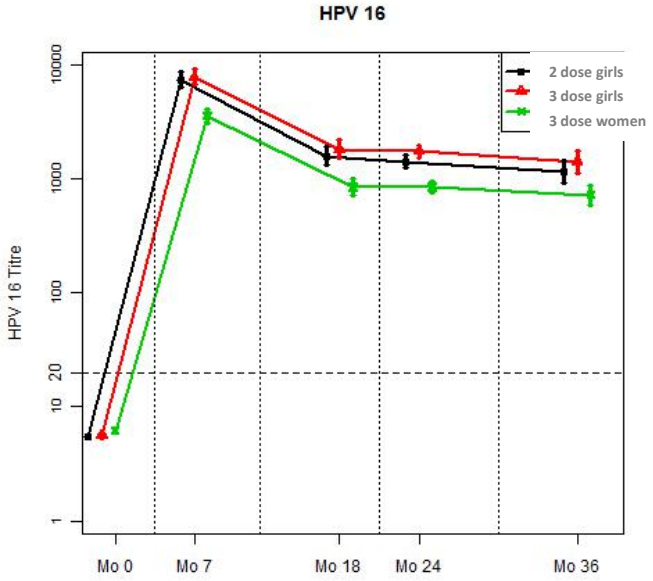


Fold difference (girls/women)	2.15	2.39	2.54	2.46	2.51	2.96	1.67	1.60	2.55
95% CI	*(1.83, 2.53)*	*(2.03, 2.82)*	*(2.14, 3.00)*	*(2.05, 2.96)*	*(2.10, 3.00)*	*(2.50, 3.50)*	*(1.38, 2.03)*	*(1.36, 1.87)*	*(2.15, 3.01)*

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**

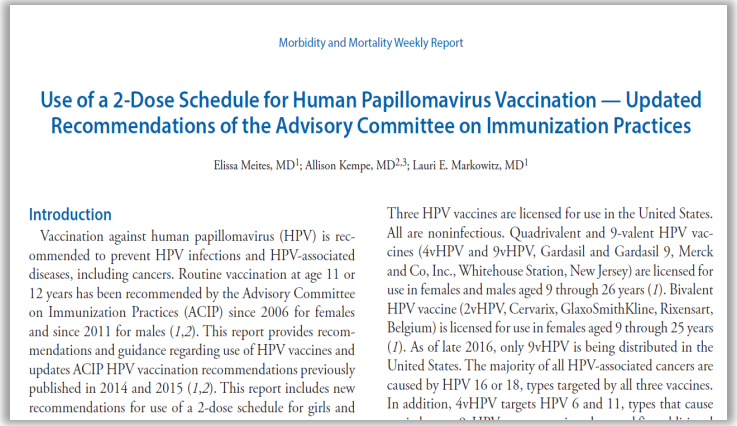


Dashed line is serostatus cut-off
Antibody measured by cLIA

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



Morbidity and Mortality Weekly Report

Use of a 2-Dose Schedule for Human Papillomavirus Vaccination — Updated Recommendations of the Advisory Committee on Immunization Practices

Elissa Meites, MD[1]; Allison Kempe, MD[2,3]; Lauri E. Markowitz, MD[1]

Introduction

Vaccination against human papillomavirus (HPV) is recommended to prevent HPV infections and HPV-associated diseases, including cancers. Routine vaccination at age 11 or 12 years has been recommended by the Advisory Committee on Immunization Practices (ACIP) since 2006 for females and since 2011 for males (*1*,*2*). This report provides recommendations and guidance regarding use of HPV vaccines and updates ACIP HPV vaccination recommendations previously published in 2014 and 2015 (*1*,*2*). This report includes new recommendations for use of a 2-dose schedule for girls and

Three HPV vaccines are licensed for use in the United States. All are noninfectious. Quadrivalent and 9-valent HPV vaccines (4vHPV and 9vHPV, Gardasil and Gardasil 9, Merck and Co, Inc., Whitehouse Station, New Jersey) are licensed for use in females and males aged 9 through 26 years (*1*). Bivalent HPV vaccine (2vHPV, Cervarix, GlaxoSmithKline, Rixensart, Belgium) is licensed for use in females aged 9 through 25 years (*1*). As of late 2016, only 9vHPV is being distributed in the United States. The majority of all HPV-associated cancers are caused by HPV 16 or 18, types targeted by all three vaccines. In addition, 4vHPV targets HPV 6 and 11, types that cause

sBLA, Supplemental Biologics Licensure Application

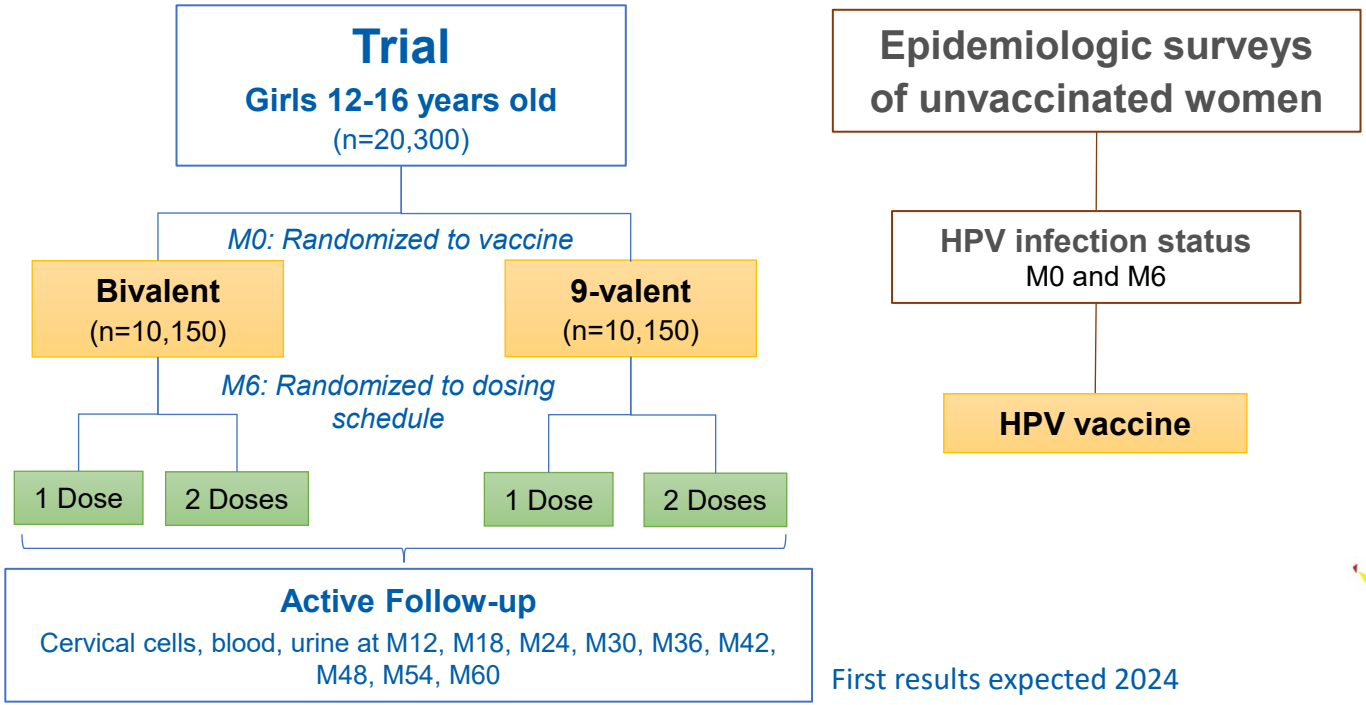
Evidence on 1-dose HPV vaccination

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



Porras, et al. Vaccine 2022

First results expected 2024

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

[1] WHO. Global Market Study, HPV. who-hpv-vaccine-global-market-study-april-2022.pdf
[2] Bruni L, et al. Preventive Medicine 2019

Trials with data on 1-dose HPV vaccination

Trial/country	Evidence	Vaccine	Age (yrs) at vaccination	Description
CVT Costa Rica	Efficacy/ Immunogenicity	2vHPV	18–25	Post-hoc analyses: participants randomized to 3 doses or control, but analyzed as 1-, 2-, 3-dose groups
India IARC India	Efficacy/ Immunogenicity	4vHPV	10–18	Post-hoc analyses: participants randomized to 2 or 3 doses but analyzed as 1-, 2-, 3-dose groups
KEN SHE Kenya	Efficacy	2vHPV 9vHPV	15–20	Randomized trial: 1 dose of 2vHPV, 9vHPV, meningococcal vaccine
DoRIS Tanzania	Immunogenicity	2vHPV 9vHPV	9–14	Randomized trial: 1-, 2-, 3-dose groups
Thailand Impact Thailand	Impact/ effectiveness	2vHPV	grade 8	Students in one province received 1 dose; in another 2 doses

CVT, Costa Rica Vaccine Trial; IARC, International Agency for Research on Cancer. All studies conducted among girls/women

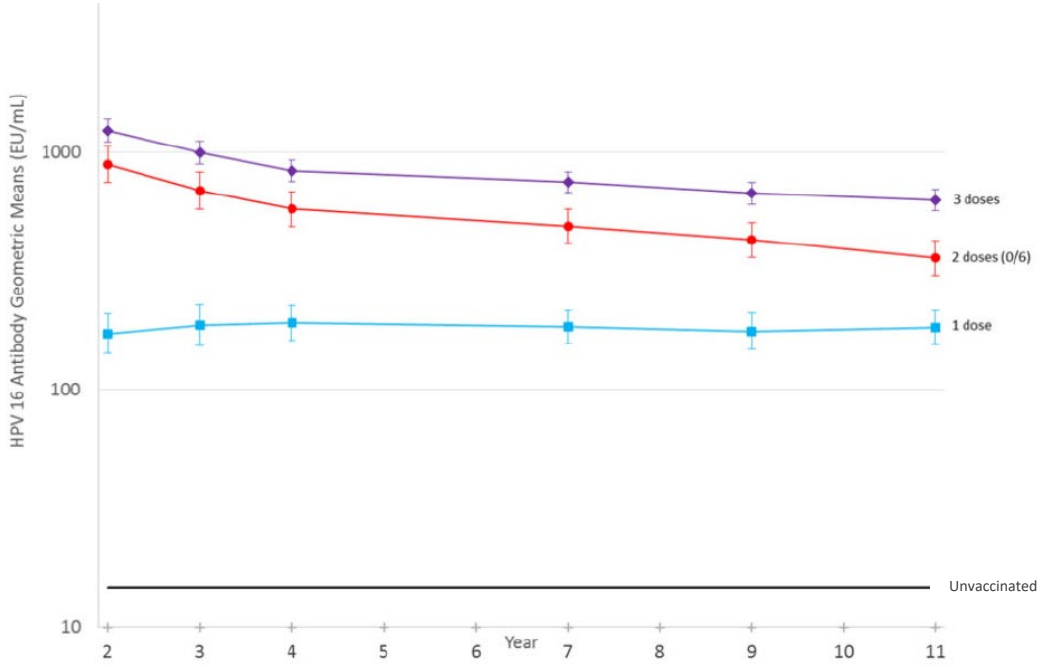
Costa Rica Vaccine Trial (CVT): protection after 1, 2 or 3 doses of 2vHPV through 11 years

- 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

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

Kreimer AR, et al. J Natl Cancer Inst 2020

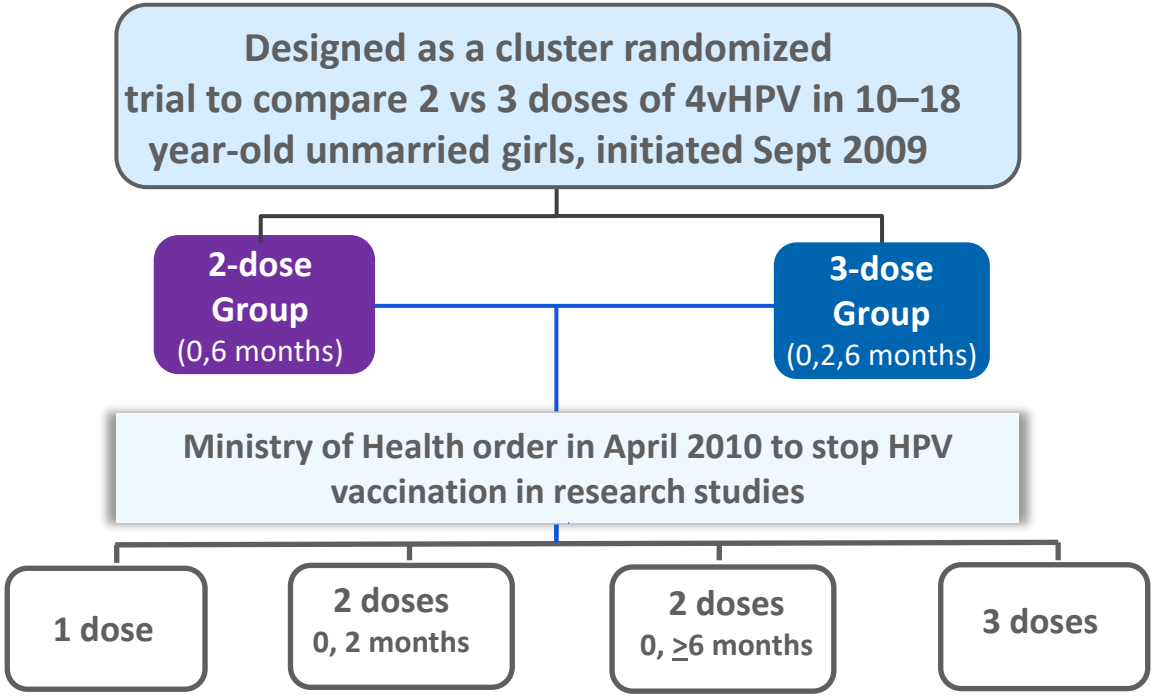
Costa Rica Vaccine Trial (CVT): HPV 16 antibody after 1, 2 or 3 doses of 2vHPV through 11 years



- 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
Kreimer AR, et al. J Natl Cancer Inst 2020

India IARC 4vHPV trial



Analyzed as observational cohort

IARC, International Agency for Research on Cancer
Sankaranarayanan R, et al. Lancet Oncol 2016

India IARC Trial: protection after 1, 2 or 3 doses of 4vHPV through 10 years

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

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

Basu P, et al. Lancet Oncology 2021, with updated data

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

Vaccine	Number	Incident persistent HPV 16/18	Incidence/ 100 PY	Vaccine efficacy % (95% CI)
9vHPV	496	1	0.17	**97.5%** (81.7–99.7)
2vHPV	489	1	0.17	**97.5%** (81.6–99.7
MCV	473	36	6.83	Reference

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

KEN SHE

- mITT analysis for efficacy against HPV 16/18/31/33/45/52/58 efficacy

Vaccine	Number	Incident persistent HPV	Incidence/ 100 PY	Vaccine efficacy % (95% CI)
9vHPV	325	4	1.03	**88.9%** (68.5–96.1)
MCV	490	29	9.42	Reference

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

- **Do**se **R**eduction **I**mmunobridging & **S**afety 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

	1 dose		2 doses		3 doses	
	N	Seropositive (%)	N	Seropositive (%)	N	Seropositive (%)
		2vHPV **(Cervarix)**				
HPV-16	148	147 (99.3%)	141	141 (100%)	141	141 (100%)
HPV-18	141	139 (98.6%)	140	140 (100%)	136	136 (100%)

VLP-based ELISA at the NCI HPV Immunology Laboratory
Watson-Jones D, et al. http://dx.doi.org/10.2139/ssrn.4055429

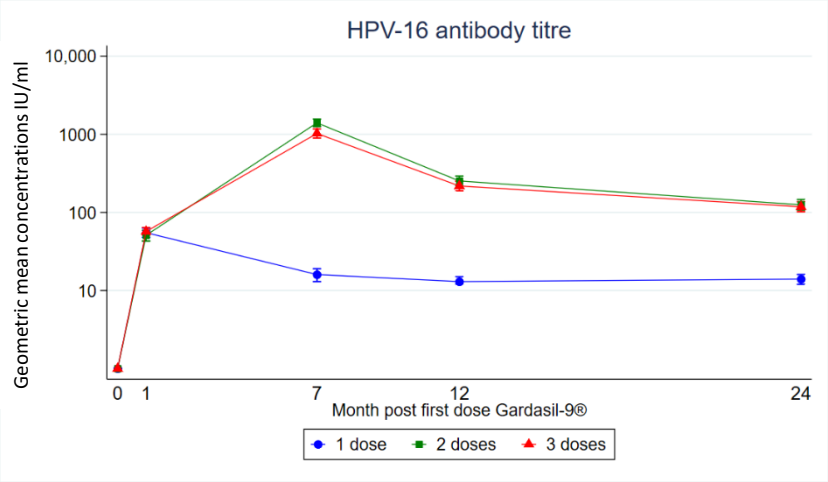
DoRIS: seroconversion results, month 24

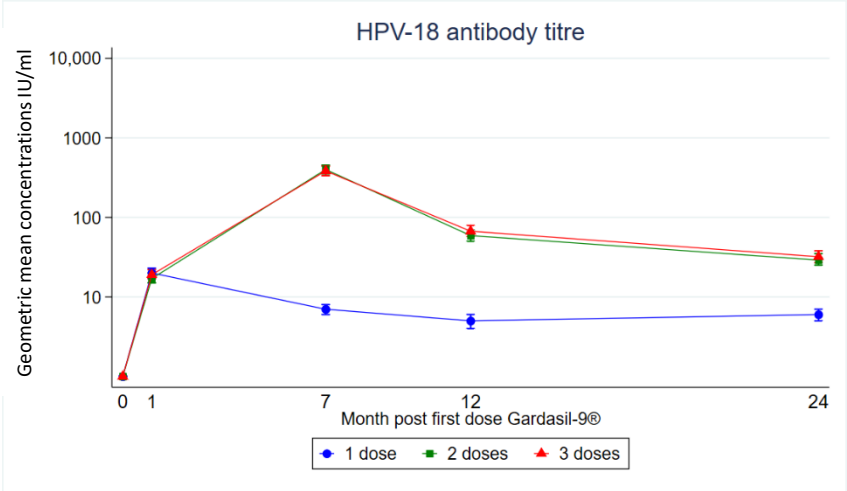
	1 dose		2 doses		3 doses	
	N	Seropositive (%)	N	Seropositive (%)	N	Seropositive (%)
		2vHPV **(Cervarix)**				
HPV-16	148	147 (99.3%)	141	141 (100%)	141	141 (100%)
HPV-18	141	139 (98.6%)	140	140 (100%)	136	136 (100%)
		9vHPV **(Gardasil-9)**				
HPV-16	145	144 (99.3%)	141	141 (100%)	140	140 (100%)
HPV-18	136	133 (97.8%)	136	136 (100%)	142	141 (99.3%)

- 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

VLP-based ELISA at the NCI HPV Immunology Laboratory
Watson-Jones D, et al. http://dx.doi.org/10.2139/ssrn.4055429

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
Watson-Jones D, et al. http://dx.doi.org/10.2139/ssrn.4055429

DoRIS: other findings

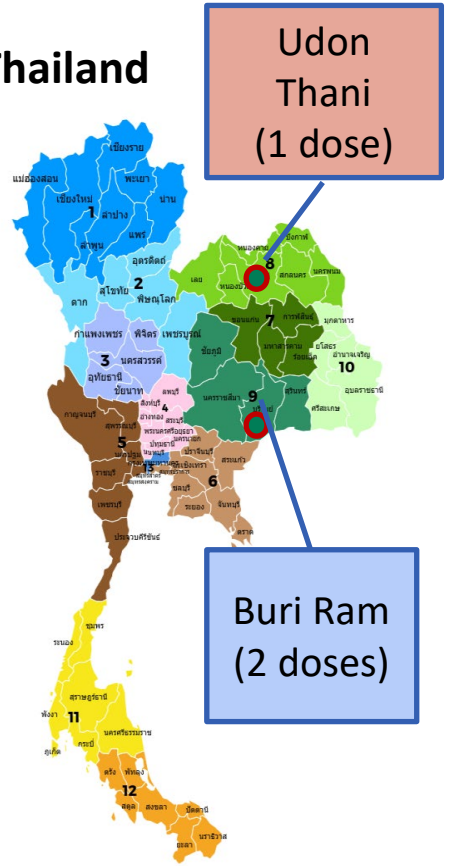
- Avidity - no difference between dose groups or vaccines
- Immunobridging - seropositivity and GMCs were non-inferior in the 1 dose groups in DoRIS compared with those in 1-dose groups in trials where efficacy observed

Watson-Jones D, et al. http://dx.doi.org/10.2139/ssrn.4055429

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

Jit M, et al. Fewer than three doses of HPV vaccine. Lancet Oncol 2015
Burger E, et al. Health and economic benefits of single-dose HPV vaccination in a GAVI-eligible country. Vaccine 2018
Prem K, et al. Global impact and cost-effectiveness of one-dose versus two-dose human papillomavirus vaccination schedules: a comparative modelling analysis. medRxiv. 2021:2021.02.08.21251186. https://terrance.who.int/mediacentre/data/sage/SAGE_Slidedeck_Apr2022.pdf

2022, 97, 261–276 No 24

World Health Organization

Organisation mondiale de la Santé

Weekly epidemiological record

Relevé épidémiologique hebdomadaire

17 JUNE 2022, 97th YEAR / 17 JUIN 2022, 97e ANNÉE

No 24, 2022, 97, 261–276

http://www.who.int/wer

Contents

261 Meeting of the Strategic Advisory Group of Experts on Immunization, April 2022: conclusions and recommendations

Sommaire

261 Réunion du Groupe stratégique consultatif d'experts sur la vaccination, avril 2022: conclusions et recommandations

Meeting of the Strategic Advisory Group of Experts on Immunization, April 2022: conclusions and recommendations

The Strategic Advisory Group of Experts (SAGE) on Immunization met on 4–7 April 2022. This report summarizes their discussions, conclusions, and recommendations.

"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."

Meeting of the Strategic Advisory Group of Experts on Immunization, April 2022: conclusions and recommendations https://apps.who.int/iris/bitstream/handle/10665/356579/WER9724-eng-fre.pdf

2017 WHO and 2022 SAGE recommendations regarding number of HPV vaccine doses

2017 WHO recommendations (current)[1]			2022 SAGE recommendations[2]
Primary age group		Girls aged 9-14 years	Girls aged 9-14 years
Vaccination Schedule	**9-14 years**	2-dose schedule	Either a 1-dose* or a 2-dose schedule can be used
	15-20 years	3-dose schedule	Either a 1-dose* or a 2-dose schedule can be used
	≧21 years	3-dose schedule	2-dose schedule can be used
	Immuno-compromised	3-dose schedule	at least 2 doses but ideally 3 doses, if programmatically feasible

[1]Human papillomavirus vaccines: WHO position paper, May 2017. WER 2017;92:241–268

[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

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

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

Thank You

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov