Expanded age range for 9-valent HPV vaccine
Background for policy considerations

Lauri Markowitz, MD
Division of Viral Diseases

Advisory Committee on Immunization Practices
October 24–25, 2018

Outline

- Expanded age range for 9vHPV
  - Data submitted in support of application
- Data from the United States
  - Vaccine coverage and impact, HPV epidemiology and sexual behavior
- Post-licensure vaccine effectiveness evaluations
  - By age at vaccination
- Update on global HPV vaccination

HPV vaccine licensure and availability, United States

Before October 2018

Vaccine	HPV types	Manufacturer	Licensure ages
Bivalent (2vHPV)	16,18	GlaxoSmithKline	Females 9–25 yrs
Quadrivalent (4vHPV)	6,11,16,18	Merck & Co	Females and males 9–26 yrs
9-valent (9vHPV)	6,11,16,18, 31,33,45,52,58	Merck & Co	Females and males 9–26 yrs

Availability

- Since end of 2016, only 9vHPV has been available in the United States
- 2vHPV and 4vHPV continue to be available in other countries

HPV vaccine licensure and availability, United States

October 2018

Vaccine	HPV types	Manufacturer	Licensure ages
Bivalent (2vHPV)	16,18	GlaxoSmithKline	Females 9–25 yrs
Quadrivalent (4vHPV)	6,11,16,18	Merck & Co	Females and males 9–26 yrs
9-valent (9vHPV)	6,11,16,18, 31,33,45,52,58	Merck & Co	**Females and males 9–45 yrs**

Availability

- Since end of 2016, only 9vHPV has been available in the United States
- 2vHPV and 4vHPV continue to be available in other countries

Vaccine licensure and use in mid-adults in other countries

- HPV vaccines have been licensed through age 45 years or older in other countries
- No country has a public health HPV vaccine program targeting mid-adults

Current recommendations for HPV vaccination in the United States

- **Routine HPV vaccination at age 11 or 12 years**
  - The vaccination series can be started beginning at age 9 years
- **HPV vaccination is also recommended for the following persons if not adequately vaccinated previously**
  - Females through age 26 years
  - Males through age 21 years
  - Certain populations through age 26 years*
- **Males aged 22 through 26 years may be vaccinated**

*Men who have sex with men, transgender persons, and persons with certain immunocompromising conditions
MMWR 2014;63 (RR05) MMWR 2015;64:300-4 MMWR 2016; 65:2105-8

Expanded age range for use of 9vHPV

FDA Summary Basis for Regulatory Action

- Results of a randomized, double-blind, placebo-controlled trial (base study) of 4vHPV that included women 27–45 years of age

  Munoz et al. Lancet 2009
  Castellsague et al. Br J Cancer 2011 (end of study results)

- Observational follow-up of a subset of women in the base study showing effectiveness against anogenital warts and CIN up to 10 years post-vaccination

  Luna et al. PLoS One 2013 (6 year follow-up)
  Luxembourg (10 year follow-up presented at ACIP June 2018)

CIN, cervical intraepithelial neoplasia

https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM622941.pdf

Expanded age range for use of 9vHPV

FDA Summary Basis for Regulatory Action

- A cross-study immunogenicity analysis showing statistical non-inferiority of immune responses to 4vHPV in males aged 27–45 years compared with males aged 16–26 years, the age in which efficacy was demonstrated

  Antibody data from open label, single arm study of 150 men aged 27–45 years
  Giuliano et al. Vaccine 2015

  Compared with antibody data in males aged 16–26 years in 4vHPV efficacy trial
  Giuliano et al. N Engl J Med 2011
  Palefsky et al. N Engl J Med 2011

https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM622941.pdf

Expanded age range for use of 9vHPV

FDA Summary Basis for Regulatory Action

- Extrapolation of effectiveness against the additional 5 HPV types covered by 9vHPV in individuals 27–45 years of age
  - Based on understanding of HPV pathophysiology and immune responses to those types elicited by 9vHPV in individuals 9–26 years of age
- Extrapolation of safety of 9vHPV in individuals 27–45 years of age
  - Based on safety experience with 4vHPV in individuals 9–45 years of age and safety experience with 9vHPV in individuals 9–26 years of age

https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM622941.pdf

4vHPV randomized controlled efficacy, safety and immunogenicity trial in mid-adult women, FUTURE III

Population	Women aged 24–45 years
Location	Multi-national – 7 countries
Number enrolled	3,819
Primary endpoint	Vaccine type 6-month persistent infection or vaccine-type related CIN1 or worse, external genital lesions
Duration of follow-up	4 years

CIN1, cervical intraepithelial neoplasia, grade 1

4vHPV randomized controlled efficacy, safety and immunogenicity trial in mid-adult women, FUTURE III

HPV 6,11,16,18-related Outcomes	Cases		Efficacy	(95% CI)
	Vaccine	Control		
Per-protocol				
Persistent infection, CIN, EGL	10	86	**88.7%**	(78.1, 94.8)
CIN2+	1	6	**83.3%**	(-37.6, 99.6)
Intention-to-treat				
Persistent infection, CIN, EGL	116	214	**47.2%**	(33.5, 58.2)
CIN2+	21	27	**22.4%**	(-42.5, 58.3)

This analysis includes 24–45 year old women; per-protocol: received 3 doses PCR negative and seronegative to relevant vaccine type at day 1 and through month 7
CIN, cervical intraepithelial neoplasia, EGL, external genital lesions; CIN2+: CIN grade 2 or worse
Mean follow-up time 46 months

Castellsague et al. Br J Cancer 2011

Mid-adult long term follow-up study

- After base study, placebo-recipients were offered vaccine
- 685 Colombian subjects who received 4vHPV in the base study consented to participate in a long-term follow-up for 10 years
- Vaccine effectiveness was evaluated by incidence probability
  - Primary effectiveness endpoint:HPV6/11/16/18-related CIN or condyloma in per-protocol population
  - No vaccine-type CIN or condyloma during follow-up
  - Cases (few) of non-vaccine type outcomes during follow-up, suggesting ongoing exposure to HPV.

Luna et al. PLoS One 2013; Luxembourg, ACIP June 2018

Evidence for expanding range for use of 9vHPV

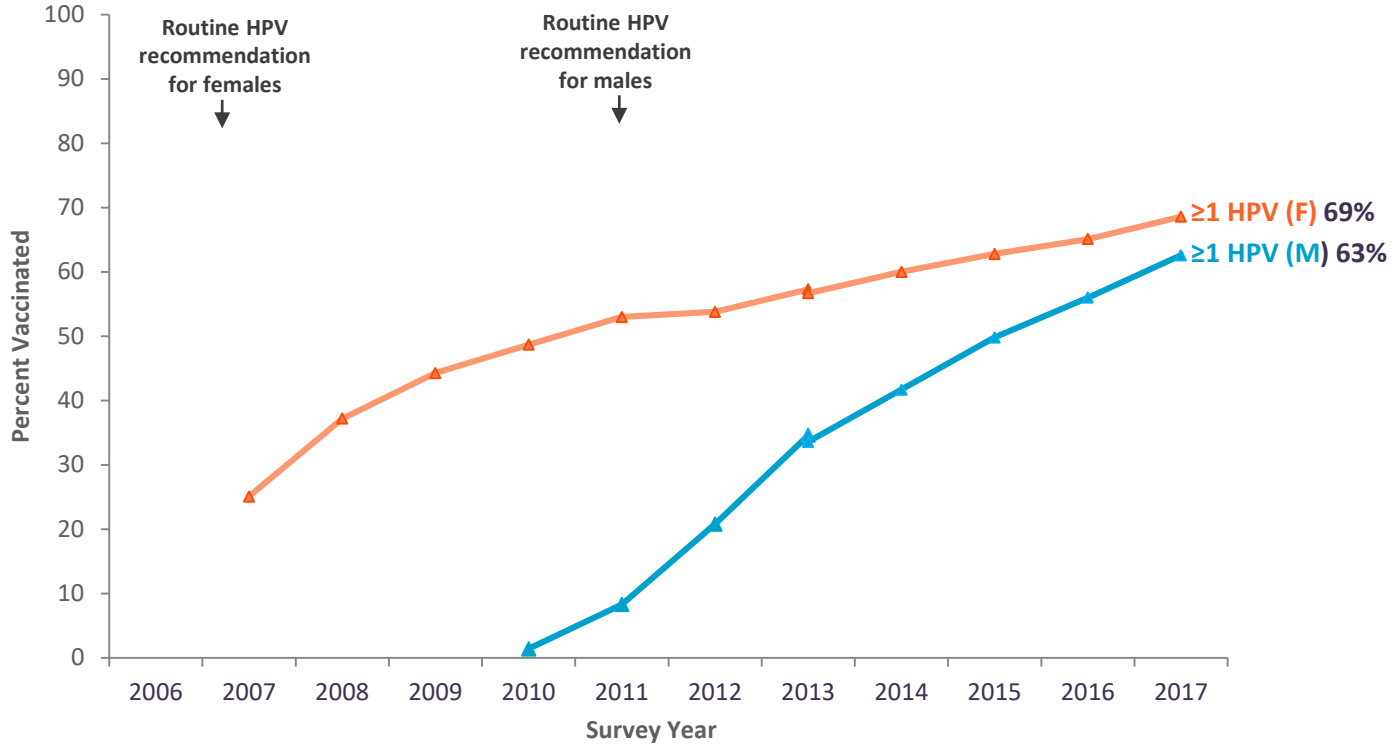
- Data considered for regulatory approval, as well as data from other studies, included in GRADE
- There are no efficacy or immunogenicity data on 9vHPV in persons older than age 27 years
- Manufacturer is conducting a study of immunogenicity and safety of 9vHPV in women aged 16–45 years*
  - Primary Objective: Compare antibody titers and adverse events at month 7 in women aged 16–26 years to women aged 27–45 years
  - Results expected in Q2 2019

*NCT 03158220

Data from the United States

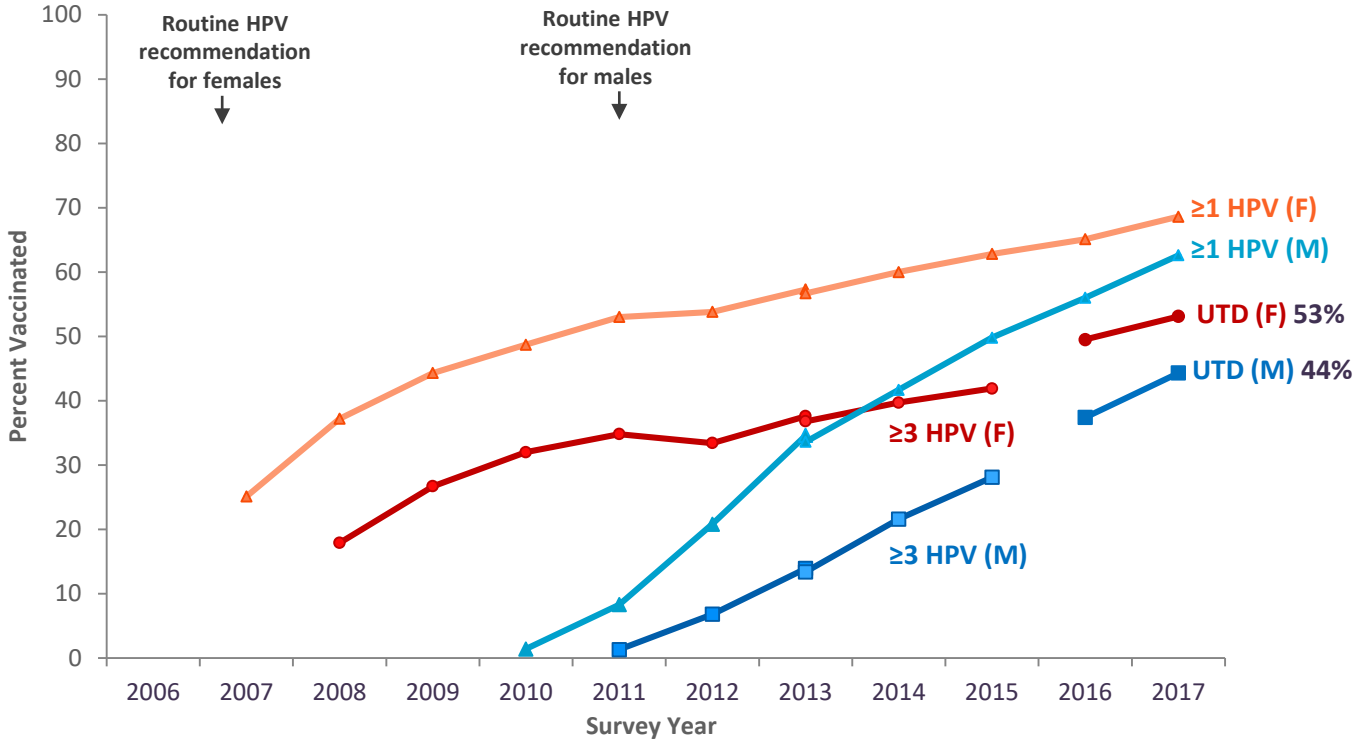
HPV vaccine coverage and impact
HPV epidemiology and sexual behavior

Estimated HPV vaccination coverage among adolescents aged 13–17 years, NIS-Teen, United States, 2006–2017



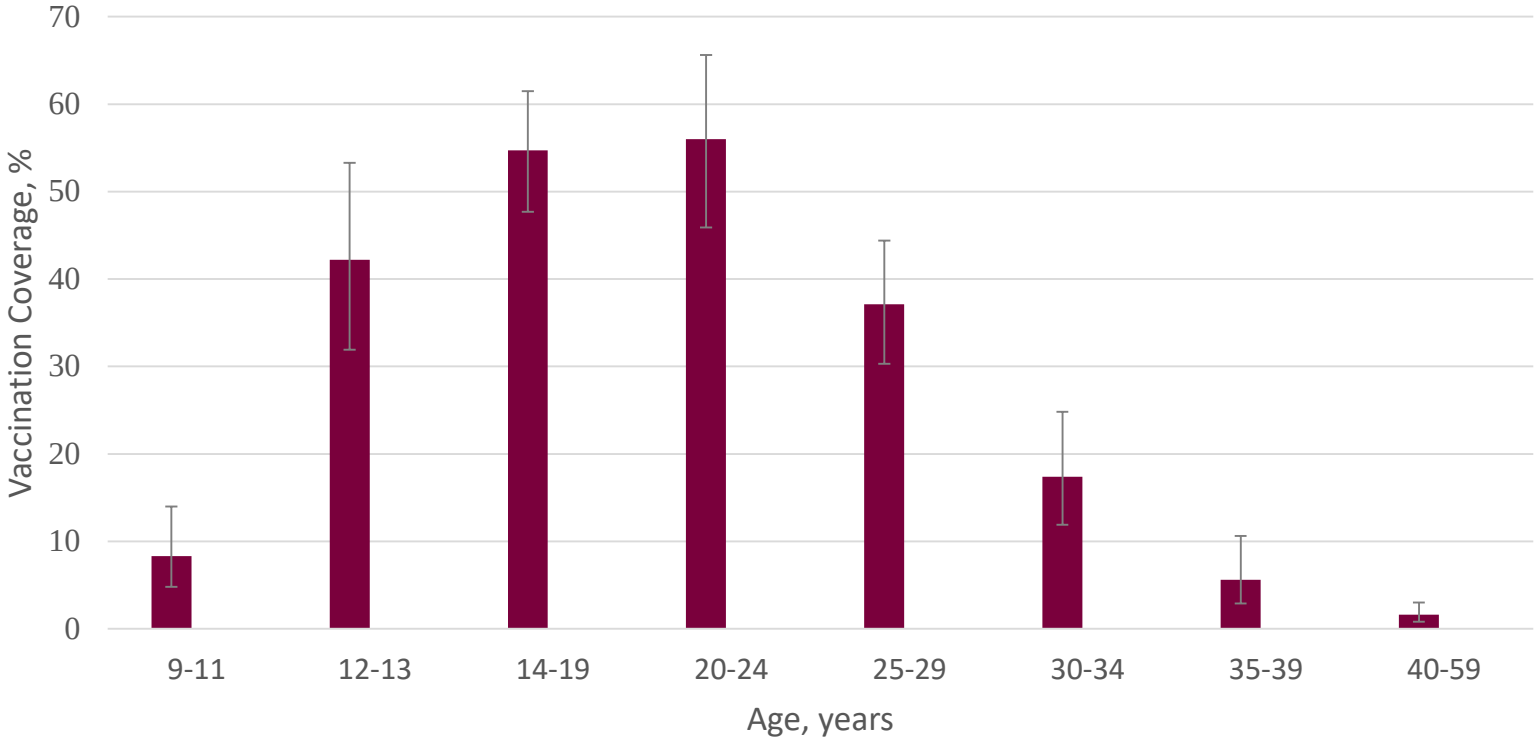
Adapted from Walker et al. MMWR 2018; NIS-Teen, National Immunization Survey-Teen; UTD, Up-to-date
Note: revised definition of adequate provider data in 2013

Estimated HPV vaccination coverage among adolescents aged 13–17 years, NIS-Teen, United States, 2006–2017



Adapted from Walker et al. MMWR 2018; NIS-Teen, National Immunization Survey-Teen; UTD, Up-to-date
Note: revised definition of adequate provider data in 2013

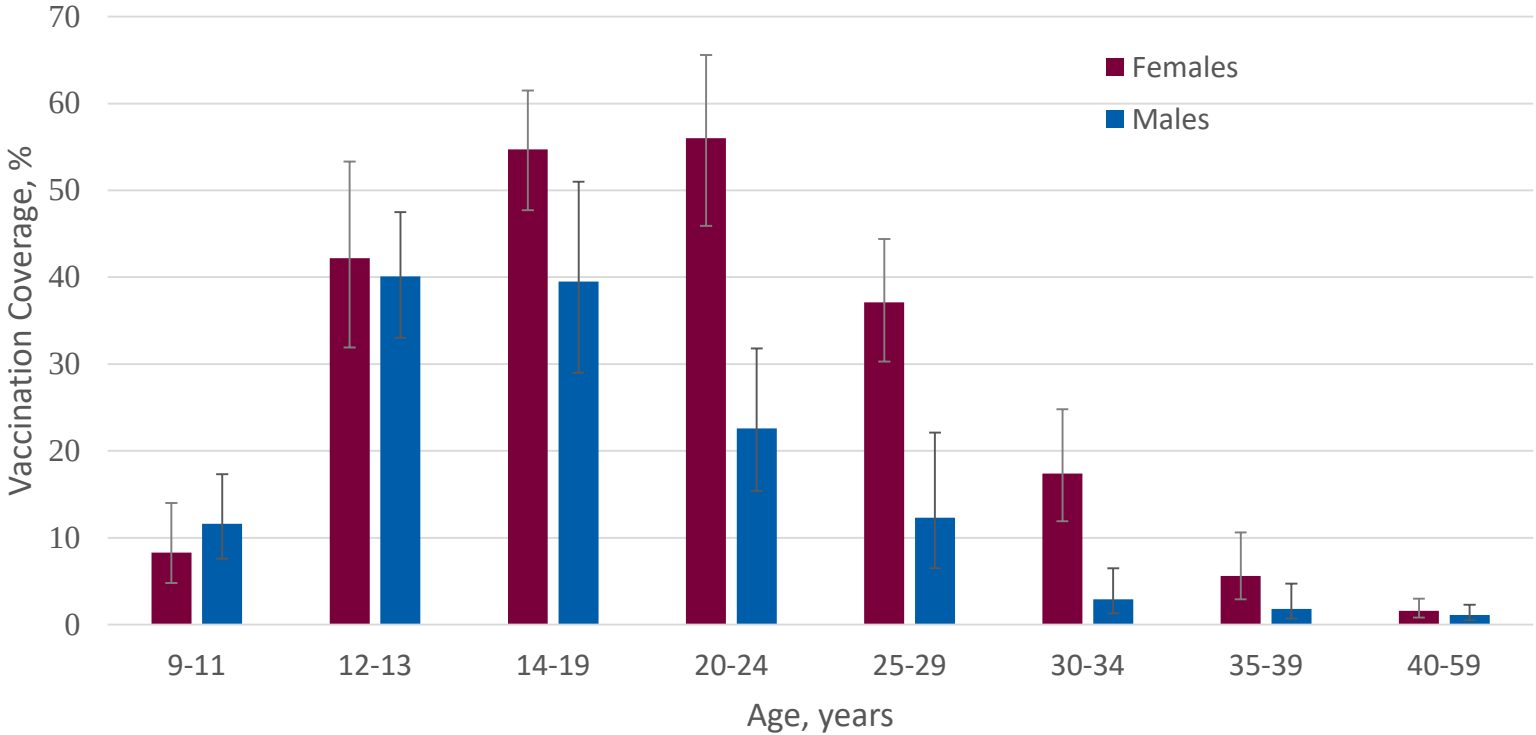
HPV vaccination coverage of ≥1 dose among females NHANES, 2015–2016



Adapted from Lewis and Markowitz, Vaccine 2018

NHANES, National Heath and Nutrition Examination Survey

HPV vaccination coverage of ≥1 dose, females and males NHANES, 2015–2016

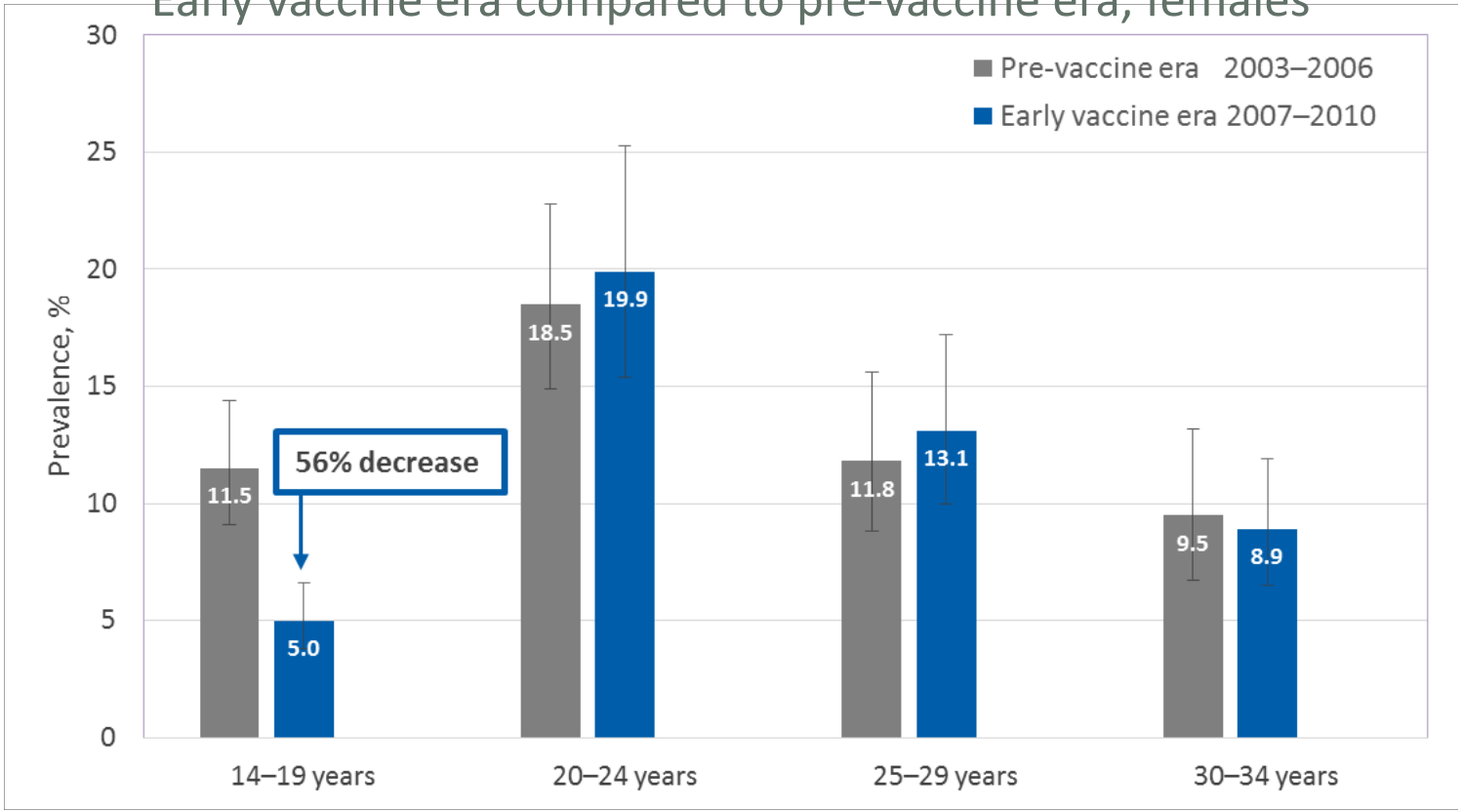


Adapted from Lewis and Markowitz, Vaccine 2018

NHANES, National Heath and Nutrition Examination Survey

Impact of the HPV vaccination program
Vaccine type prevalence (HPV 6,11,16,18), NHANES

Early vaccine era compared to pre-vaccine era, females

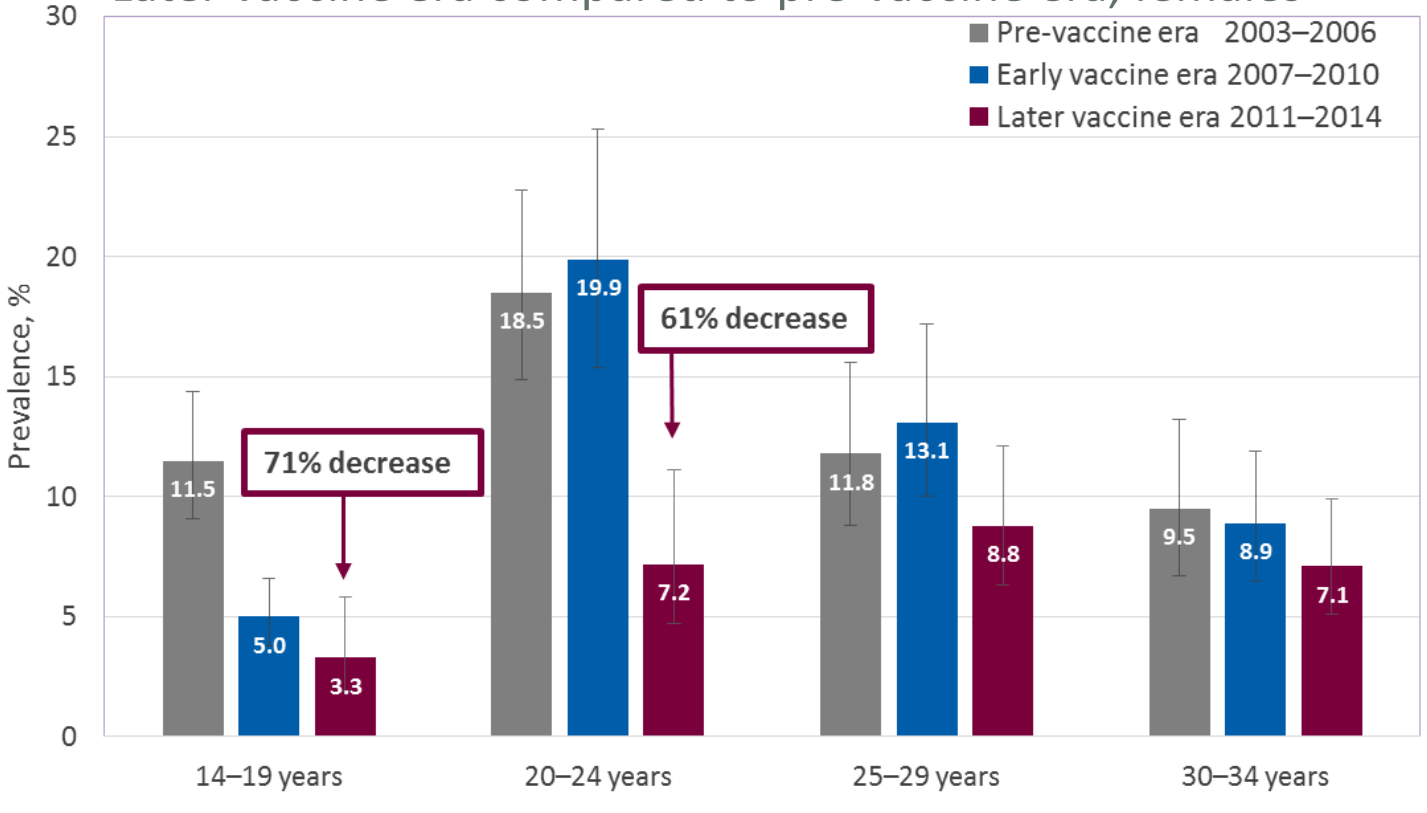


Markowitz et al. JID 2013

NHANES, National Health and Nutrition Examination Survey

Impact of the HPV vaccination program
Vaccine type prevalence (HPV 6,11,16,18), NHANES

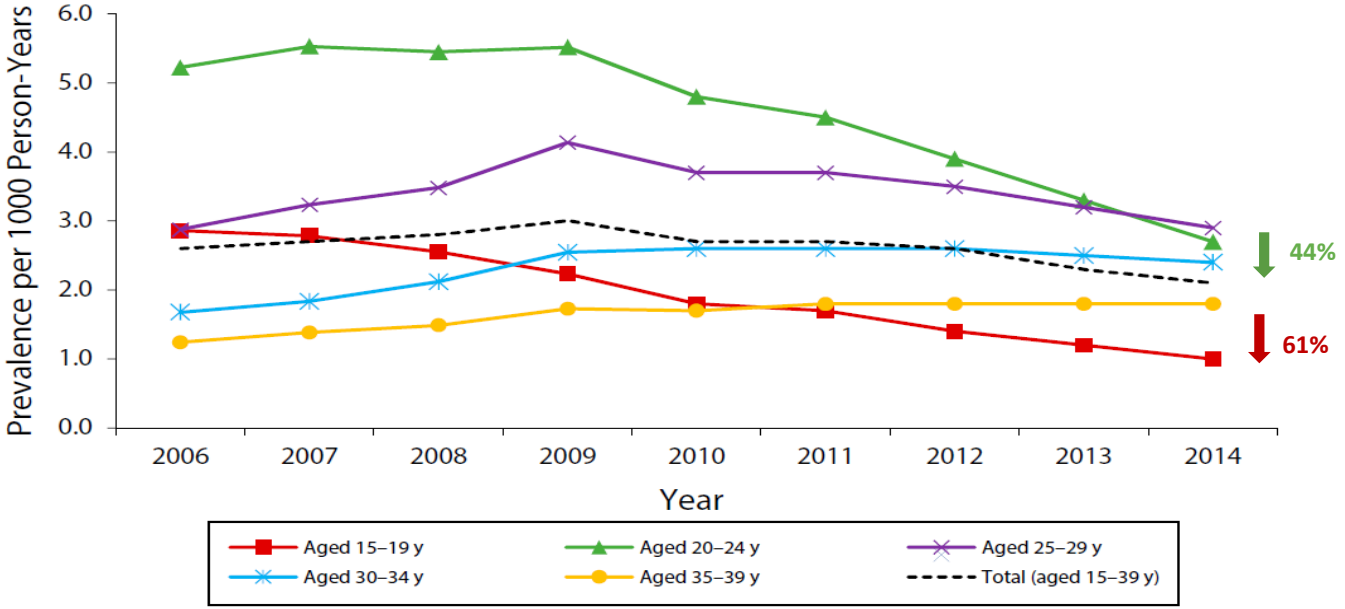
Later vaccine era compared to pre-vaccine era, females



Oliver et al. JID 2017

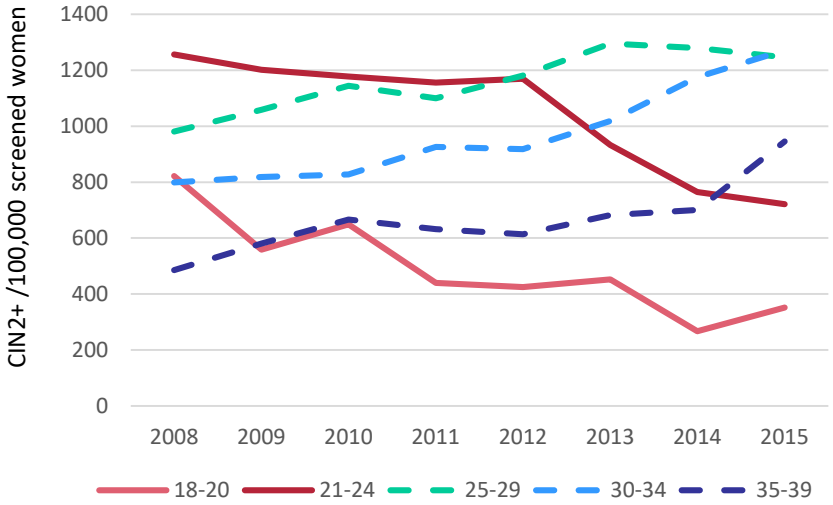
NHANES, National Health and Nutrition Examination Survey

Anogenital wart prevalence among 15–39 year-olds females with private insurance, United States, 2006–2014



Flagg et al. AJPH 2017

Estimated cervical precancer incidence rates per 100,000 screened women, HPV IMPACT Project



- CIN2+ rates decreased significantly in estimated screened women aged 18-20 and 21-24 years
- CIN2+ rates increases in screened women aged 25-29, 30-34, and 35-39 years
  - Could be attributable to longer screening intervals and/or increased sensitivity of screening or diagnostic tests

CIN2+, cervical intraepithelial neoplasia, grade 2 or worse or adenocarcinoma in situ

Gargano et al. CID in press

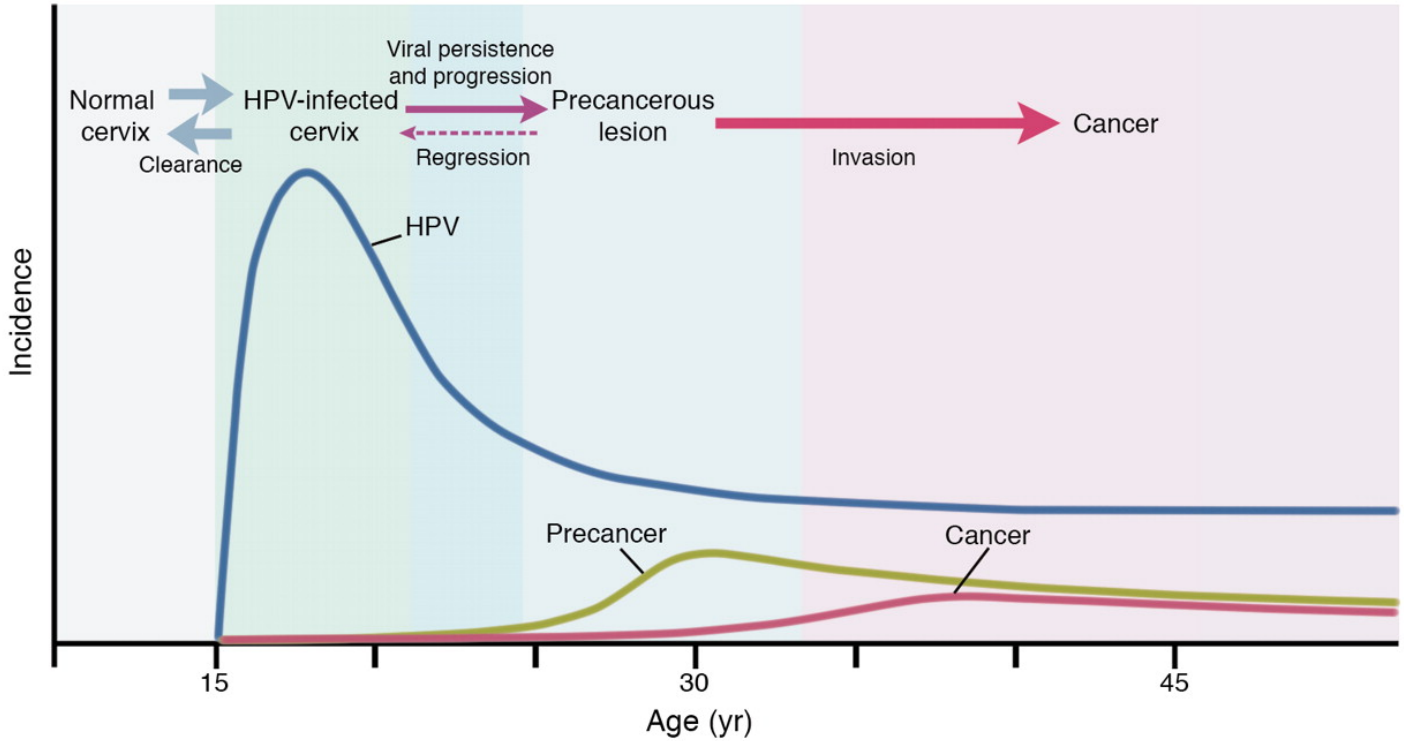
Estimated HPV-attributable cancers per year United States, 2011–2015

Cancer site	Percentage attributable to HPV	Estimated number attributable to any HPV type per year		
		Female	Male	Total
Cervix	91%	10,800	0	10,800
Vagina	75%	600	0	600
Vulva	69%	2,700	0	2,700
Penis	63%	0	800	800
Anus*	91%	4,000	1,900	5,900
Oropharynx	70%	2,200	10,700	12,900
TOTAL		**20,300**	**13,400**	**33,700**

*Includes anal and rectal squamous cell carcinomas

Sources: https://www.cdc.gov/cancer/hpv/statistics and Saraiya et al. J Natl Cancer Inst. 2015

HPV natural history

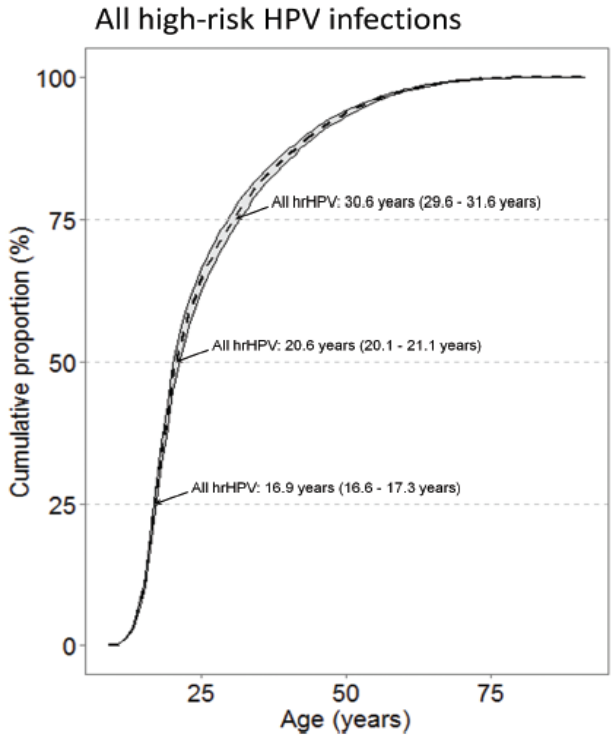


Schiffman et al. NEJM 2005

What proportion of cervical cancers are caused by HPV infections acquired by different ages?

Modeling estimate:

- 50% of women acquired causal HPV infection by age 21 years
- 75% of women acquired causal HPV infection by age 31 years



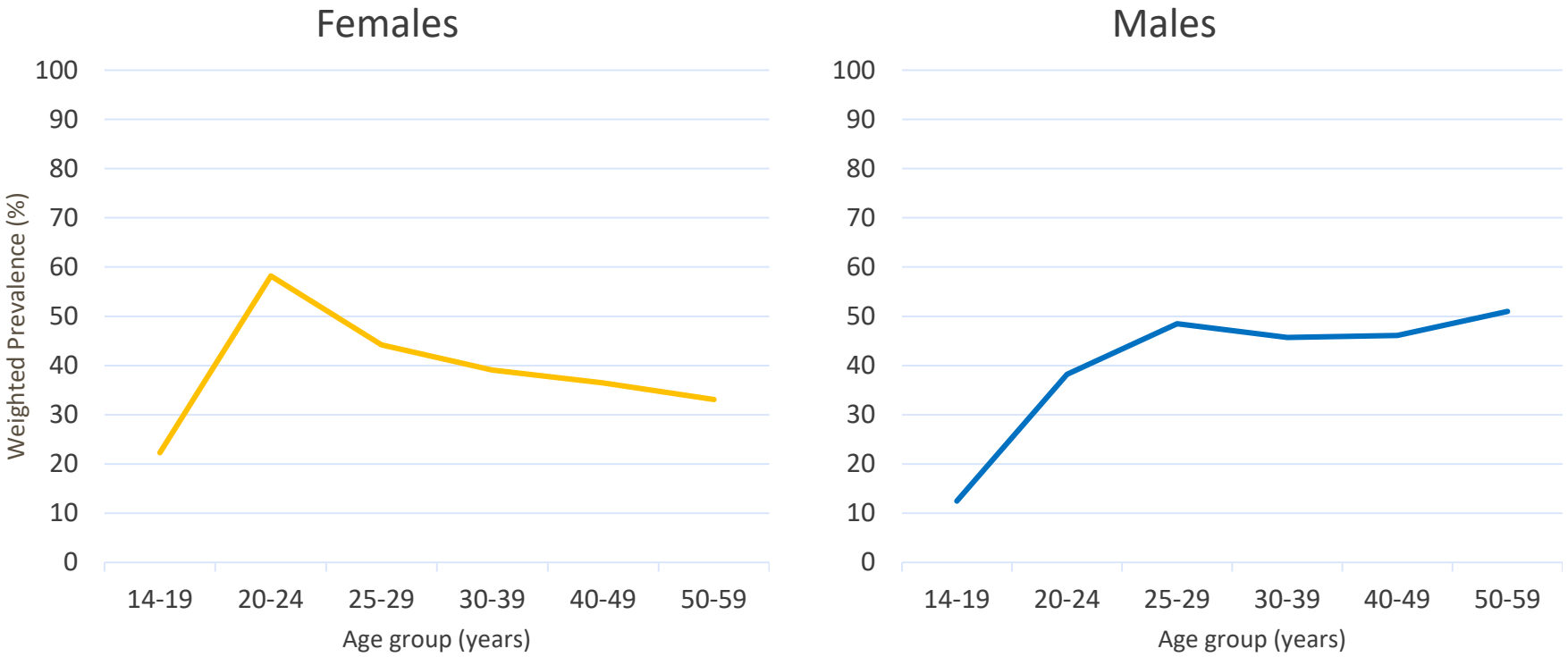
Burger at al. CID 2017

Expanded age indication: Defining the problem and potential benefit of vaccination

Benefit and potential impact of HPV vaccination in mid-adults is influenced by

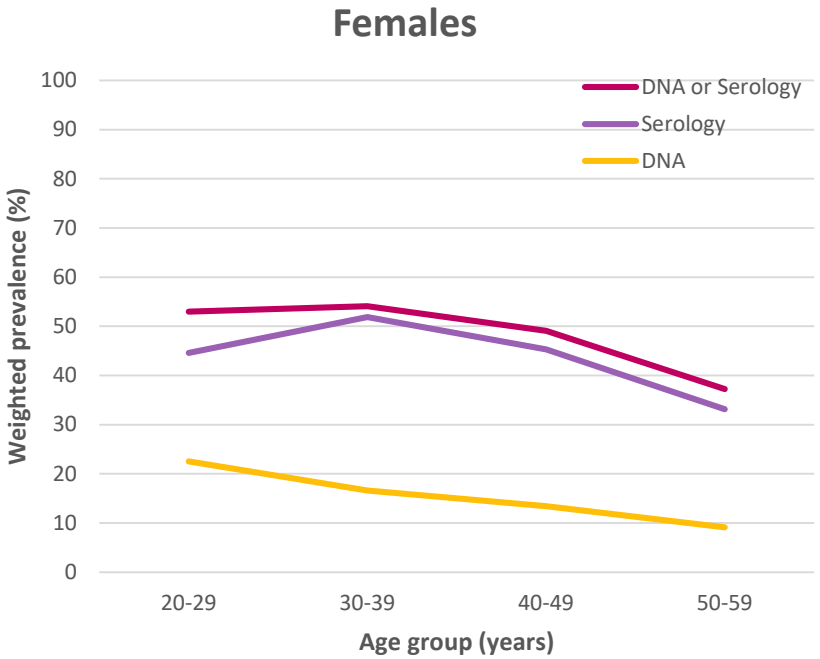
- Likelihood of already having had vaccine-type infection
- Immunity after natural infection
- Risk of incident infection
- Risk of development of disease from incident infection
- Vaccine efficacy against reinfection with a type previously cleared

Any HPV type prevalence by age group and sex NHANES, 2013–2014



CDC, unpublished data; adapted from Lewis et al. JID 2018; NHANES, National Heath and Nutrition Examination Survey

Any 9vHPV-type DNA prevalence and seroprevalence 20–59 year-old females, NHANES, 2005–2006

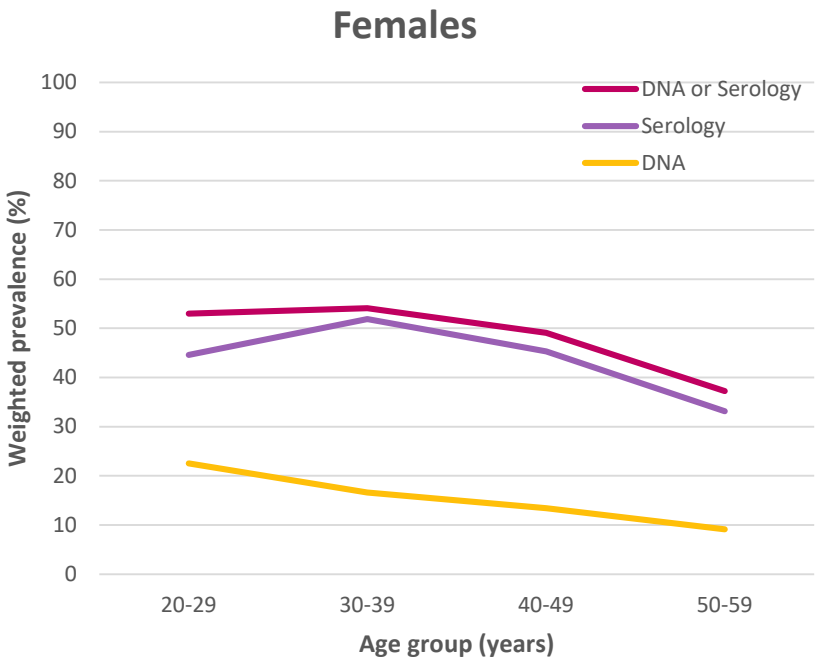


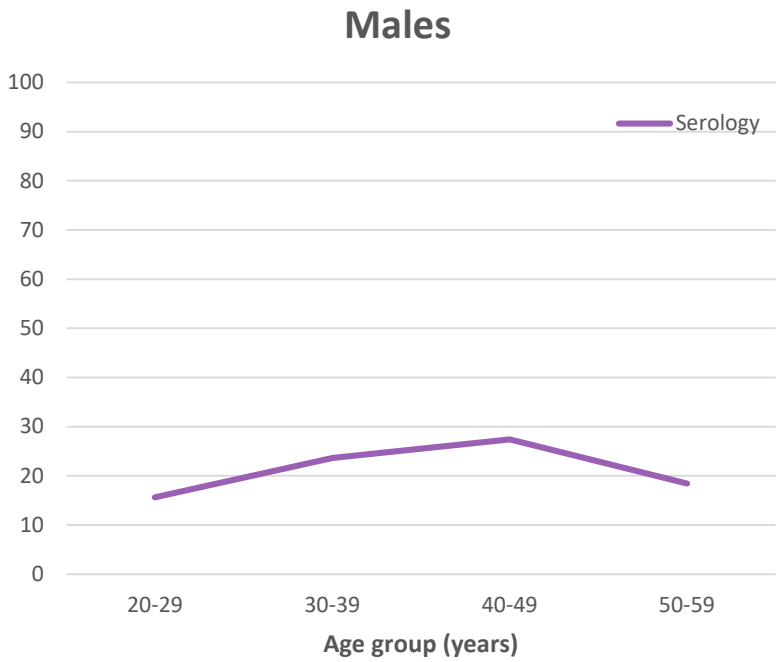
- DNA and antibody detection are imperfect measures of current and past infection
- Not all persons develop antibody after HPV infection; varies by HPV type
  - Females 50–70%
  - Males 4–36%

Antibody measured by competitive Luminex immunoassay
Adapted from Liu et al. JID 2016 and Liu et al. STD 2016

Carter et al, JID 2000
Edelstein et al. JID 0211

Any 9vHPV-type DNA prevalence and seroprevalence 20–59 year-olds, NHANES, 2005–2006





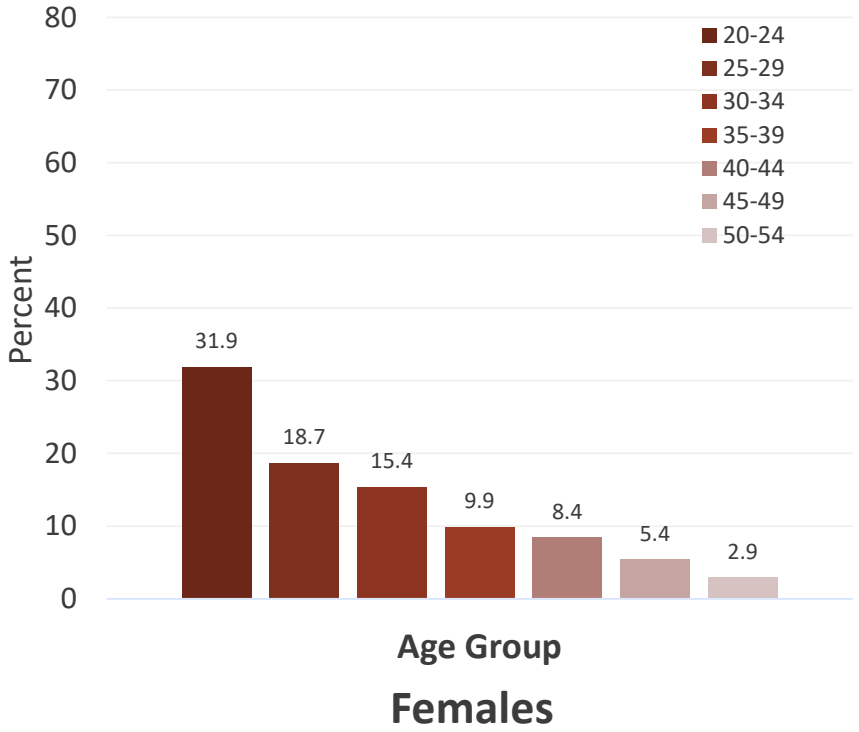
Antibody measured by competitive Luminex immunoassay
Adapted from Liu et al. JID 2016 and Liu et al. STD 2016

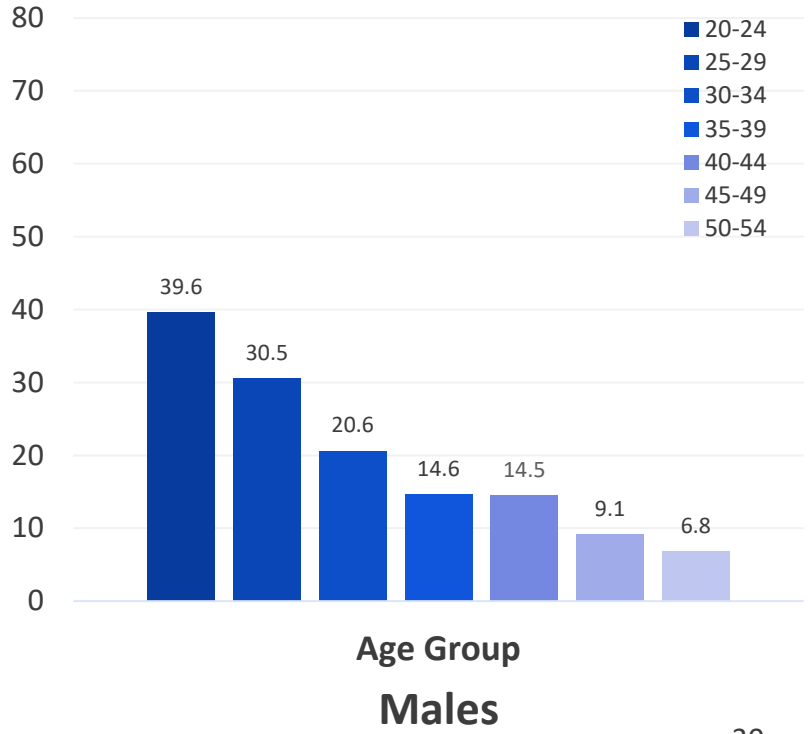
U.S. studies of HPV incidence in mid-adult women

	Major U.S. cities Winer et al. JID 2016	**Baltimore, MD** Rositch et al. Cancer Res 2012
Population	On-line daters	OB/GYN clinic attendees
Age range, yrs	25–65	35–60
New male partner	50%	10%
Incident HPV detection	High risk HPV 29.5/100 women-yrs	Any HPV 14/100 women-yrs

In women with new partners, 64-82% of new detections attributed to newly acquired infection

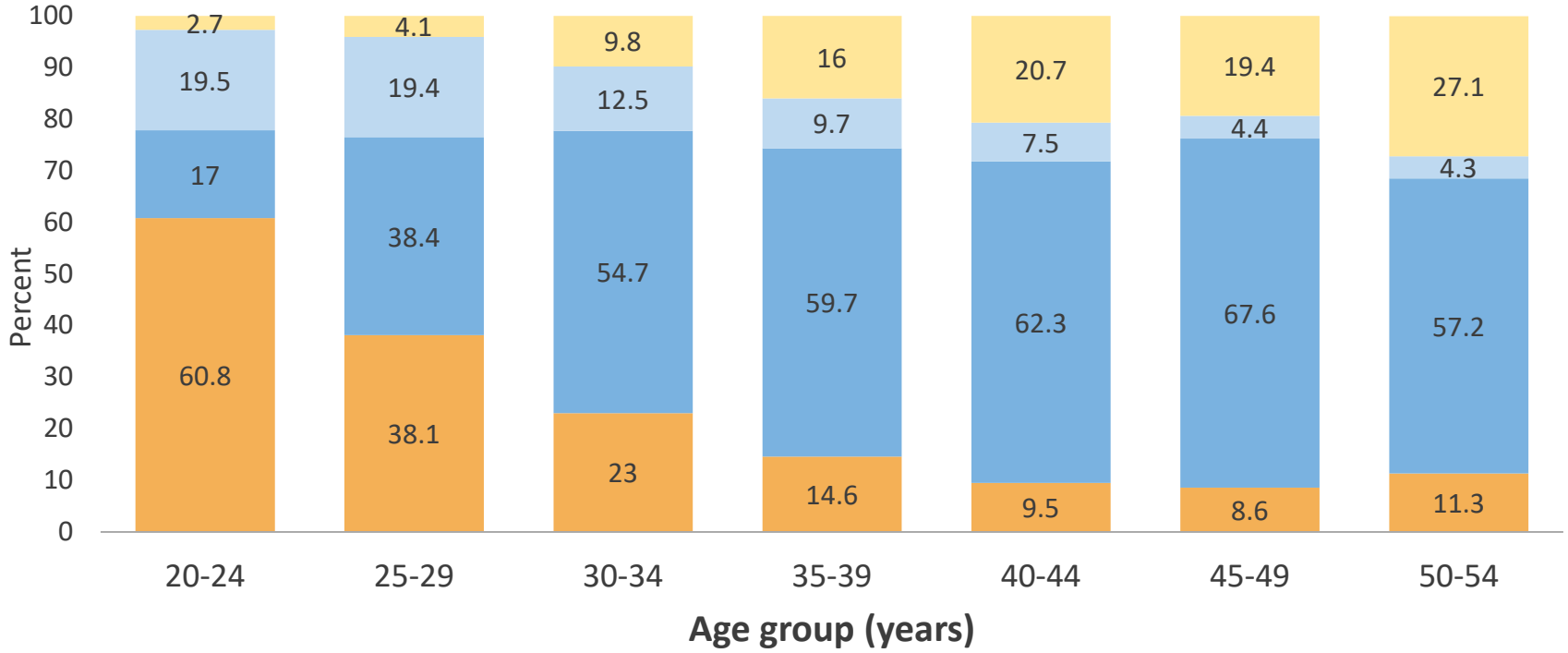
>1 new sex partner in past year, by age group and sex United States, 2013–2016





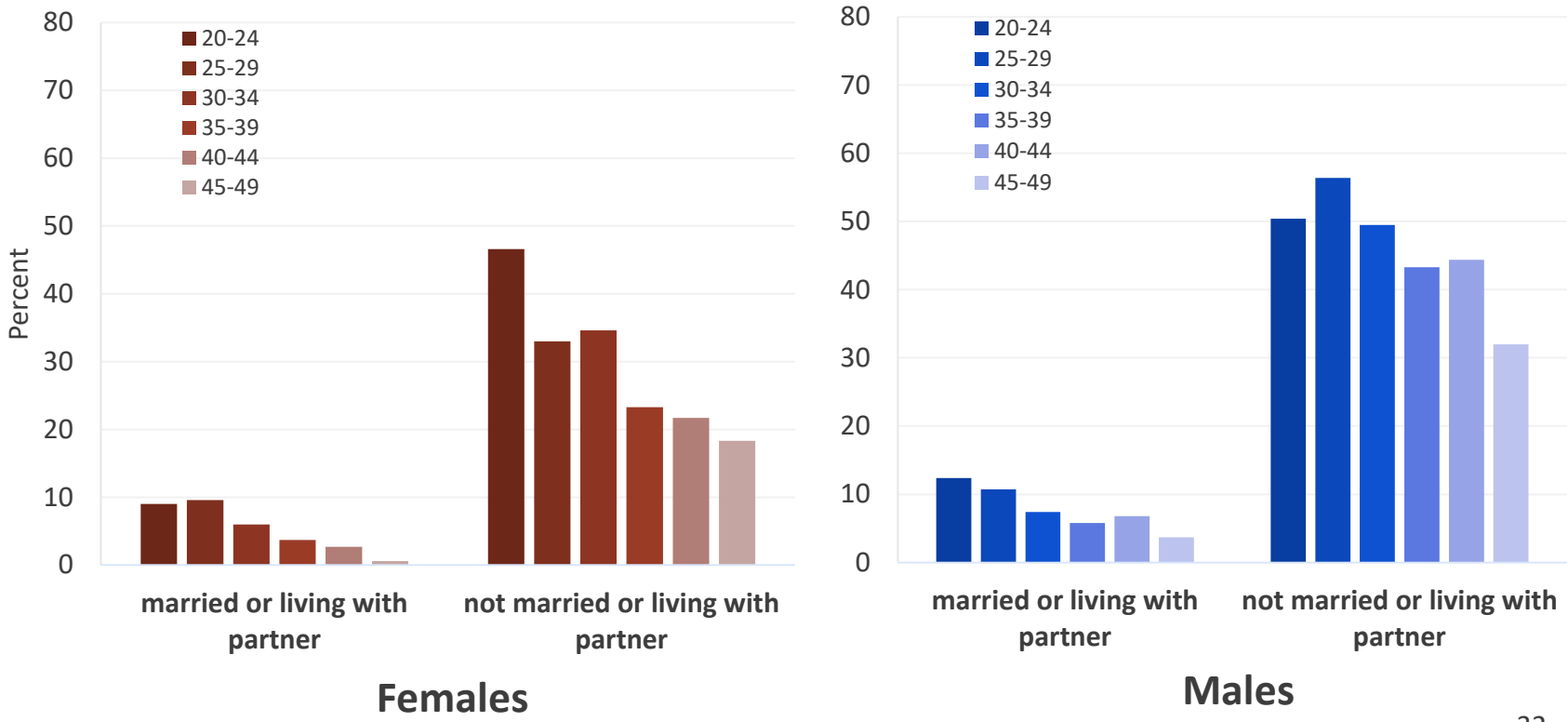
CDC, NHANES unpublished data; ≥1 past year new partner among those who reported ever having sex

Marital status, by age group, females
United States, 2013–2016



CDC, NHANES unpublished data

≥1 new partner in past year, by sex, age group and marital status, United States, 2013–2016



CDC, NHANES unpublished data; ≥1 past year new partner, among those who reported ever having sex

Understanding the potential benefit of vaccination in mid-adults is complex

- HPV infection is common, infection occurs soon after first sexual activity
- Challenges in studies of HPV incidence
  - HPV DNA detection can not distinguish between new, persistent, or redetection of infection
- New HPV infections occur in adults and sex with a new partner remains a risk for infections
  - Percent of adults with a new sex partner in past year is lower with increasing age
- Not all infected individuals develop antibody: males < females
  - Uncertainly about immunity after clearance of infection
  - No protective antibody level identified

Vaccine effectiveness studies

Background

- High efficacy found in clinical trials in mid-adult women in per-protocol analyses, but lower efficacy in intent-to-treat analyses
- Vaccine effectiveness studies can provide information on real world effectiveness of vaccine and vaccination programs
- Studies in countries with catch-up vaccination have been able to evaluate effectiveness by age at vaccination

Review of HPV vaccine effectiveness studies

- Reviewed post-licensure effectiveness studies that included analyses by age at vaccination
  - Limited to evaluations of 3 vaccine doses
  - Extracted basic information on
    - Study design, age at outcome, age at vaccination
    - Buffer period: time between vaccination and case counting
    - Relative risk or other measure

HPV vaccine effectiveness studies that included analyses by age at vaccination

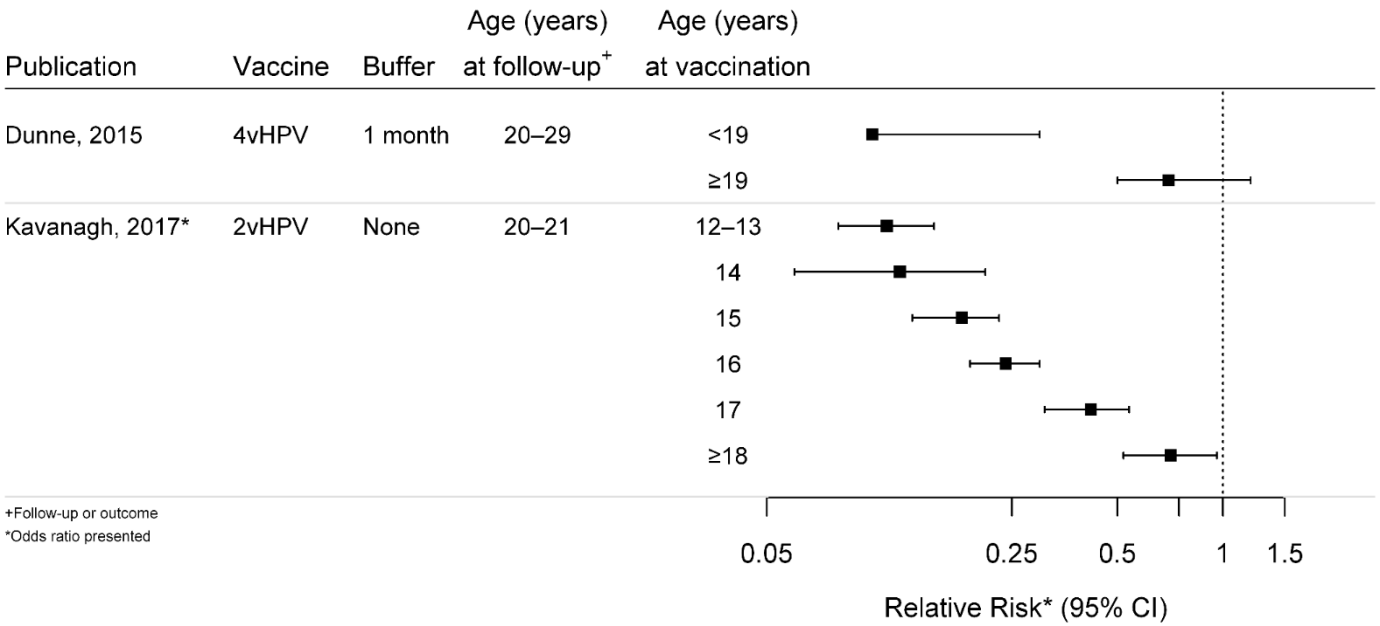
Outcome	Number of studies	Country
HPV vaccine-type prevalence	2	United States, Scotland
Anogenital warts	5	United States, Sweden, Belgium, Canada
Cervical lesions	4	United States, Sweden, Australia

Studies evaluating effectiveness against HPV vaccine-type prevalence

Publication	Country	Study Design
Dunne, 2015	United States	Women screened for cervical cancer at an integrated health care delivery system
Kavanagh, 2017	Scotland	Women screened for cervical cancer and national registries

Dunne, J Infect Dis 2015; Kavanagh, Lancet 2017

Risk reduction for vaccine-type prevalence, by age at vaccination



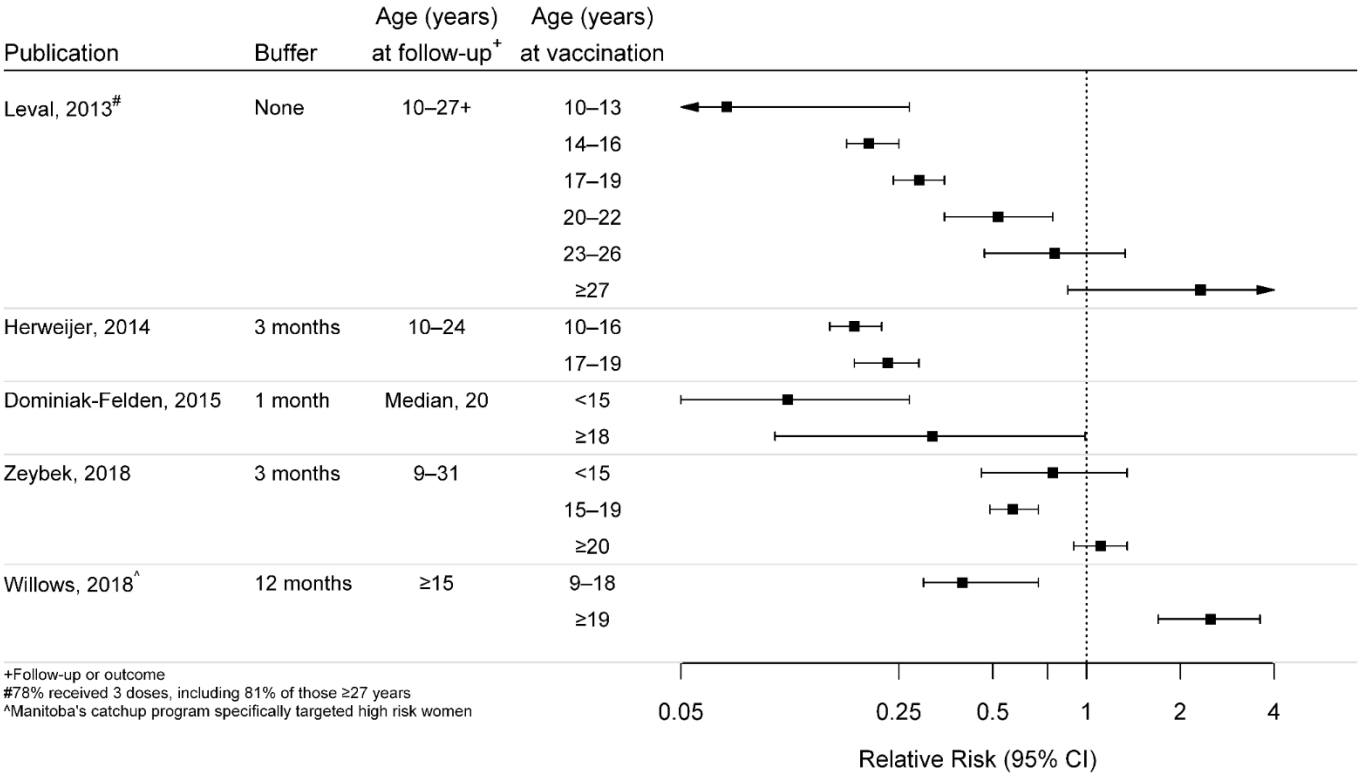
Relative risk - measured as prevalence ratio, hazard ratio or incidence rate ratio
Dunne, J Infect Dis 2015; Kavanagh, Lancet 2017

Studies evaluating effectiveness against anogenital wart by age at vaccination

Publication	Country	Study Design
Leval, 2013	Sweden	Retrospective cohort study using population-based health registries
Herweijer, 2014	Sweden	Retrospective cohort study using population-based health registries
Dominiak-Felden, 2015	Belgium	Retrospective cohort study using sick-fund/ insurance data
Zeybek, 2018	United States	Retrospective matched cohort study using health insurance claims data
Willows, 2018	Canada	Retrospective matched cohort study using population-based health registries

Leval, JNCI 2013; Herweijer, JAMA 2014; Dominiak-Felden, Plos One 2015; Zeybek, JLGTD 2018; Willows, Sex Trans Dis 2018

Risk reduction for anogenital warts, by age at vaccination



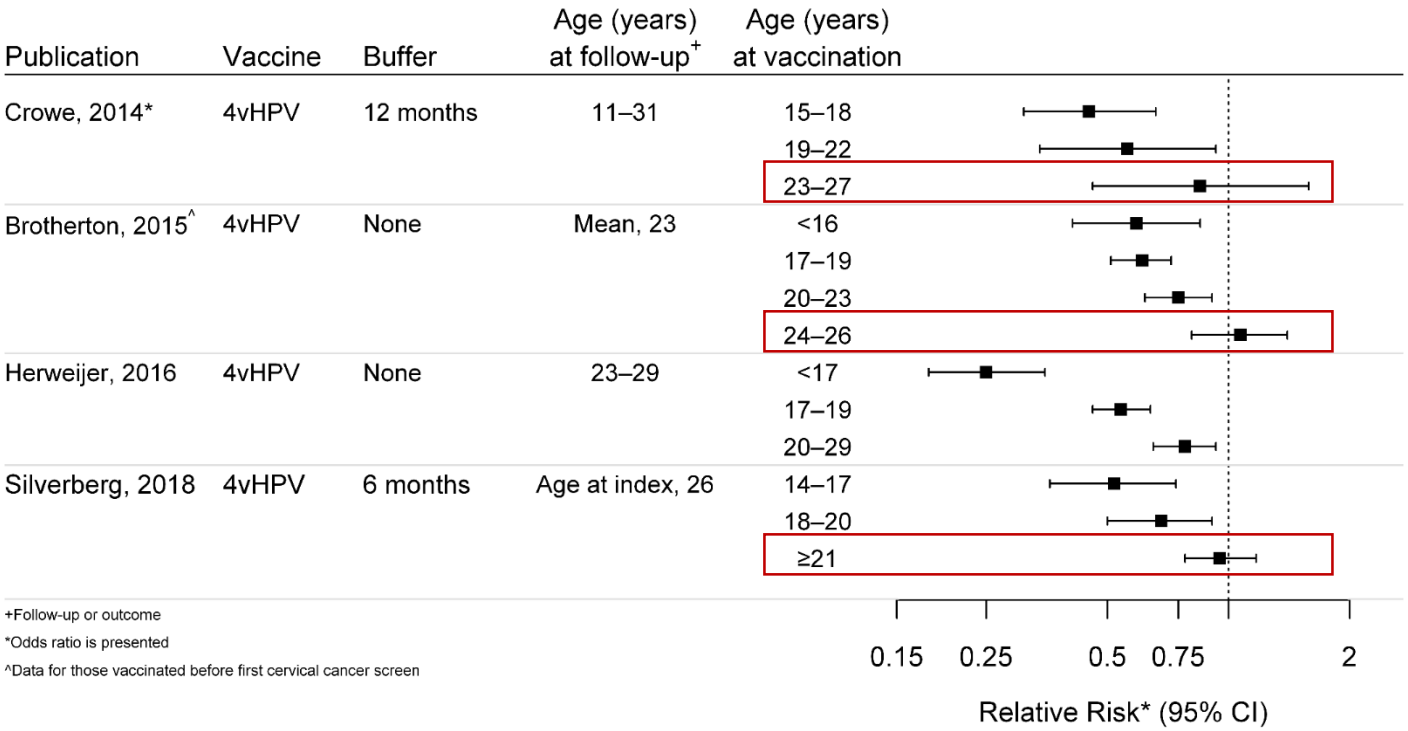
Relative risk - measured as prevalence ratio, hazard ratio or incidence rate ratio
Leval, JNCI 2013; Herweijer, JAMA 2014; Dominiak-Felden, Plos One 2015; Zeybek, JLGTD 2018; Willows, Sex Trans Dis 2018

Studies evaluating effectiveness against cervical intraepithelial neoplasia grade 2 or worse (CIN2+), by age at vaccination

Publication	Country	Study Design
Crowe, 2014	Australia	Case control study using linked data from registries
Brotherton, 2015	Australia	Retrospective cohort using linked regional data registries
Herweijer, 2016	Sweden	Retrospective cohort using linked national registries
Silverberg, 2018	United States	Nested case-control study using electronic medical records from integrated health-care delivery system

Crowe, BMJ 2014; Brotherton, Papillomavirus Res 2015; Hertweijer, Int J Cancer 2016; Silverberg, Lancet Child-Adol 2018

Risk reduction for CIN2+, by age at vaccination



Relative risk - measured as prevalence ratio, hazard ratio or incidence rate ratio

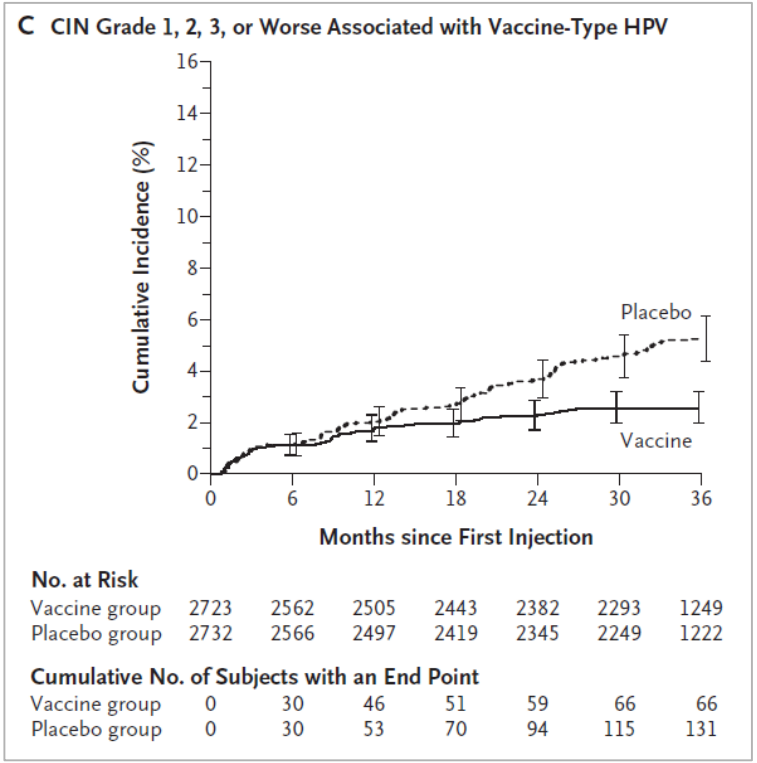
Crowe, BMJ 2014; Brotherton, Papillomavirus Res 2015; Herweijer, Int J Cancer 2016; Silverberg, Lancet Child Adolesc Health 2015

Summary

- 11 studies reviewed, conducted in 6 different countries
- All found lower effectiveness with increasing age at vaccination
  - 7 found no significant effectiveness in the oldest age group evaluated

Intention-to-treat analyses in HPV vaccine clinical trials

- Intention-to-treat population includes
  - Individuals with vaccine type infection at time of vaccination
- No efficacy observed in first year
  - Most cases had evidence of infection or disease that was prevalent at enrollment
- During second year, incidence of vaccine-type disease
  - Placebo group - continued to increase
  - Vaccine group - began to plateau



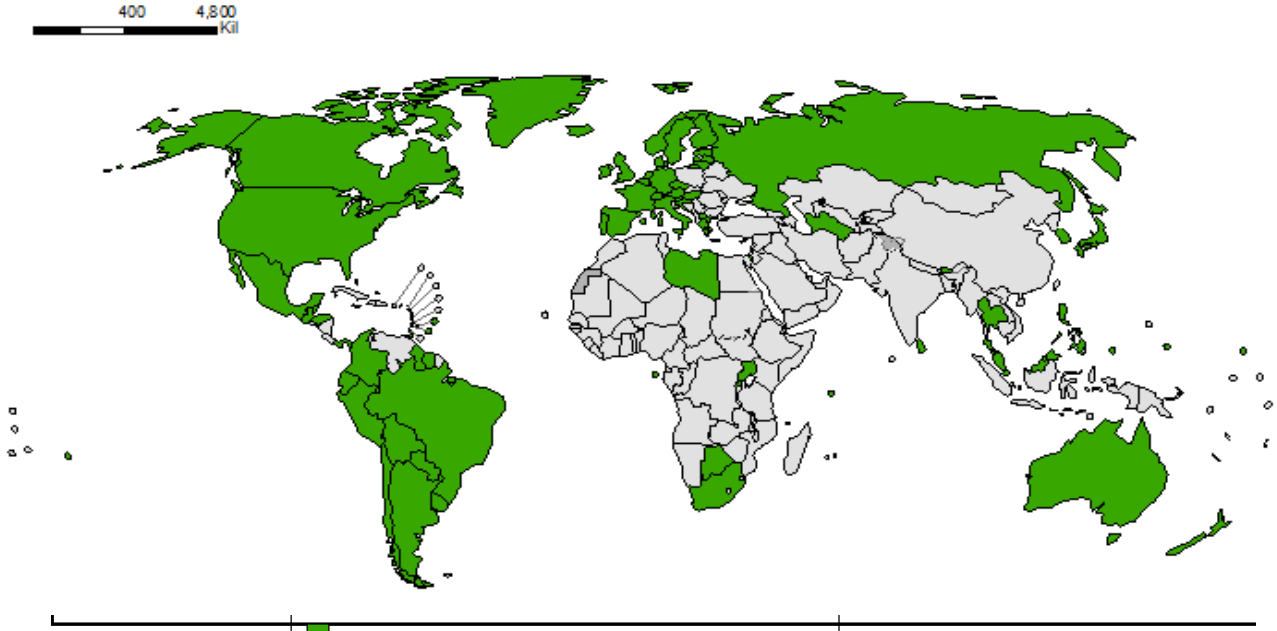
Garland et al. New Eng J Med 2007

Conclusions

- Estimated vaccine effectiveness lower with increasing age at vaccination
  - Due to higher HPV prevalence at time of vaccination
- Methodological challenges for evaluating vaccine effectiveness
  - Biases due to differences in vaccinated and unvaccinated persons
  - Some findings could be result of higher risk persons in older age groups being targeted for vaccination at beginning of vaccine program (reported in one study)
  - Time between vaccination and case counting in published studies likely impacts ability to observe vaccine effectiveness among persons vaccinated at older ages
- Data support importance of vaccination in early adolescence

Global HPV vaccine issues

Countries with HPV vaccine in the national immunization program, 2018

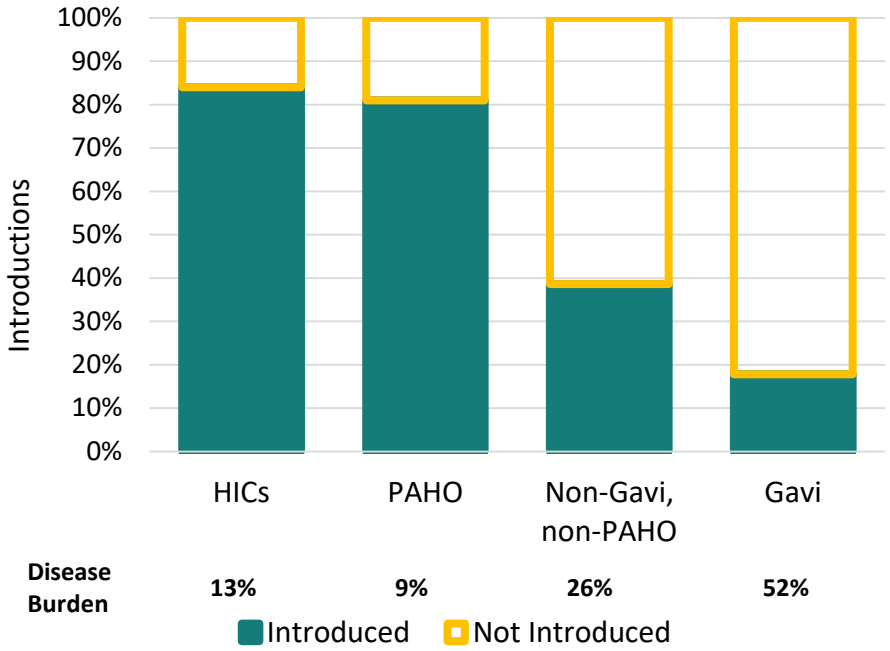


* Includes partial introduction

Data source: WHO/IVB Database, as of 15 May 2018
Map production Immunization Vaccines and Biologicals (IVB),
World Health Organization

HPV Vaccine Introduction Status

Middle income countries (MICs) and Gavi countries lag far behind high income countries (HICs) and PAHO procuring countries



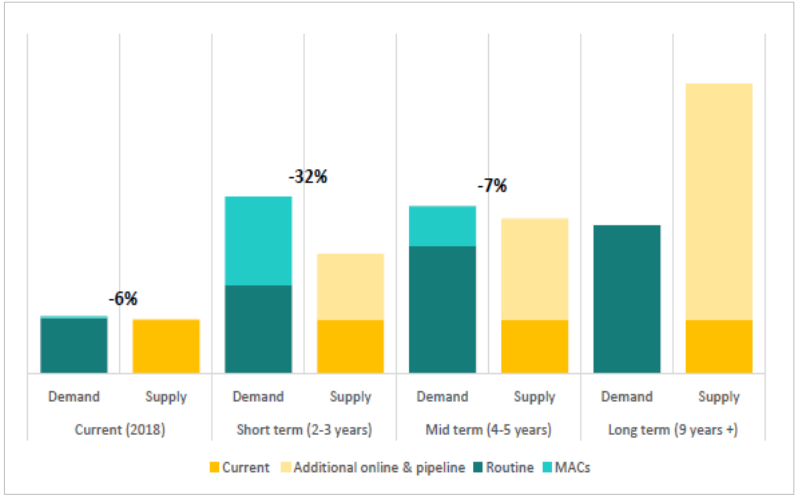
- Countries that have introduced account for only 25% of the global target population
- Only 13 of 73 Gavi countries have introduced HPV, but have >50% of HPV disease burden
- MICs, of which only 39% have introduced, account for greater disease burden than HICs and PAHO combined

World Health Organization

MI4A MARKET INFORMATION FOR ACCESS TO VACCINES

Source: WHO/IVB Database, as of 15 May 2018. HPV Burden – WHO Position Paper 2017

Global demand/supply balance – HPV vaccine



- Vaccine supply is currently insufficient to meet demand; some countries have or will have to postpone introductions
- Demand/supply imbalance is forecasted to grow and remain through 2023
- From 2024 onward supply is expected to support demand

MACs, multi-age cohorts (ages 9-13 years)
World Health Organization/Global Market, September 2018
http://www.who.int/immunization/programmes_systems/procurement/v3p/platform/module2/WHO_HPV_market_study_public_summary.pdf?ua=1

Summary

- Data submitted to FDA in support of expanded age range through age 45 years
  - Include a RCT: efficacy high in women naïve to vaccine type; lower efficacy in intent-to-treat population
- United States data to inform the policy considerations
  - HPV vaccine coverage is increasing in adolescents
  - Impact of the vaccination program has been observed among females in teens and twenties
  - Most adults have already been exposed to a 9vHPV type, but not all 9vHPV types
  - HPV incidence is lower at older ages, but new infections can occur in adults
  - New sex partner is a risk factor for incident HPV infection
- Post-licensure vaccine effectiveness evaluations
  - Vaccine effectiveness is lower with increasing age at vaccination
- Update on global HPV vaccination
  - Less than 50% of countries have introduced HPV vaccination
  - Global vaccine shortage is limiting introductions in some countries
  - No current HPV vaccine shortage in the United States

Acknowledgements

Rayleen Lewis
Raiza Amiling
Julia Gargano
Elissa Meites
Elizabeth Unger
Mona Saraiya
Harrell Chesson

ACIP HPV Vaccines Work Group

ACIP Members
Peter Szilagyi (Chair)
Jose Romero

Ex Officio Members
Jeff Roberts (FDA)
Joohee Lee (FDA)

CDC Lead
Lauri Markowitz

Liaison Representatives
Vinita Dubey (NACCI)
Linda Eckert (ACOG)
Sandra Fryhofer (ACP)
Amy Middleman (SAHM)
Chris Nyquist (AAP)
Sean O'Leary (PIDS)
Robin O'Meara (AAFP)
Patricia Whitley-Williams (NMA)
Jane Zucker (AIM)

Consultants
Joseph Bocchini
Tamera Coyne-Beasley
John Douglas
Sam Katz
Allison Kempe
Aimee Kreimer (NCI)
Debbie Saslow (ACS)
Rodney Willoughby
Rachel Winer

CDC Contributors

Jorge Arana
Harrell Chesson
Robin Curtis
Julianne Gee
Elissa Meites
Jeanne Santoli
Mona Saraiya
Shannon Stokley
Lakshmi Panagiotakogoulos
Elizabeth Unger