

Introduction to policy considerations: Reduced number of HPV vaccine doses

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Advisory Committee on Immunization Practices
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Outline

- **Brief introduction to human papillomavirus (HPV)**
- **HPV vaccines and vaccination recommendations in the United States**
- **Overview of data on vaccination with a reduced number of doses**
- **World Health Organization recommendations and international landscape**

Introduction

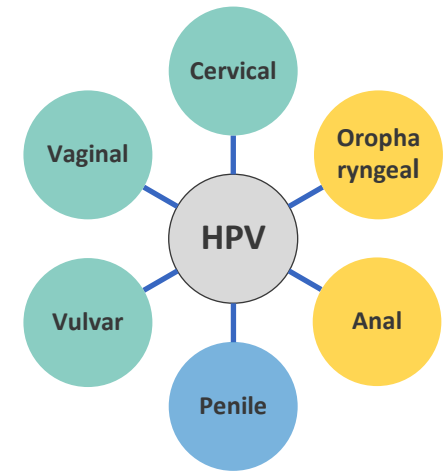
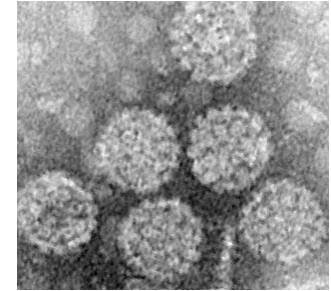
18 years since first HPV vaccine licensure

- High vaccine efficacy in clinical trials
- High population impact in real world settings
- Strong herd effects of vaccination programs
- Implementation challenges in many countries
- Lag in vaccine introduction in low- and middle-income countries

**[HPV VACCINE IS
CANCER PREVENTION.]**

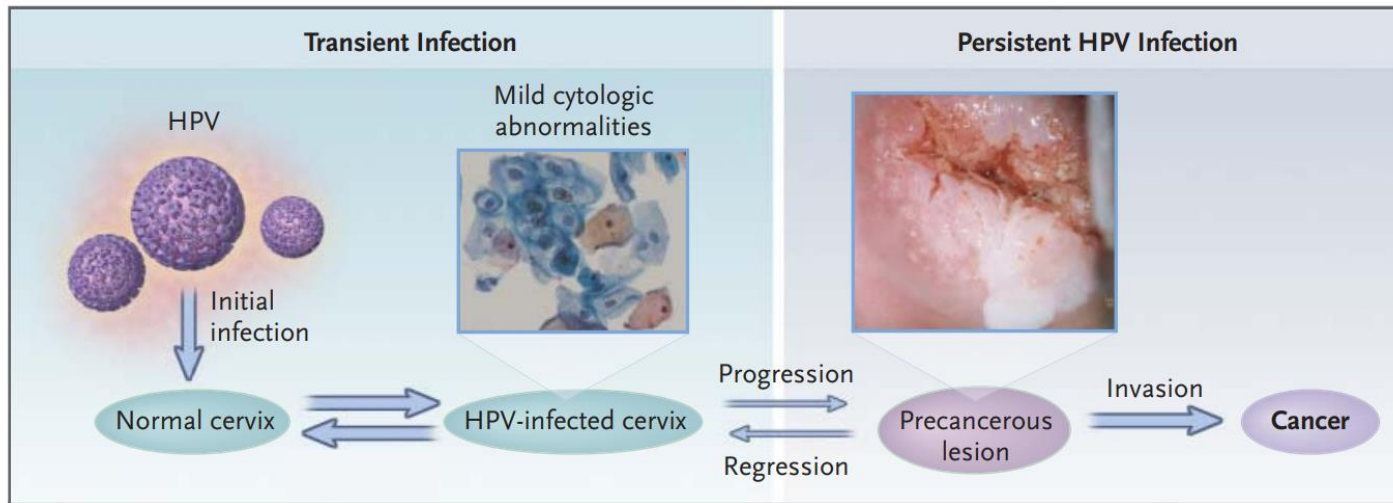
Human papillomaviruses

- **Double-stranded DNA virus (8 kb circular genome)**
- **> 200 closely related types**
 - L1 is major capsid protein
 - Sequence of L1 gene determines type
- **12 types classified as high-risk (oncogenic)**
 - HPV 16 and HPV 18 responsible for most HPV-attributable cancer
- **Low-risk HPV types**
 - HPV 6 and HPV 11 cause most anogenital warts and recurrent respiratory papillomatosis
- **Most common sexually transmitted infection**
 - ~ 13 million persons in the United States become infected with a disease-causing HPV type each year
 - Over 90% become undetectable in 2 years



HPV-attributable cancer

HPV infection causes cervical cancer (and other cancers) after years to decades



HPV-associated and estimated HPV-attributable cancer cases per year, United States, 2017–2021

Cancer site	Number of HPV-associated cancers	Percentage probably caused by any HPV type	Estimated number probably caused by any HPV type*		
			Female	Male	Both sexes
Cervix	11,959	91%	10,800	-	10,800
Vagina	898	75%	700	-	700
Vulva	4,418	69%	2,900	-	2,900
Penis	1,381	63%	-	900	900
Anus**	7,854	91%	5,000	2,200	7,200
Oropharynx	21,474	70%	2,300	12,900	15,200
TOTAL	47,984	79%	21,800	16,000	37,800

*Estimates were rounded to the nearest 100. Estimated counts might not sum to total because of rounding.

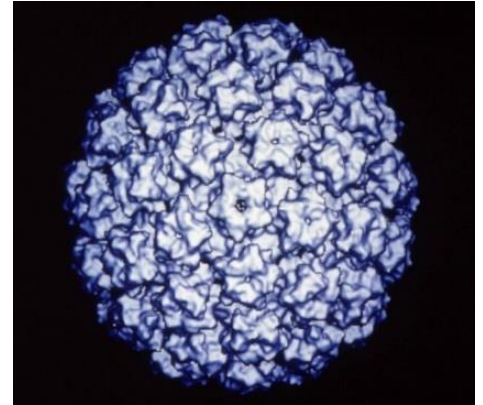
**Includes anal and rectal squamous cell carcinomas

Sources: [Cancers Linked With HPV Each Year](#) | [Cancer](#) | [CDC](#) and <http://www.cdc.gov/cancer/dataviz>

HPV vaccines and recommendations

Available prophylactic HPV vaccines

- Virus-like particle (VLP) vaccines
- L1 major capsid proteins self-assemble into VLPs
- High efficacy with durable protection



HPV VLP

HPV vaccines licensed in the United States

Vaccine and brand name	Bivalent (2vHPV) Cervarix	Quadrivalent (4vHPV) Gardasil	9-valent (9vHPV) Gardasil 9
Types	16, 18	16, 18, 6, 11	16, 18, 6, 11 31, 33, 45, 52, 58
Prevents	cancer	cancer anogenital warts	cancer anogenital warts
Adjuvant	AS04 500 µg aluminum hydroxide 50 µg 3-O-desacyl-4' monophosphoryl lipid A	AAHS 225 µg amorphous aluminum hydroxyphosphate sulfate	AAHS 500 µg amorphous aluminum hydroxyphosphate sulfate
Year licensed	2009	2006	2014
Manufacturer	GlaxoSmithKline	Merck & Co.	Merck & Co.

HPV 16 and 18 are oncogenic types that cause most HPV-attributable cancers; HPV 31,33,45,52,58 are oncogenic types that cause about 12% of HPV-attributable cancers; HPV 6,11 cause most anogenital warts and recurrent respiratory papillomatosis

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After the end of 2016, only 9vHPV available in the United States

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

Randomized controlled efficacy trials in ~15–26-year-old women

Endpoints:

- cervical precancers and external genital lesions

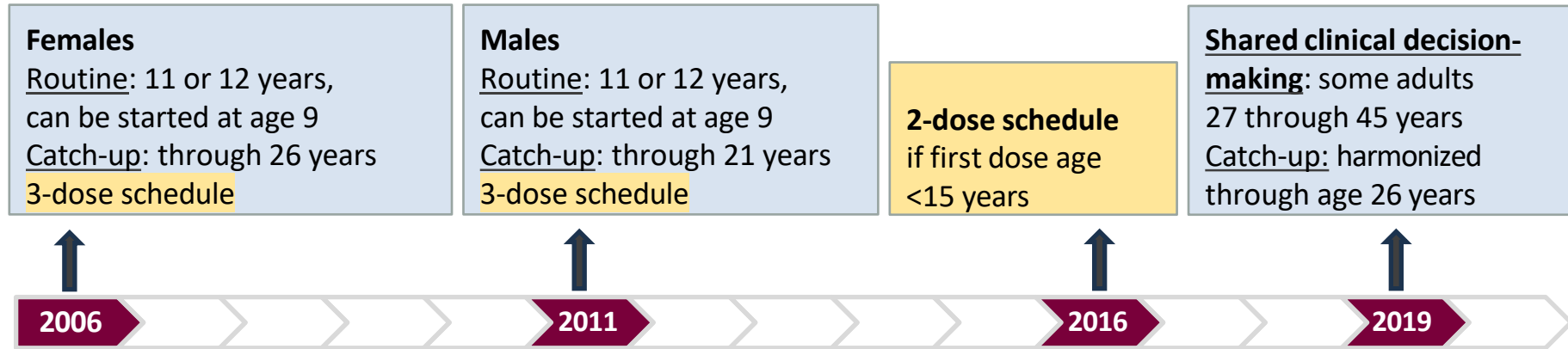
Per protocol analyses:

- efficacy >96%
- seroconversion ~ 100%

Immunobridging trials in 9–15-year-olds

Licensure based on non-inferior antibody response compared with women in efficacy trials

Evolution of HPV vaccination recommendations – United States



Current HPV vaccination recommendations, United States

Routine vaccination

- Age 11 or 12 years
- Can be started at age 9 years

Catch-up vaccination

- Through age 26 years

Shared clinical decision-making

- Age 27–45 years

Number of doses

2 doses (0, 6-12 months)
if starting series before 15th birthday

3 doses (0,1-2, 6 months)
if starting series on or after 15th birthday or
if immunocompromising condition

How did we get to 2 doses?

- **Post hoc analyses of a 3-dose randomized trial (2vHPV vs control vaccine)**
 - Not all participants completed 3-dose schedule
 - Efficacy against HPV16/18 infection similar after 3, 2, 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 Rodríguez, 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



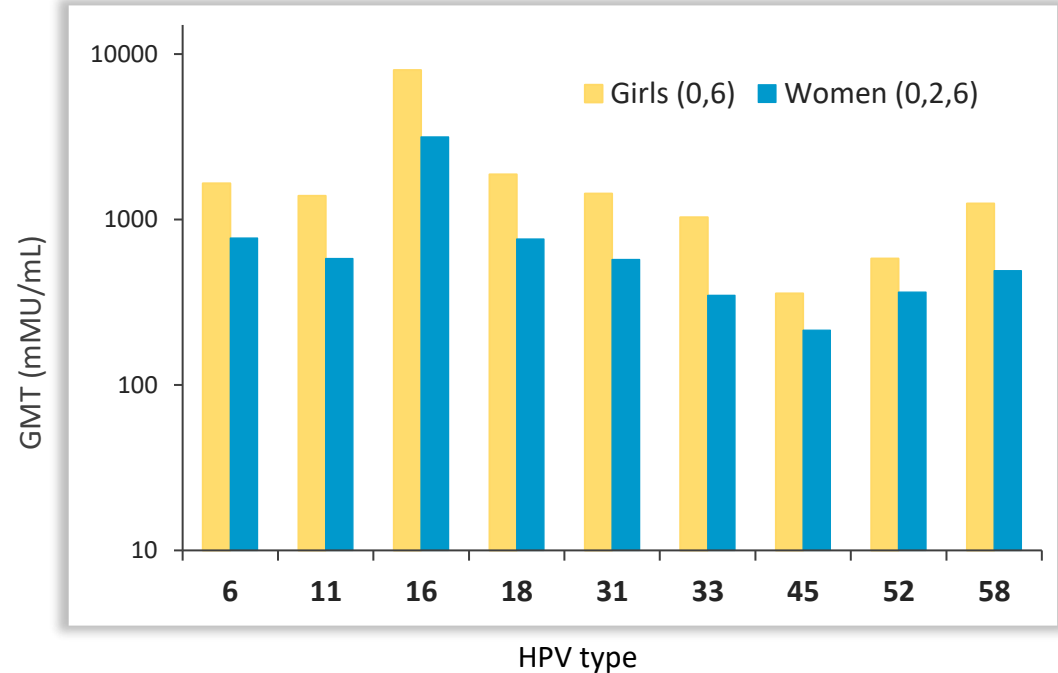
- **Immunobridging trials**
 - **2 doses** in 9–14-year-olds vs **3 doses** in young adult women
 - Seroconversion and GMTs were non-inferior in 2-dose group

Data from 9vHPV immunobridging trial

2 doses (0,6 or 0,12 months) in adolescents (9-14 years)

compared with

3 doses (0,2,6 months) in women (16-26 years)



Similar findings for 2vHPV and 4vHPV: Romanowski, Hum Vaccin Immunother 2016; Puthanakit, JID 2016; Lazcano-Ponce, Vaccine 2014; Dobson, JAMA 2013; Hernández-Ávila, Hum Vaccin Immunother 2016; Iversen et al. JAMA 2017

Iversen et al. JAMA 2017

Licensure and recommendations for a 2-dose HPV vaccination schedule

Manufacturers submitted supplemental applications for 2 doses in 9–14-yr-olds



FDA and other regulatory authorities approved

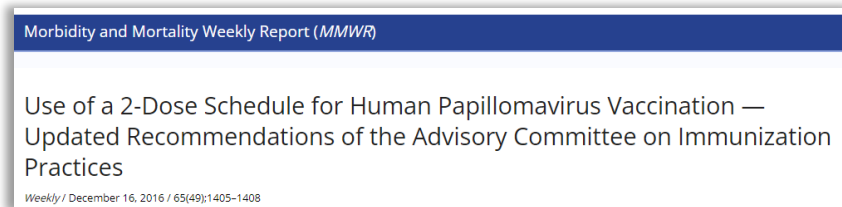


WHO, ACIP, other advisory groups recommended a 2-dose series at 9–14 years

2014



2016



Evidence on single-dose vaccination

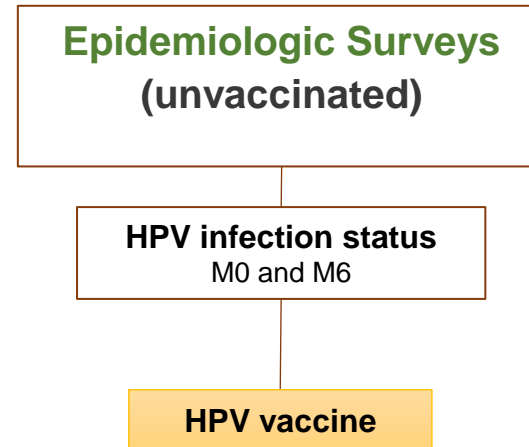
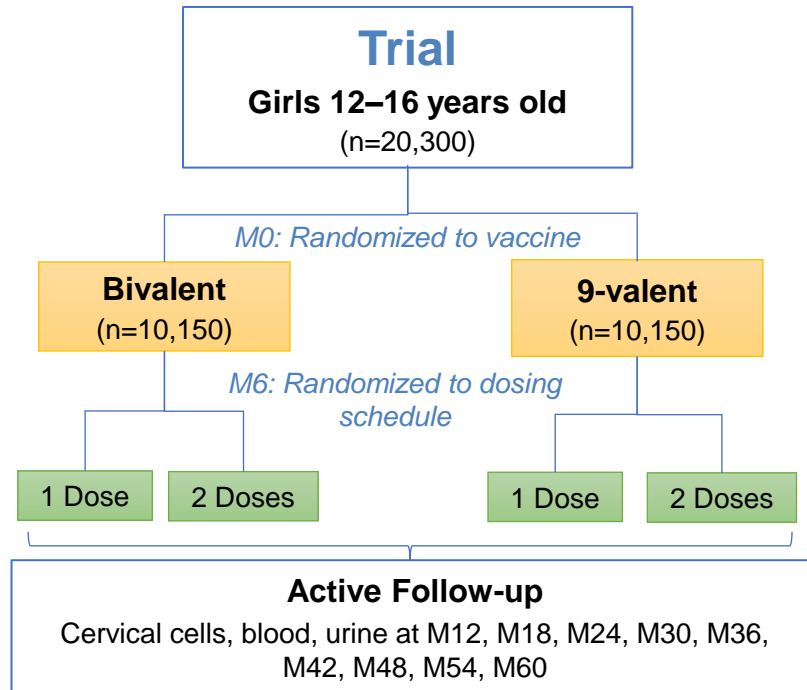
Single-dose HPV vaccination – initial interest

- Stimulated by same studies that led to 2-dose schedules
- Immunobridging trials not possible for single-dose
 - Single 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



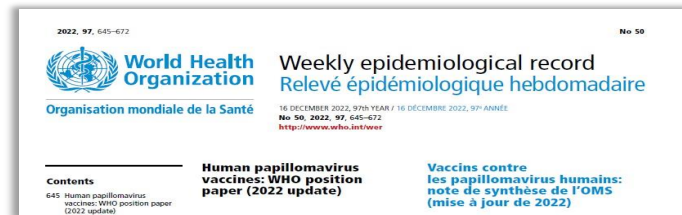
ESCUDDO, Costa Rica (data available 2025)

- Randomized trial to evaluate non-inferiority of one vs two doses of 2vHPV (Cervarix) and 9vHPV (Gardasil 9) for prevention of new cervical HPV16/18 infections that persist at least 6 months
- Evaluate one dose compared to zero doses



Single-dose HPV vaccination – increasing interest

- Studies that initially provided data had further encouraging data
- Recognition of a global HPV vaccine supply/demand imbalance
- Additional studies were planned and conducted
- Review of data led to revised World Health Organization recommendations including, “as an off-label option, a single-dose schedule can be used in girls and boys aged 9–20 years.”



Trials with data on single-dose HPV vaccination considered by the World Health Organization in 2022

Trial/country	Evidence	Vaccine	Age (yrs) at vaccination	Description
CVT Costa Rica	Efficacy/ Immunogenicity	2vHPV	18–25	<u>Post-hoc analyses</u> Original trial: randomized to 3 doses or control, but analyzed as 1-, 2-, 3-dose groups
IARC-India India	Efficacy/ Immunogenicity	4vHPV	10–18	<u>Post-hoc analyses</u> Original trial: randomized to 2 or 3 doses but analyzed as 1-, 2-, 3-dose groups
KEN SHE Kenya	Efficacy	2vHPV 9vHPV	15–20	<u>Randomized trial</u> 1 dose 2vHPV, 9vHPV or MCV
DoRIS Tanzania	Immunogenicity	2vHPV 9vHPV	9–14	<u>Randomized trial</u> 1-, 2-, 3-dose groups

Costa Rica Vaccine Trial (CVT)

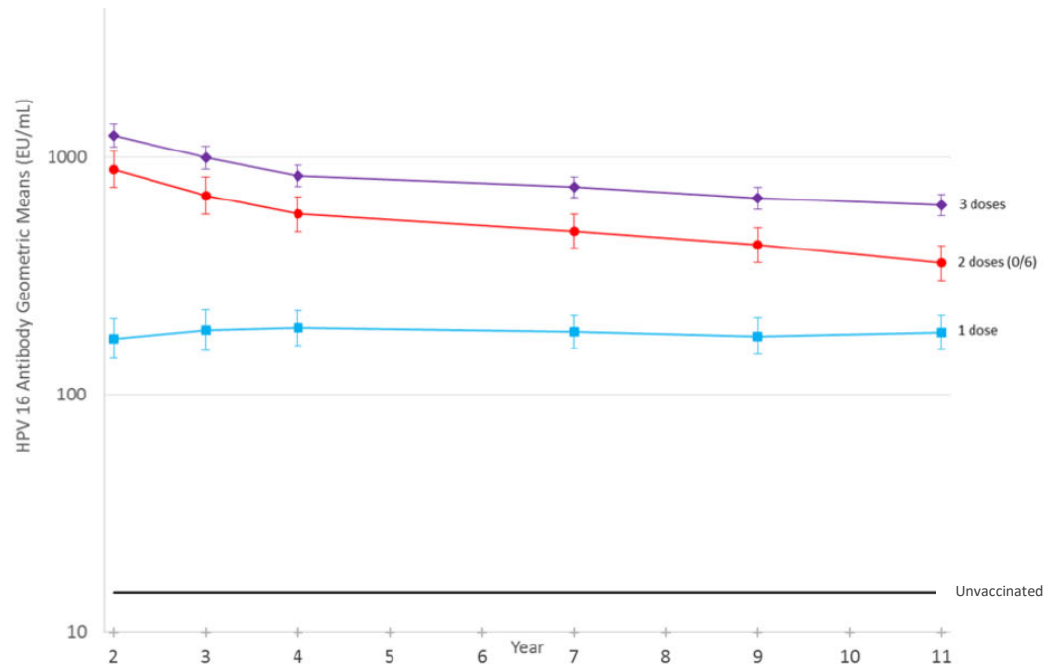
Protection against prevalent HPV after 2vHPV, through 11 years

- Post-hoc analysis of RCT: females vaccinated at age 18–25 years
- Randomized to receive 3 doses of 2vHPV or control vaccine

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)
Unvaccinated	1783	10.0 (8.7–11.4)	Reference

Costa Rica Vaccine Trial (CVT)

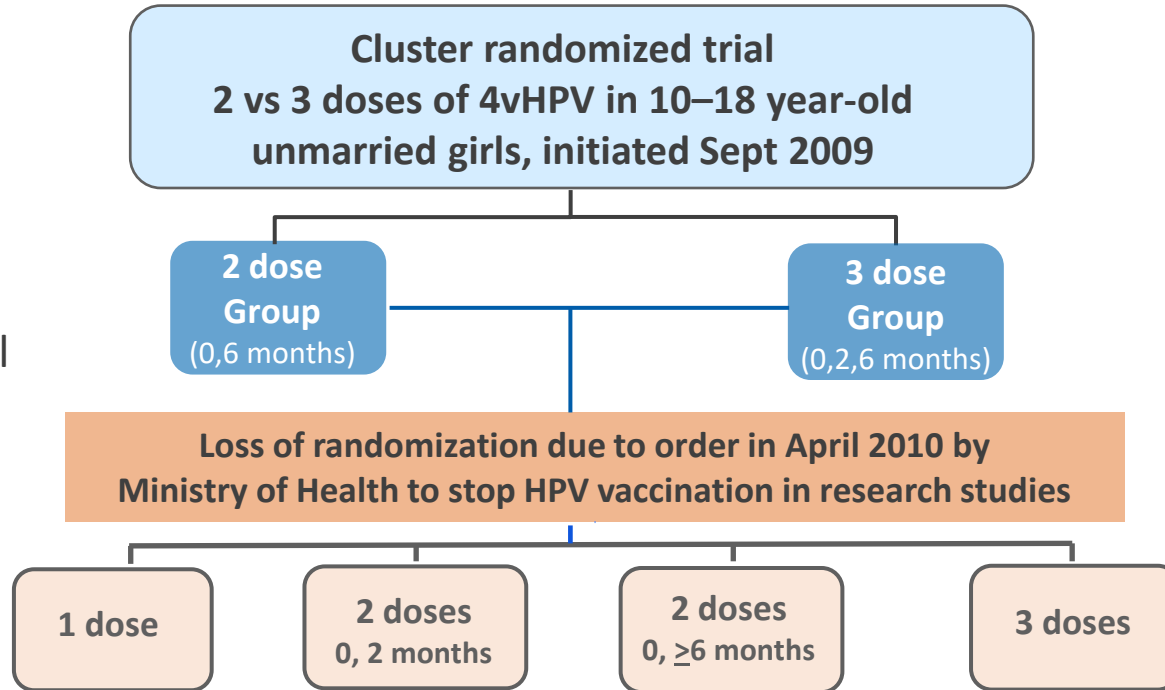
HPV 16 antibody after 1, 2 or 3 doses of 2vHPV, through 11 years



- Stable HPV 16 and 18 antibody levels through 11 years post vaccination with all dosing schedules
- 1 dose levels at least 10-fold above level at enrollment among unvaccinated

IARC-India Trial: provides data on immunogenicity and efficacy of 1, 2 and 3 doses of 4vHPV (Gardasil)

Randomized trial design lost and analyzed as observational cohort



IARC-India Trial

Protection after 1, 2 or 3 doses of 4vHPV, through 10 years

- Post hoc analysis of randomized trial: females vaccinated at age 10–18 years
- Randomized to receive 2 or 3 doses 4vHPV

Doses	Number	Persistent HPV16/18		Vaccine efficacy % (95% CI)
		Events	%	
3 doses	1460	1	0.07	93.3% (77.5–99.9)
2 doses	1452	1	0.07	93.1% (77.3–99.8)
1 dose	2135	1	0.05	95.4% (85.0–99.9)
Control	1260	32	2.54	Reference

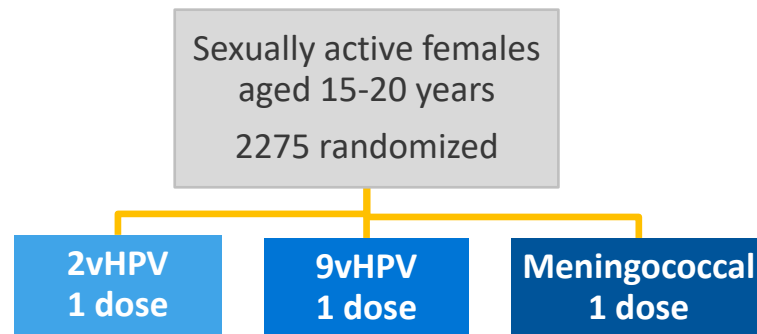
Unvaccinated women age-matched to married vaccinated participants recruited as controls

Persistent infection defined as the same HPV type detected in consecutive samples at least 10 months apart

VE adjusted for background HPV infection frequency, time between date of marriage and first cervical specimen collection, and number of cervical specimens per participant

KEN SHE Trial - Kenya

- Double-blind, RCT
- Sexually active females aged 15-20 years
- Trial groups
 - 2vHPV (Cervarix)
 - 9vHPV (Gardasil 9)
 - Meningococcal (delayed HPV vaccination)
- Primary objectives
 - Efficacy in preventing incident persistent infection*
 - HPV-16/18
 - HPV-16/18/31/33/45/52/58



*Defined as vaccine-type specific HPV detected at two consecutive time points no less than 4 months apart
Barnabas R, et al. NEJM Evidence 2022

KEN SHE: RCT of single-dose HPV vaccination

Incident persistent 16/18 infections and vaccine efficacy

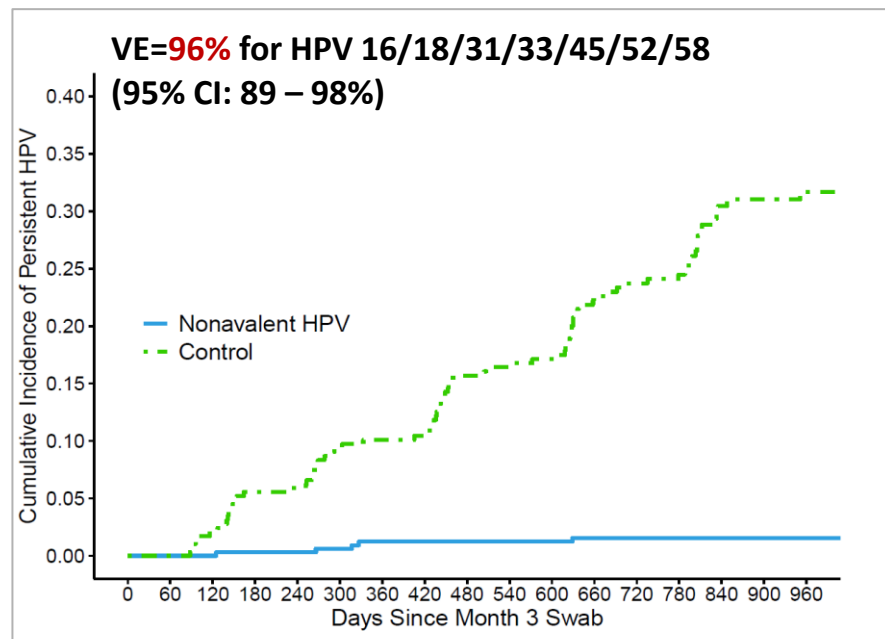
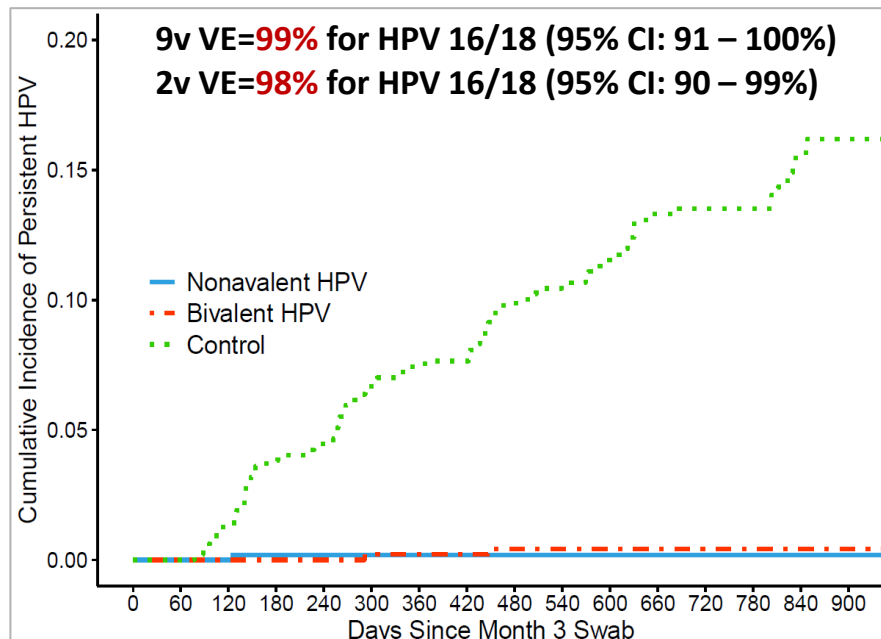
- 1458 evaluated for efficacy in mITT cohort

Vaccine	N	18 months			36 months		
		Incident persistent HPV 16/18	Incidence/100 PY	VE % (95% CI)	Incident persistent HPV 16/18	Incidence/100 PY	VE % (95% CI)
9vHPV	496	1	0.17	97.5% (81.7–99.7)	1	0.08	98.8% (91.3–99.8)
2vHPV	489	1	0.17	97.5% (81.6–99.7)	2	0.16	97.5% (90.0–99.4)
Meningococcal	473	36	6.83	Reference	72	6.70	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

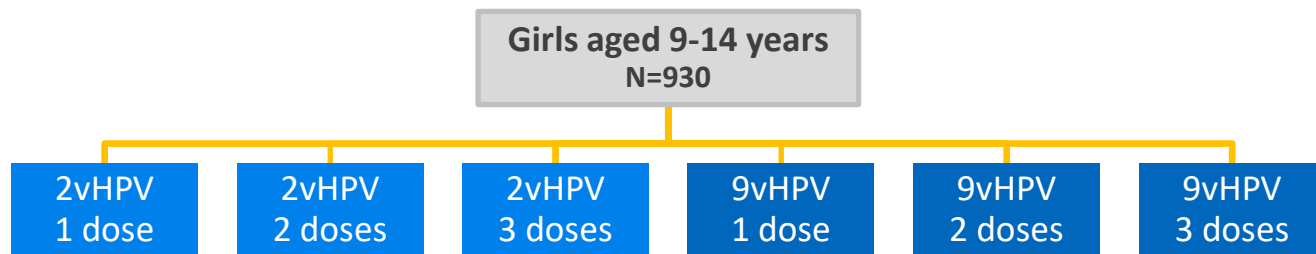
KEN SHE: RCT of single-dose HPV vaccination

Through three years after vaccination, 1-dose HPV vaccine efficacy remained high



DoRIS - Tanzania

- **D**ose **R**eduction **I**mmunobridging & **S**afety Study
- Randomized, open label trial in girls aged 9-14 years
- 1, 2, 3 doses of 2vHPV (Cervarix) or 9vHPV (Gardasil 9)
- Objectives – demonstrate noninferiority
 - HPV 16 and 18 antibody response after 1 vs 2 or 3 doses of same vaccine
 - HPV 16 and 18 GMCs: 1 dose in DoRIS vs 1 dose in studies that evaluated efficacy



DoRIS conclusions

Immunogenicity and safety of one-dose human papillomavirus vaccine compared with two or three doses in Tanzanian girls (DoRIS): an open-label, randomised, non-inferiority trial



Deborah Watson-Jones, John Changalucha*, Hilary Whitworth*, Ligia Pinto, Paul Mutani, Jackton Indangasi, Troy Kemp, Ramadhan Hashim, Beatrice Kamala, Rebecca Wiggins, Twaib Songoro, Nicholas Connor, Gladys Mbwangi, Miquel A Pavon, Brett Lowe, Devis Mmbando, Saidi Kapiga, Philippe Mayaud, Silvia de SanJosé, Joakim Dillner, Richard J Hayes, Charles J Lacey, Kathy Baisley*

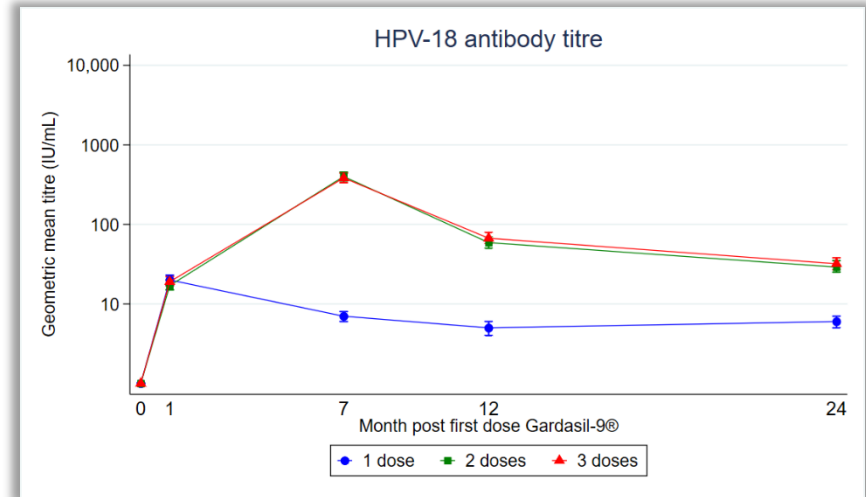
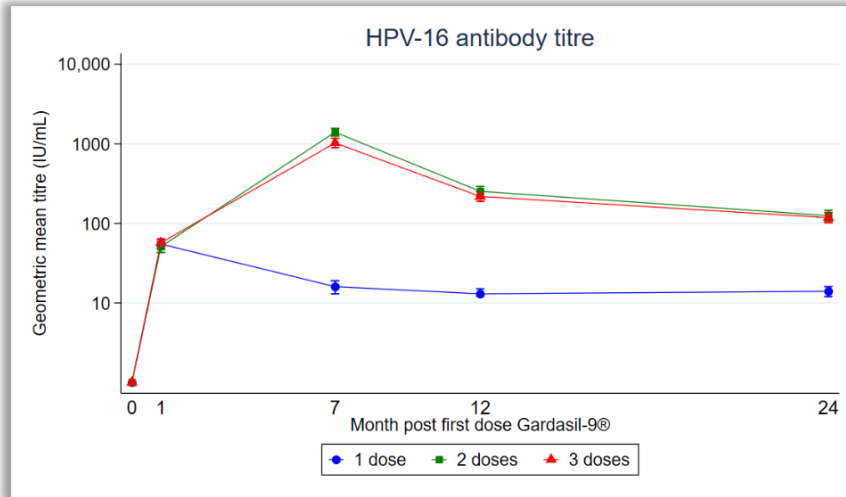


DoRIS conclusions

- Seropositivity >97.8% after vaccination for all vaccine groups

DoRIS conclusions

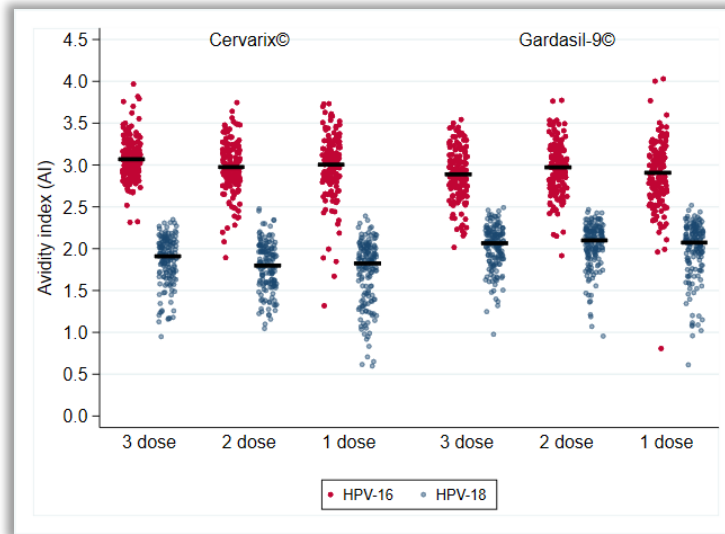
- Seropositivity >97.8% after vaccination for all vaccine groups
- Antibody levels lower after 1 dose compared with 2 or 3 doses
 - Kinetics, with plateau, similar for all doses



9vHPV vaccine groups

DoRIS conclusions

- Seropositivity >97.8% after vaccination for all vaccine groups
- Antibody levels lower after 1 dose compared with 2 or 3 doses
 - Kinetics, with plateau, similar for all doses
- **Avidity for each HPV type was similar for 3, 2 and 1 doses for both vaccines**



DoRIS conclusions

- Seropositivity >97.8% after vaccination for all vaccine groups
- Antibody levels lower after 1 dose compared with 2 or 3 doses
 - Kinetics, with plateau, similar for all doses
- Avidity for each HPV type was similar for 3, 2 and 1 doses for both vaccines.
- **Immunobridging: 1-dose responses were non-inferior in DoRIS (9-14 year-olds) compared with those among women in studies where 1-dose efficacy observed**

Comparing one dose of HPV vaccine in girls aged 9–14 years in Tanzania (DoRIS) with one dose in young women aged 15–20 years in Kenya (KEN SHE): an immunobridging analysis of randomised controlled trials

Kathy Baisley, Troy Kemp, Nelly R Mugo, Hilary Whitworth, Mariclanah A Onono, Betty Njoroge, Jackson Indangasi, Elizabeth A Bukusi, Priya R Prabhu, Paul Mutani, Denise A Galloway, David Mwanzalime, Saidi Kapiga, Charles J Lacey, Richard J Hayes, John Changalucha, Ligia A Pinto, Ruanne V Barnabas, Deborah Watson-Jones



Lancet Global Health 2024

Additional studies evaluating single-dose HPV vaccination, data forthcoming

Study/ country	Evidence	Vaccine	Age (yrs) at vaccination	Description
HOPE South Africa	Impact/ Effectiveness	2vHPV	15–16	1 dose as catch-up in grade 10. Baseline and cross sectional prevalence surveys; includes WLWH
Thailand Impact Thailand	Effectiveness	2vHPV	Grade 8 age <15 yrs	1 or 2 doses, by province; Baseline and post-vaccination cross sectional prevalence surveys
HANDS The Gambia	Immunogenicity	9vHPV	4–8, 9–14 15–26	Randomized trial of 1 or 2 doses vs 3 doses in 15–26-year-olds
Primavera Costa Rica	Immunogenicity	2vHPV 9vHPV	9–14 18–25	1 dose 3 doses
PRISMA Costa Rica	Efficacy	2vHPV 4vHPV 9vHPV	18–30	Randomized trial of 1 dose of three different HPV vaccines vs unvaccinated
ESCUDDO Costa Rica	Efficacy/ Immunogenicity	2vHPV 9vHPV	12–16	Randomized trial of 1 vs 2 doses

Additional data from studies reviewed today

Study/ country	Evidence	Vaccine	Age (yrs) at vaccination	Data expected
CVT Costa Rica	Efficacy/ Immunogenicity	2vHPV	12–16	14-, 16- and 20-year data
IARC-India India	Efficacy/ Immunogenicity	4vHPV	10-18	12-year data and further
DoRIS Tanzania	Immunogenicity	2vHPV 9vHPV	9-14	36- and 60-month data

2vHPV, Cervarix; 9vHPV, Gardasil 9

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

Two HPV vaccine doses for persons aged ≥ 15 years

- **Studies of single-dose also provide data on a 2-dose schedule**
 - Studies with a 2-dose group (0, 6 months)
 - CVT (2vHPV): 18–25-year-olds
 - IARC-India (4vHPV): 10–18-year-olds
- **Immunogenicity trial of 2 vs 3 doses of 9vHPV***
 - U.S. study in 15–26-year-olds
 - Ongoing - interim data published

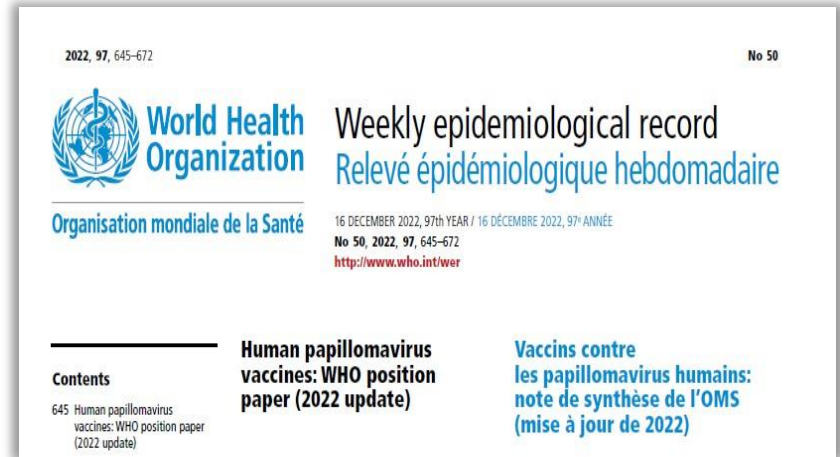
2022 World Health Organization recommendations and global landscape

WHO recommendations for HPV vaccination

December 2022:

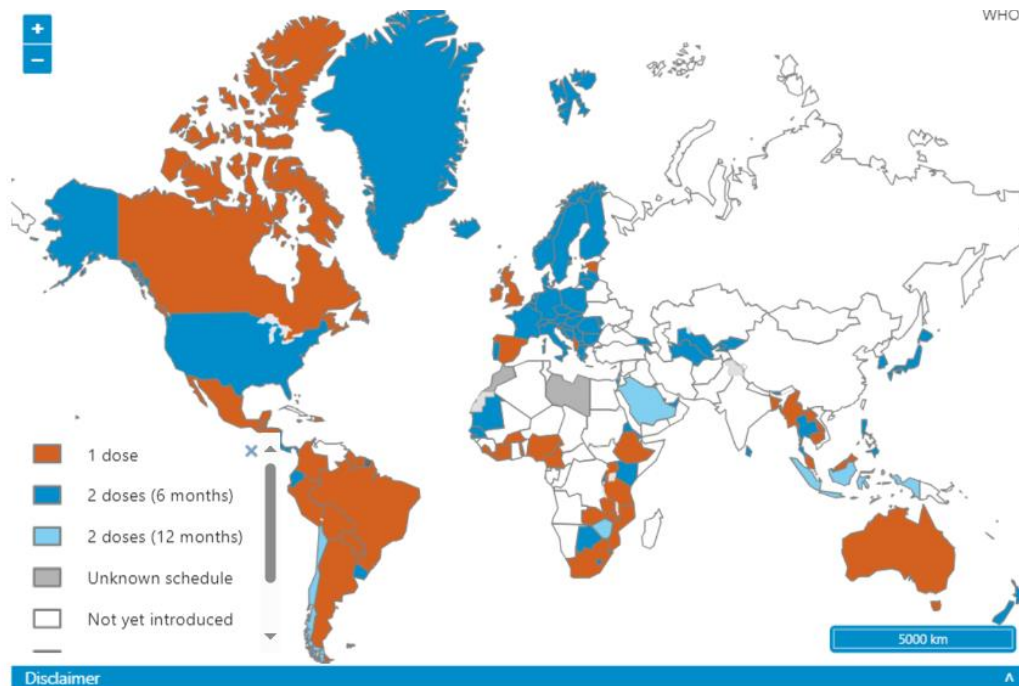
Evidence supports a 2-dose schedule from age 9 years and for all older age groups for which HPV vaccines are licensed.

As an off-label option, a single-dose schedule can be used in girls and boys aged 9–20 years.



Recommended HPV vaccine schedules in 9–14-year-olds, by country

Doses-interval	No. of countries
1 dose	58
2 doses (12 months)	5
2 doses (6 months)	76
Not yet introduced	50
Unknown schedule	5



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Policy changes since updated WHO HPV vaccination recommendations in 2022

- **Some of the first countries to change to a routine single-dose schedule**
 - England, Ireland, Australia
- **Change from a 3-dose to a 2-dose schedule for persons ages >14 years**
 - Netherlands and Sweden
- **Single-dose recommendations by regional advisory groups**
 - PAHO in 2023 and AFRO in 2024

Outstanding questions for single-dose vaccination

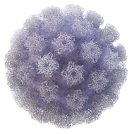


- Longer term efficacy and immunogenicity
- Protection at sites other than the cervix
- Efficacy and immunogenicity in males*
- Efficacy and immunogenicity in immunocompromised persons
- Efficacy and immunogenicity in older age groups

Additional data expected over the next year will address some of these questions

Announcement from Merck, March 2024

- Plan to conduct two prospective clinical trials, one in females (16-26 years) and one in males (ages 16-26 years).
- These randomized, double-blind, multi-year clinical trials will examine the short and long-term efficacy and immunogenicity of a single-dose of Gardasil 9 versus the currently approved three-dose regimen.
- Merck is in discussions with FDA about the protocols and the timeline.



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.
- Data are available on single-dose HPV vaccination, including from a RCT with 3 years of follow-up, showing high efficacy against incident persistent infection.
- Long term follow-up suggests protection for >10 years with a single dose.
- WHO 2022 updated recommendations: 2 doses for persons aged 9 years and older, with option for single-dose HPV vaccination through age 20 years, except those immunocompromised.
- Countries are considering new or updated HPV vaccination policy and an increasing number have recommended single-dose HPV vaccination.
- Further data on 1 and 2 doses will be available over the next year.

Next steps for ACIP HPV Vaccines Work Group

- **Review further evidence**
 - 1- and 2-dose schedules
 - Modeling data
 - Other relevant data
- **Evaluate evidence using GRADE and evaluate policy questions using the Evidence to Recommendations framework**
 - Should a 1-dose schedule be recommended in some age groups?
 - Should a 2-dose schedule, instead of a 3-dose schedule, be recommended in some age groups older than 9–14 years?

Questions for ACIP

What questions does ACIP have regarding the policy questions being addressed?

Thank You

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

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.

