

# Reduced number of doses for HPV vaccination series: Work Group progress and literature update

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# Outline

- **PICO and outcomes**
- **Introduction to systematic review**
- **Updated data from studies of interest**
- **Observational studies of HPV vaccine effectiveness**
- **Outstanding questions for reduced number of HPV vaccine doses**

**PICOs and outcomes**

# PICO questions<sup>1</sup>

<b>Policy question</b>	<b>Should 1 dose of HPV vaccine be used for prevention of HPV infection and HPV attributable disease, instead of the currently recommended vaccination schedule?</b>		<b>Should 2 doses of HPV vaccine be used for prevention of HPV infection and HPV attributable disease, instead of the currently recommended vaccination schedule?</b>
<b>Population</b>	Persons aged 9–14 yrs  Except persons with immunocompromising conditions	Persons aged 15–X yrs <sup>2</sup>  Except persons with immunocompromising conditions	Persons aged 15–X yrs <sup>2</sup>  Except persons with immunocompromising conditions
<b>Intervention</b>	1 dose of HPV vaccine		2 doses of HPV vaccine
<b>Comparison</b> <i>(current recommendation)</i>	2 doses for persons who initiate at ages 9–14 yrs	3 doses for persons who initiate at age ≥15 yrs	3 doses for persons who initiate at age ≥15 yrs

<sup>1</sup>We are not intending this to change the recommendation of shared clinical decision-making for persons aged 27-45 years, although the number of recommended doses in this age group may change.

<sup>2</sup>Upper age to be discussed by Work Group after we review data

Note: We will review data on 1 vs 2 doses in persons aged 15+, but are focusing PICOs on comparing to current recommendations

# Outcomes

Outcome	Importance
HPV-associated cancers	Critical
Pre-cancers (CIN2+ or AIN2+)	Critical
Serious adverse events related to vaccination	Critical
Incident-persistent HPV infection	Critical
Prevalent HPV infection	Important
Incident HPV infection	Important
Immunogenicity	Important
Anogenital warts	Important
Low-grade histological abnormalities (CIN1 or AIN1)	Important
Recurrent respiratory papillomatosis	Important

# Introduction to systematic review

# Systematic review of the literature

- **Cochrane reviewed the global literature on HPV vaccination schedules with reduced number of doses in 2022**
  - 59 studies (73 publications) were included in review; 49 studies were later excluded due to serious risk of bias
- **We are starting with Cochrane's review but putting it into U.S. context**
  - Only including studies of vaccines that are licensed in the United States
  - Using 18 publications from Cochrane's systematic review
- **Updated Cochrane's literature search for publications during 2022–2024**
  - Yielded 22 additional publications; 3 excluded due to serious risk of bias
  - 37 total included publications

# Included studies in alphabetical order

Study name or first author	Study design	Population and age at vaccination	Vaccine
Batmunkh 2020 (Mongolia)	Retrospective cohort	Females, 11-17y	4vHPV
Berenson 2024 (USA)	RCT	Females, 15-26y	9vHPV
Bornstein 2021 (global)	RCT	Girls and boys, 9-14y	9vHPV
Costa Rica Vaccine Trial (CVT)	Post-hoc analysis of RCT	Females, 18-25y	2vHPV
CVT/PATRICIA	Post-hoc analysis of 2 RCTs	Females, 15-25y	2vHPV
DoRIS (Tanzania)	RCT	Females, 9-14y	2vHPV and 9vHPV
Hariri 2018 (USA)	Retrospective cohort	Females, age NR	4vHPV
HOPE (South Africa)	Repeat cross-sectional	Females, 15-16y	2vHPV
IARC-India	Post-hoc analysis of RCT	Females, 10-18y	4vHPV
Jiamsiri 2024 (Thailand)	Repeat cross-sectional	Females, 13-14y	2vHPV
KEN SHE (Kenya)	RCT	Females, 15-20y	2vHPV and 9vHPV
Klein 2024 (USA)	Cohort	Girls and boys, 9-14y	9vHPV
Moss 2024 (USA)	Cohort	Females, 15-45y	9vHPV
Reyburn 2023 (Fiji)	Retrospective cohort	Females, 9-12y	4vHPV
Wu 2025 (Sweden)	Retrospective cohort	Females, 10-35y	4vHPV
Zeng 2023 (USA)	Cohort	Girls and boys, 9-11y	9vHPV



# Critical outcomes: Studies contributing data and time since vaccination

Outcome	# of studies	RCTs	Post-hoc analysis of RCTs	Observational studies
HPV-associated cancers	1		IARC-India (15y; 0 cases)	
Pre-cancers (CIN2+ or AIN2+)	2		IARC-India (15y)	Wu-Sweden (8-12y)
Incident-persistent HPV infection	3	KEN SHE (4.5y)	IARC-India (15y), CVT/PATRICIA (4y)	
Serious adverse events related to vaccination	n/a - data to be summarized in narrative review			

# Important outcomes: Studies contributing data and time since vaccination

Outcome	# of studies	RCTs	Post-hoc analysis of RCTs	Observational studies
Prevalent HPV infection	5		CVT (11y)	Reyburn-Fiji (8y), Batmunkh-Mongolia (6y), Jiamsiri-Thailand (4y), HOPE-South Africa (2y)
Incident HPV infection	2		IARC-India (15y), CVT (11y)	
Immunogenicity	11	DoRIS-Tanzania (5y), KEN SHE (2y), Bornstein-global (1y), Berenson-USA (1m)	CVT (16y), IARC-India (10y)	Batmunkh-Mongolia (6y), Jiamsiri-Thailand (4y), Zeng-USA (6m), Moss-USA (1m), Klein-USA (follow-up varied)
Anogenital warts	2			Reyburn-Fiji (8y), Hariri-USA (follow-up NR)
Low-grade histological abnormalities (CIN1 or AIN1)	1		IARC-India (15y)	
Recurrent respiratory papillomatosis	n/a			

**Updated data from studies of interest**

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

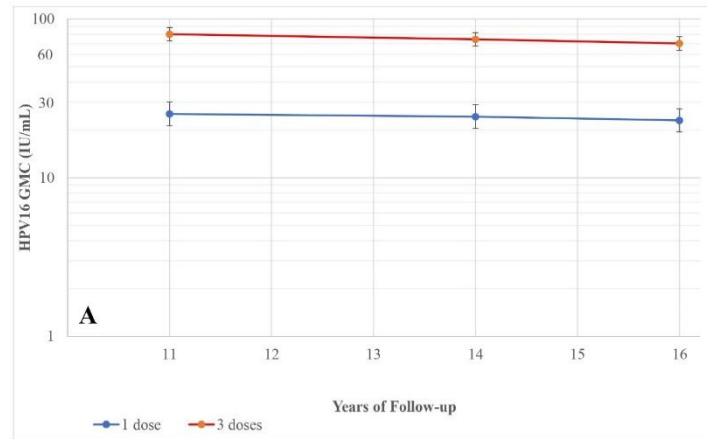
Trial/country	Evidence	Vaccine	Age (yrs) at vaccination	Description
<b>CVT</b> Costa Rica	Efficacy/ Immunogenicity	2vHPV	18–25	<u>Post-hoc analyses</u> Original trial: randomized to 3 doses or control, but analyzed as 1-, 2-, 3-dose groups
<b>IARC-India</b> India	Efficacy/ Immunogenicity	4vHPV	10–18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

# Costa Rica Vaccine Trial (CVT)

- **Women aged 18–25 years were randomly assigned to receive 3 doses of 2vHPV or hepatitis A vaccine**
- **Some women did not receive all 3 doses due to pregnancy, colposcopy referral, a medical condition, participant refusal, or missing a study visit**
  - Reasons for receiving fewer doses were balanced within each dosage group between women receiving the HPV and control vaccines
- **Data evaluated as cohort study of women who received 1, 2, or 3 doses**
- **We previously reviewed data on protection against prevalent infection and immunogenicity through 11 years**

# Costa Rica Vaccine Trial (CVT): 2024 update

- 16 years after vaccination, HPV 16/18 seropositivity was very high (>98%)
- During years 11–16 after vaccination, small but statistically significant declines in antibodies observed in women who received 3 doses and 1 dose



# IARC-India Trial

- **Unmarried girls aged 10–18 years were randomly assigned to receive either 2 or 3 doses of 4vHPV**
- **A ministerial decree to halt vaccination in trials resulted in the creation of cohorts of women who received 1, 2, or 3 doses**
- **Cervical screening with an HPV test was initiated at age 25 years for married participants**
  - Positive screening → colposcopy; negative screening → repeat in 5 years
- **Age- and site-matched unvaccinated married women recruited as controls**
- **We previously reviewed data on protection against persistent infection through 10 years**

# IARC-India Trial: 2024 update

- **Median follow-up time = 12 years; time since study began = 15 years**
  - Currently aged 25–33 years
- **VE against persistent HPV 16/18 infection by number of doses:**
  - 1 dose: 92.0% (95% CI: 87.0%–95.0%)
  - 2 doses: 94.8% (95% CI: 90.0%–97.3%)
  - 3 doses: 95.3% (95% CI: 90.9%–97.5%)
- **No CIN2+ associated with HPV 16/18 detected among vaccinated participants (compared with 8 among unvaccinated women)**
- **No cases of invasive cervical cancer associated with HPV 16/18 in study**



# DoRIS (Tanzania)

- **Dose Reduction Immunobridging & Safety Study**
- **Girls aged 9–14 years were randomly assigned to 1, 2, or 3 doses of either 2vHPV or 9vHPV**
- **All participants followed until month 36; 1- and 2-dose groups invited to join long-term extension (through 9 years)**
- **Objective was to 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
- **We previously reviewed data on immunogenicity (seropositivity and GMCs) and immunobridging to KEN SHE through 2 years**

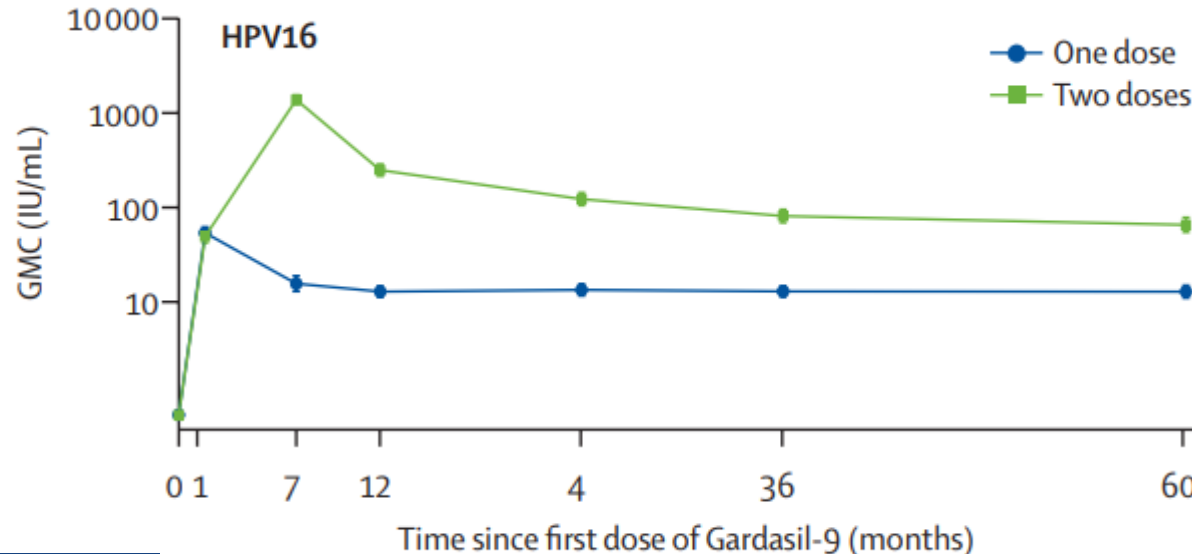
# DoRIS: 2025 update (9vHPV results) – 5 years after vaccination

- **Seropositivity:**
  - HPV 16: 100% seropositive in 1-dose and 2-dose arms
  - HPV 18: 93% seropositive in 1-dose arm, 98% seropositive in 2-dose arm
  - Non-inferiority of HPV 18 seropositivity was not met

# DoRIS: 2025 update (9vHPV results) – 5 years after vaccination

- **GMCs:**

- 1-dose arm: plateaued at month 12, relatively constant through month 60
- 2-dose arm: declined after peak at month 7
- Lower in 1-dose arm than in 2-dose arm, as expected



**Observational studies of vaccine effectiveness**

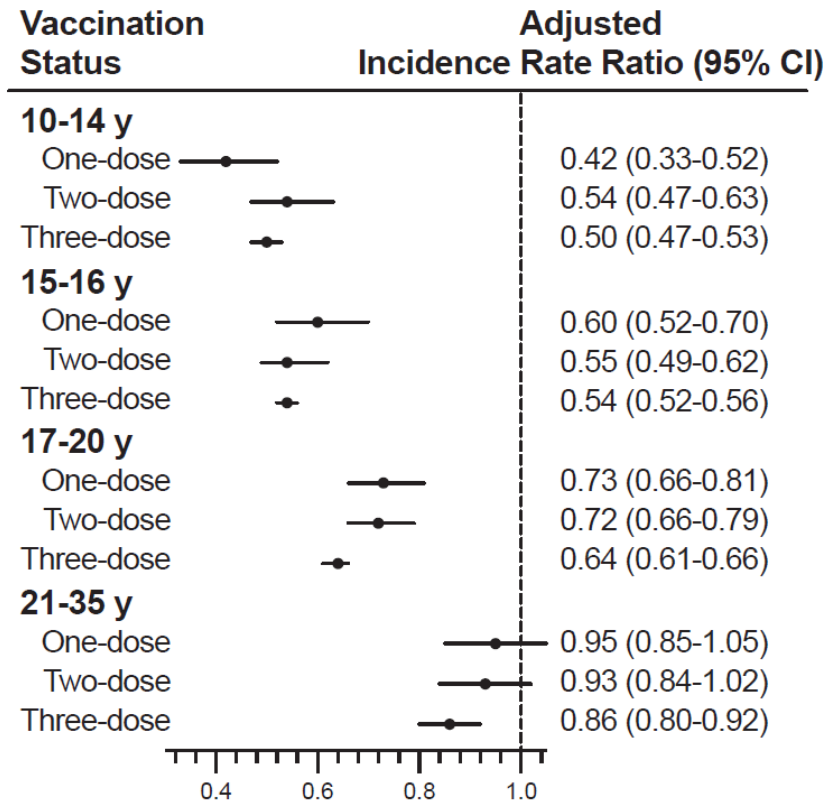
# Bias in observational studies of HPV vaccine effectiveness by number of doses

- **Most important sources of bias:**
  - Differences between dose groups in risk of prevalent infection at time of vaccination
  - Differences between dose groups in risk of HPV acquisition during follow-up
  - Potential impact of interval between 1st and 2nd dose on vaccine effectiveness
- **Serious bias would likely result in lower effectiveness with fewer doses**
- **Ways investigators attempt to control for biases:**
  - Using buffer periods to exclude outcomes caused by prevalent infections at vaccination
  - Stratifying results for age at vaccination or restricting the population to younger ages
  - Adjusting for indicators of sexual activity and socio-demographic characteristics
  - Stratifying results for 2 doses by the interval between 1st and 2nd dose (e.g., <5 , ≥5m)

# Wu-Sweden 2025: methods summary

- Cohort study of 2.2M females aged 10–35, residents of Sweden 2006–2022
- Linked several registries, including vaccination and cervical screening
- Exposure (time-varying): number of doses of 4vHPV
- Outcome: CIN2+
- Used Poisson models to estimate incidence rate ratios (IRR) vs. unvaccinated
  - Adjusted for age, calendar year, county of residence, maternal history of high-grade cervical lesions, mother's country of birth, parental education, and household income
  - 1 year buffer
- Median years of follow-up (IQR):
  - Unvaccinated: 8.4 (2.3–15.3); Vaccinated: 12.4 (8.7–17.0)

# Wu-Sweden 2025: CIN2+ by age at vaccination



**Outstanding questions for reduced  
number of HPV vaccine doses**



# Outstanding questions for reduced number of HPV vaccine doses

- 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

# Outstanding questions for reduced number of HPV vaccine doses

- **Longer term efficacy and immunogenicity**
  - Longest efficacy data: IARC-India (15 years)
  - Longest immunogenicity data: Costa Rica Vaccine Trial (16 years)
- **Protection at sites other than the cervix**
  - No data on protection at sites other than the cervix
- **Efficacy and immunogenicity in males**
  - 13/16 studies include only females
  - No efficacy data in males
  - Some evidence of lower antibody titers in adolescent males versus females after 1 dose
- **Efficacy and immunogenicity in immunocompromised persons**
  - Limited data available; not planning to make changes to recommendation
- **Efficacy and immunogenicity in older age groups**
  - Limited data available; need to decide appropriate upper age for our PICOs

# Thank you!

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

