Possible expanded age indication for 9-valent HPV vaccine through age 45 years

Considerations and ACIP HPV Vaccines Work Group plans

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Outline

- Introduction to policy considerations
- Overview of evidence to help assess burden/benefit
  - HPV prevalence, incidence, immunity after natural infection
- Range of policy options
- Plans for October ACIP meeting

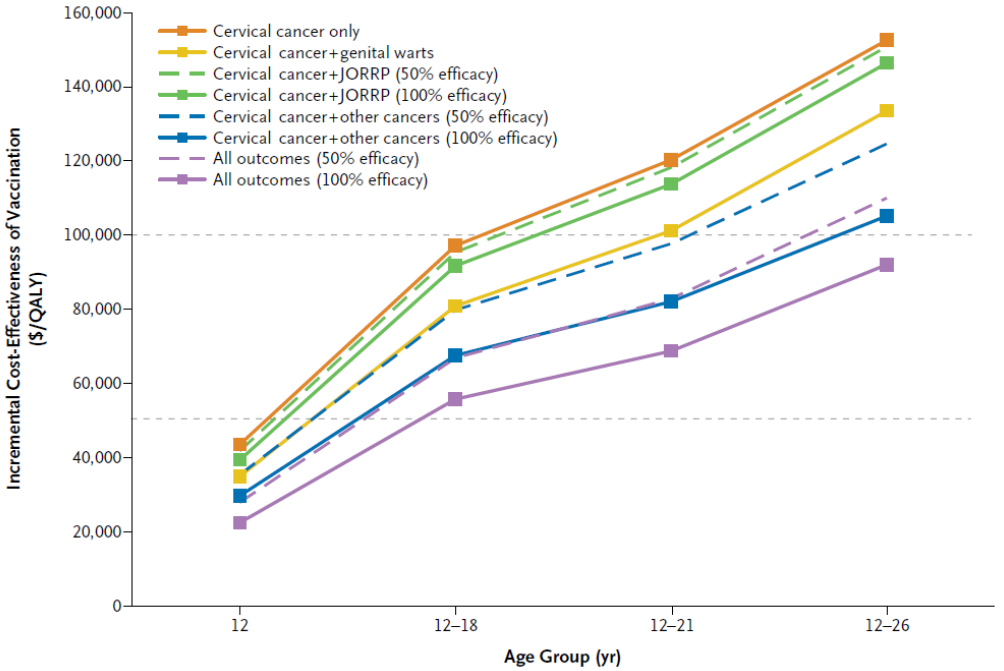
Introduction to policy considerations:
Possible expanded age indication

- Available HPV vaccines are prophylactic
- HPV vaccination will have greatest impact when administered before onset of sexual activity and HPV exposure
- Over 90% of men and women are sexually active by mid 20's
- Models show cost effectiveness of HPV vaccination becomes less favorable as age at vaccination increases*

*Kim et al. NEJM 2008; Kim et al. Ann Intern Med 2009; Canfell et al. Vaccine 2012

Cost-effectiveness of HPV vaccination of females in the United States

Modeling considered for vaccine policy at the beginning of the vaccination program in the United States



Kim et al. NEJM 2008

Policy considerations:
Possible expanded age indication

- **No change in routine age for HPV vaccination**
  - Age 11-12 years
  - Can be started at age 9 years
- **Could impact recommendations for**
  - Catch-up
  - Persons older than determined catch-up age

Consideration of possible expanded age indication for 9vHPV through age 45 years

- Work Group will be using the *Evidence to Recommendations* framework
- This presentation: overview of some of the data needed to understand the burden of disease – to inform the problem and potential benefits of vaccination

Evidenceto Recommendations framework

- PICO question and background
- Problem
- Benefits and harms
- Values
- Acceptability
- Resource use
- Feasibility of implementation
- Balance of consequences
- Type of recommendation and recommendation text

Diseases associated with HPV

- **Oncogenic (high risk) types – e.g. HPV 16, 18**
  - Cervix cancers
  - Vagina cancers
  - Vulva cancers
  - Penis cancers
  - Anus cancers
  - Oropharynx cancers
  - High grade intraepithelial neoplasias
- **Non-oncogenic types – e.g. HPV 6, 11**
  - Anogenital warts
  - Recurrent respiratory papillomatosis

Burden: Estimated HPV-attributable cancers per year United States, 2010–2014

Cancer site	Percentage attributable to HPV	Estimated number attributable to any HPV type per year		
		Female	Male	Total
Cervix	91%	10,600	0	10,600
Vagina	75%	600	0	600
Vulva	69%	2,600	0	2,600
Penis	63%	0	800	800
Anus*	91%	3,800	1,900	5,700
Oropharynx	70%	2,100	10,100	12,200
TOTAL		**19,700**	**12,800**	**32,500**

*Includes anal and rectal squamous cell carcinomas

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

Possible expanded age indication: Defining the problem and benefit of vaccination

Benefit and potential impact of HPV vaccination is influenced by

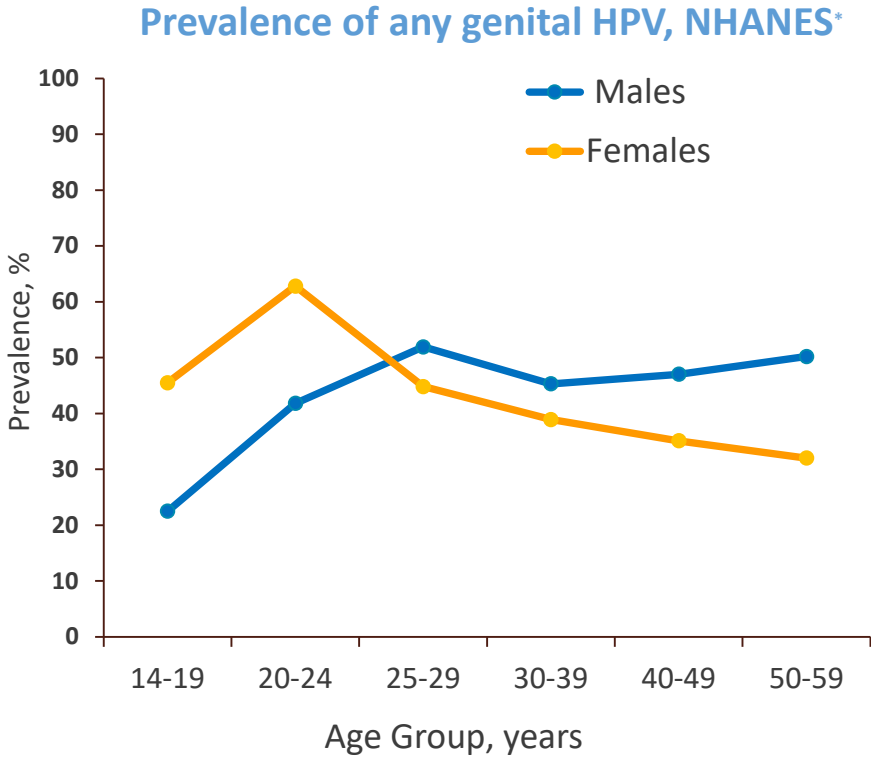
- Likelihood of already having had vaccine-type infection
- Risk of incident infection
- Risk of development of disease from incident infection
- Immunity after natural infection
- Vaccine efficacy against reinfection

HPV epidemiology

- HPV is a common sexually transmitted infection in females and males
- Prevalence and infection rates differ by age and sex
- Infection patterns differ by anatomic site
  - e.g. higher prevalence in the genital versus oral region
- Immune response to natural infection differs by anatomic site of infection
- Immune response to natural infection is stronger and more protective against re-infection in females than males

Giuliano et al. Int J Cancer 2015

HPV DNA prevalence in males and females United States, 2013-2014



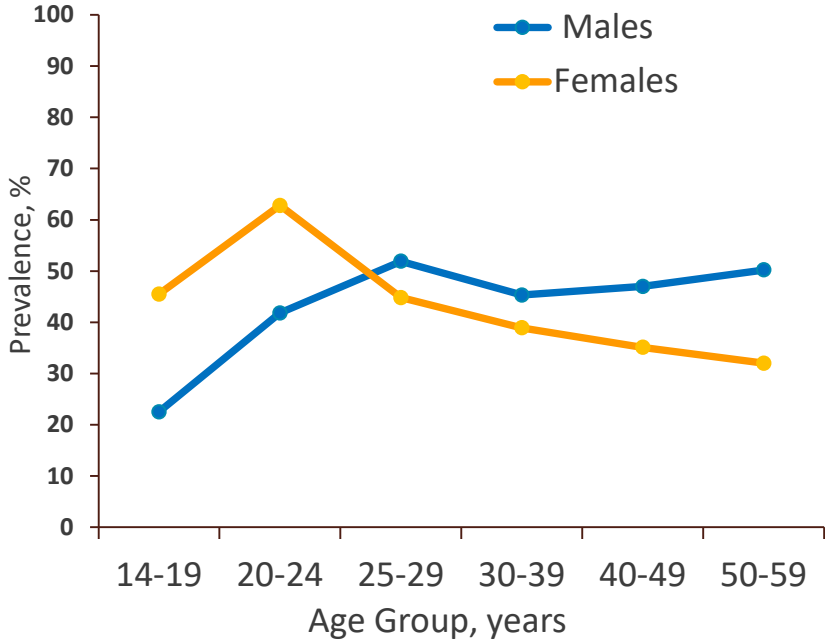
*among sexually experienced persons

- High prevalence in both males and females
- In females prevalence is highest in early 20s and is lower in older age groups
- In males prevalence is similar in age groups 25-29 and older

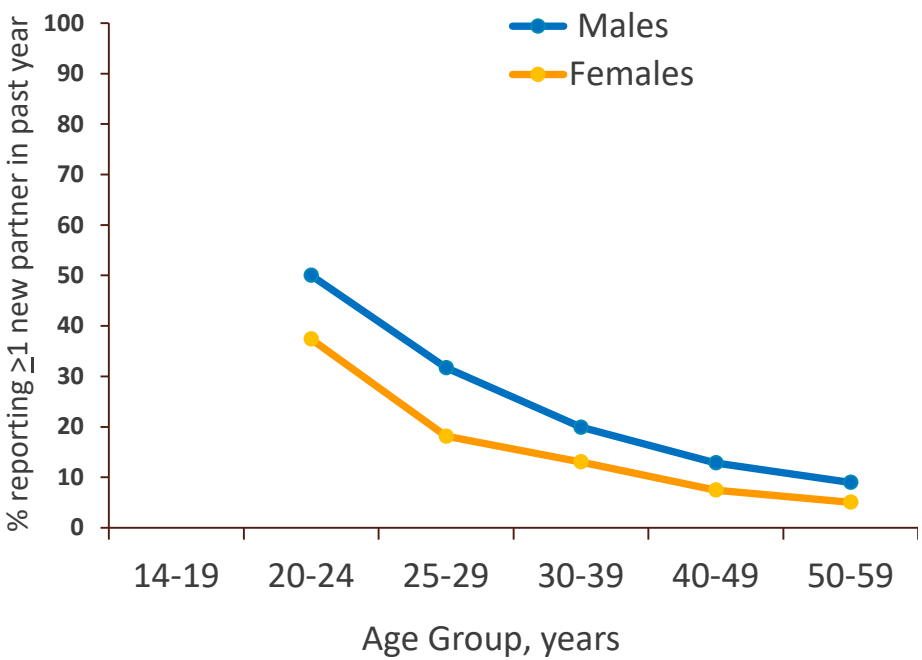
Lewis et al, JID 2018; Gargano et al, JID 2017
NHANES, National Health and Nutrition Examination Survey

HPV DNA prevalence and report of at least 1 new sex partner — United States, 2013-2014

Prevalence of any genital HPV, NHANES*



Percent reporting ≥1 new sex partner in the past year, NHANES+*



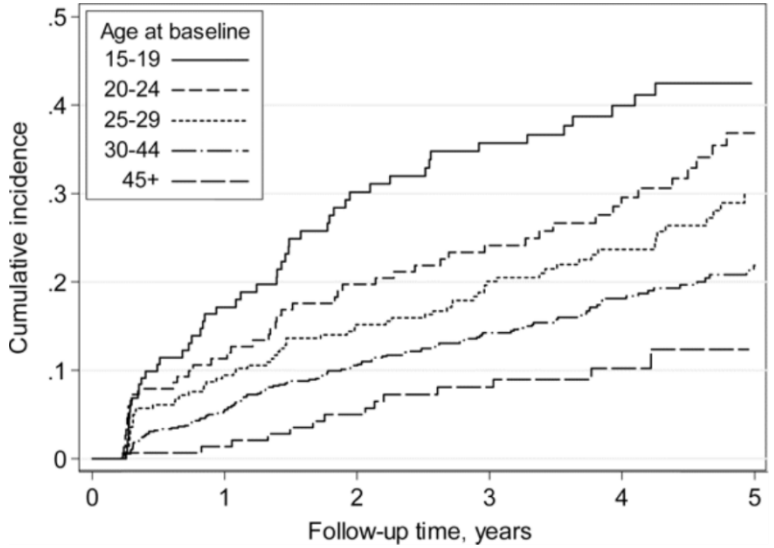
Lewis et al, JID 2018; Gargano et al, JID 2017
NHANES, National Health and Nutrition Examination Survey

*among sexually experienced persons +CDC, unpublished data

Genital HPV incidence, by age

- Study of HPV incidence among 15–85 year-old women in Columbia
- Highest cumulative risk for any HPV was in 15–19 year-olds (43%)
- Cumulative HPV incidence decreased in older age groups

Women: Cumulative risk of any HPV

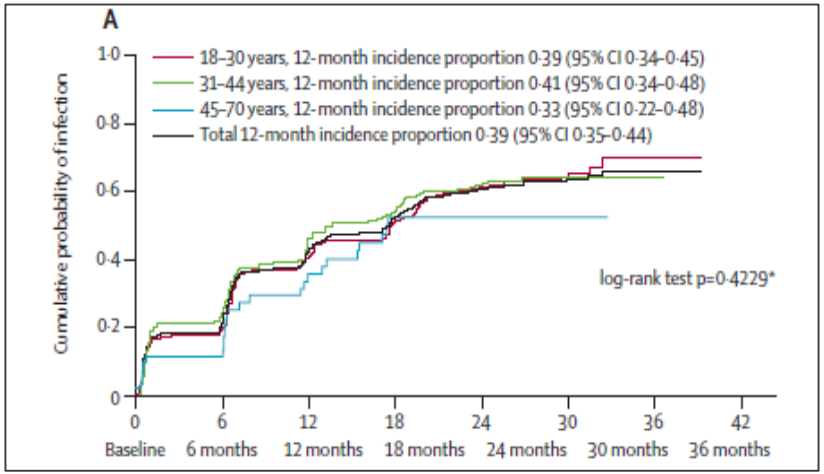


Munoz et al. JID 2004

Genital HPV incidence, by age

- Study of HPV incidence among 18–70 year-old men in U.S., Mexico and Brazil
- Incidence of any HPV did not vary significantly by age

Men: Cumulative risk of any HPV



Follow-up time, months

Giuliano et al. Lancet 2011
HIM study

New HPV infection or re-detection of previous infection?

- In adults, incident HPV detection may be a new infection or re-detection of a previously acquired infection
  - Methodologically difficult to distinguish
  - Vaccination is expected to prevent new infections
- Several studies in females have been conducted to estimate the proportion new detections due to a new infection
  - Evaluating risk factors for a new HPV detection

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

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

	Major U.S. cities Winer et al. J Infect Dis 2016	**Baltimore, MD** Rositch et al. Cancer Res 2012	**Seattle, WA** Fu et al. Int J Cancer 2016
Population	On-line daters	OB/GYN clinic attendees	Affiliated with Univ WA
Age range, yrs	25–65	35–60	30–50
New male partner	50%	10%	31%
Incident HPV detection	High risk HPV 29.5/100 women-yrs	Any HPV 14/100 women-yrs	Cumulative 6 month type-specific high-risk HPV Among seronegative, 1.2% Among seropositive, 2.9%

- Association between recent sexual behaviors and incident DNA detection only among seronegative women
- Among seropositive women, re-detection of same type likely due to reactivation or intermittent detection of persisting infection

Incident genital HPV infection in females

- Risk of incident HPV infection declines with increasing age
- Sex with a new partner is a risk factor for a new infection
- Proportion of new detectable HPV due to prior vs new infection varies by population and depends on past risk and new exposure

- What is risk of new infections in mid-adult women progressing to CIN2+?
  - Data from control arm of 2vHPV trial (Skinner et al. IJC 2016)
  - During 48 months, 3.6% (32/888) of infections progressed to CIN2+

CIN2+, cervical intraepithelial neoplasia grade 2 or worse

Incident genital HPV infection in males

- Risk of incident genital HPV infection is relatively constant with age
- Sex with a new partner is a risk factor for a new infection
- Re-detection of the same HPV type is common
  - Less clear what proportion of new detectable HPV due to prior vs new infection

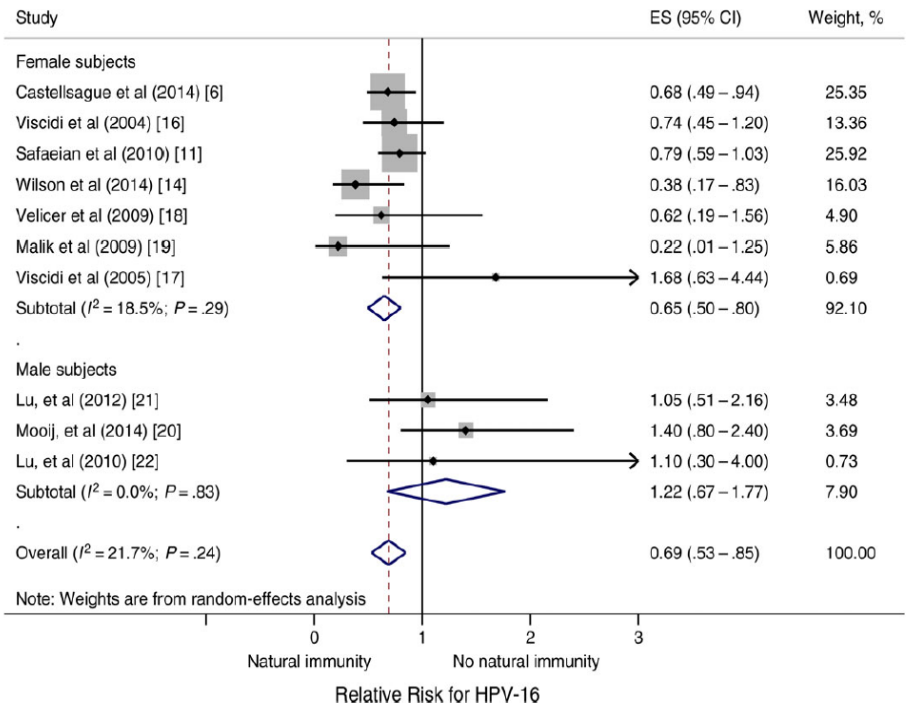
Giuliano et al. Lancet 2011; Pamnani et al. JID 2018

Naturally acquired immunity: systematic review and meta-analysis

14 studies: 11 in females, 3 in males

Conclusion: HPV antibodies acquired through natural infection provide some type-specific protection against subsequent genital infection in females but not in males

Relative risks comparing seropositive with seronegative

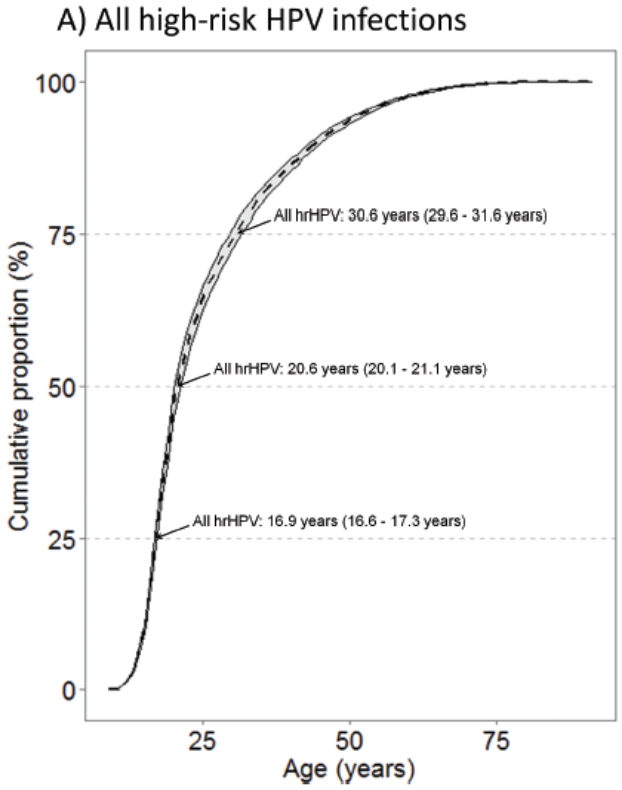


Beachler et al. JID 2016

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

Model projected that among all cervical cancers

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



Burger at al. CID 2017

Natural history and pathogenesis of oropharynx cancer

- Very few natural history studies
- Steps between oral HPV acquisition and development of HPV-positive oropharynx cancer are unknown

Knowns
Risk factors for oral HPV infection and HPV+ oropharynx cancer
Good estimates of oral HPV prevalence
Limited estimates of oral HPV incidence and persistence

Unknowns
HPV-induced precancerous lesion in the oropharynx
Time from acquisition of infection to development of cancer
Disease-relevance of infections acquired at older ages

Chaturvedi, Presented at Feb 2018 ACIP meeting

Burden of HPV infection and disease in special populations

HPV prevalence, incidence, HPV-associated disease higher in some populations

- Anal HPV prevalence is high in men who have sex with men (MSM) and MSM have high risk of anal cancer, particularly those with HIV infection
- Women with HIV/AIDS have significantly higher rates of cervical cancer and some other HPV-associated outcomes than women in the general population
- Work Group will review data related to special populations at a future meeting

https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/343/hpv

Summary

- Based on epidemiology of HPV, the population level benefit of vaccination of mid-adults would be low compared with vaccination at younger ages
- New sex partners decrease with increasing age; sex with a new partner remains a risk for HPV infection in older age groups
- There are differences by sex in HPV prevalence, incidence, immunity after infection, and HPV-associated cancers
- Immunity after natural infection is an important determinant of potential impact of vaccination; might differ for males and females
- Updated modeling and cost effectiveness analyses will provide helpful information for policy considerations

Possible expanded age indication for 9vHPV through age 45 years

Policy options that could be considered

- **For catch-up***
  - Retain current catch-up age
  - Extend catch-up through an older age
- **For persons older than the determined catch-up age**
  - No recommendation
  - Vaccination for individual decision making
  - Recommendations for specific groups

*Harmonization of upper age for catch-up vaccination for males and females could also considered

Harmonization of upper age recommendation for males and females

- Work Group has been considering harmonization of the upper age recommendation for males and females through age 26 years
- There is strong support on the Work Group for harmonization
- Surveys of Association of Immunization Managers (AIM) and of primary care physicians indicated that > 90% support harmonization*
- Harmonization will be considered as the Work Group moves forward to review data related to the possible expanded age indication

*Unpublished data

ACIP HPV Vaccines Work Group plans

June 2018

- Background
- Clinical data submitted in sBLA for an extended age indication
- Considerations and Work Group plans

October 2018

- Epidemiology of HPV/burden of disease
- Modeling and cost effectiveness
- Values, acceptability and other elements of the *Evidence to Recommendations* framework
- Policy options

sBLA, Supplemental Biologics License Application

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- Are there specific data ACIP would like presented?
- Are there specific options or other considerations the Work Group should address?

Thank You

For more information, contact CDC
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