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[1]

Policy question	**Should 1 dose of HPV vaccine be used for prevention of HPV infection and HPV attributable disease, instead of the currently recommended vaccination schedule?**		**Should 2 doses of HPV vaccine be used for prevention of HPV infection and HPV attributable disease, instead of the currently recommended vaccination schedule?**
Population	Persons aged 9–14 yrs Except persons with immunocompromising conditions	Persons aged 15–X yrs[2] Except persons with immunocompromising conditions	Persons aged 15–X yrs[2] Except persons with immunocompromising conditions
Intervention	1 dose of HPV vaccine		2 doses of HPV vaccine
Comparison (*current recommendation*)	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

[1]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.

[2]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
CVT Costa Rica	Efficacy/ Immunogenicity	2vHPV	18–25	Post-hoc analyses Original trial: randomized to 3 doses or control, but analyzed as 1-, 2-, 3-dose groups
IARC-India India	Efficacy/ Immunogenicity	4vHPV	10–18	Post-hoc analyses Original trial: 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 2vHPV, 9vHPV or MCV
DoRIS Tanzania	Immunogenicity	2vHPV 9vHPV	9–14	Randomized trial 1-, 2-, 3-dose groups

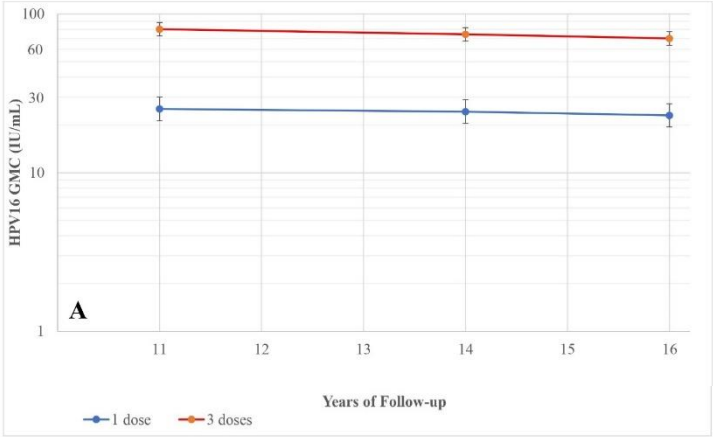
2vHPV, Cervarix; 9vHPV, Gardasil 9; CVT, Costa Rica Vaccine Trial; IARC, International Agency for Research on Cancer

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**



Porras et al 2024 https://academic.oup.com/jncimono/article/2024/67/329/7821493

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**

Malvi et al 2024 https://academic.oup.com/jncimono/article/2024/67/317/7821485

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**

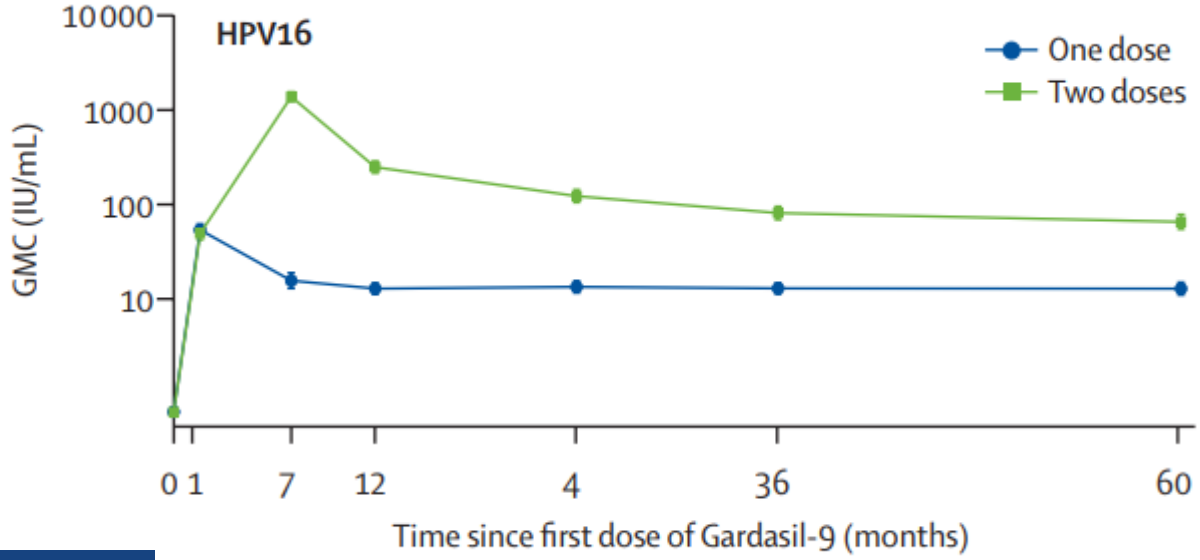
DoRIS: 2025 update (9vHPV results) – 5 years after vaccination

- **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

Watson-Jones et al 2025 https://pubmed.ncbi.nlm.nih.gov/39890232/

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

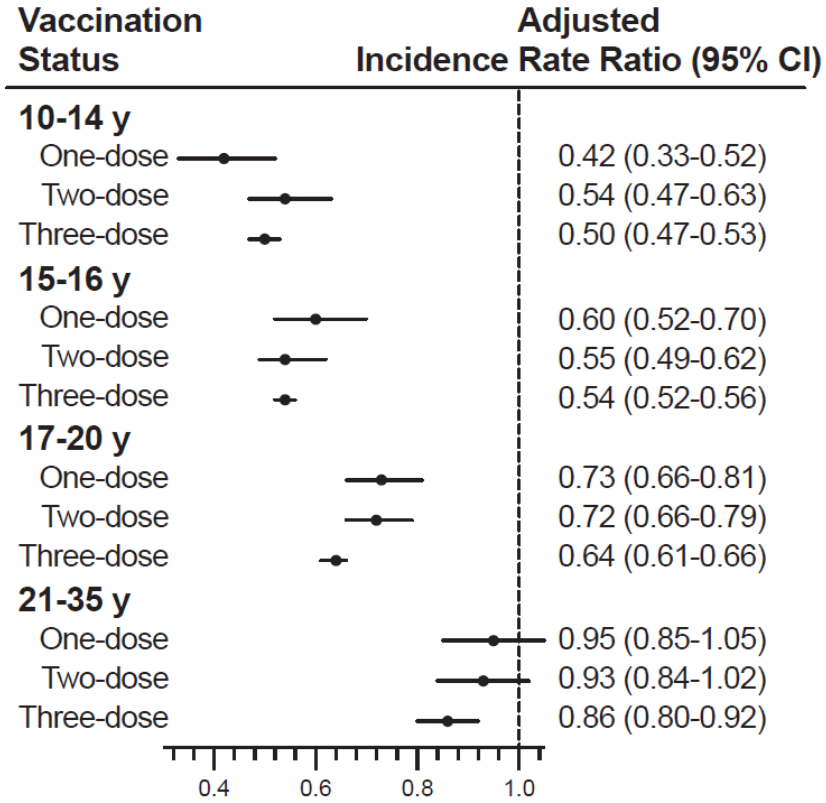
- **Most important sources of bias:**
  - Differences between dose groups in risk of prevalent infection at time of vaccination
  - Differences between dose groups in risk of HPV acquisition during follow-up
  - Potential impact of interval between 1st and 2nd dose on vaccine effectiveness
- **Serious 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)

Markowitz et al 2022 https://www.sciencedirect.com/science/article/pii/S0264410X22008349?via%3Dihub

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



Wu et al https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(24)00347-8/fulltext

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