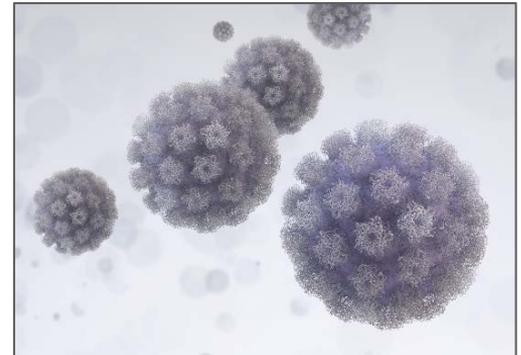


Update: Recommendations for HPV Vaccination

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Current Issues in Immunization
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Introduction

- **Advisory Committee on Immunization Practices (ACIP) reviewed data on HPV vaccine 2-dose schedules over the past year**
- **In October 2016, ACIP voted to change the dosing schedule and recommend HPV vaccine 2-doses for persons starting vaccination at age 9 through 14 years**

Overview of Talk

- **Background on HPV vaccines**
- **Summary of evidence on 2-dose schedules**
- **Updated HPV vaccination recommendations**
- **Case examples**

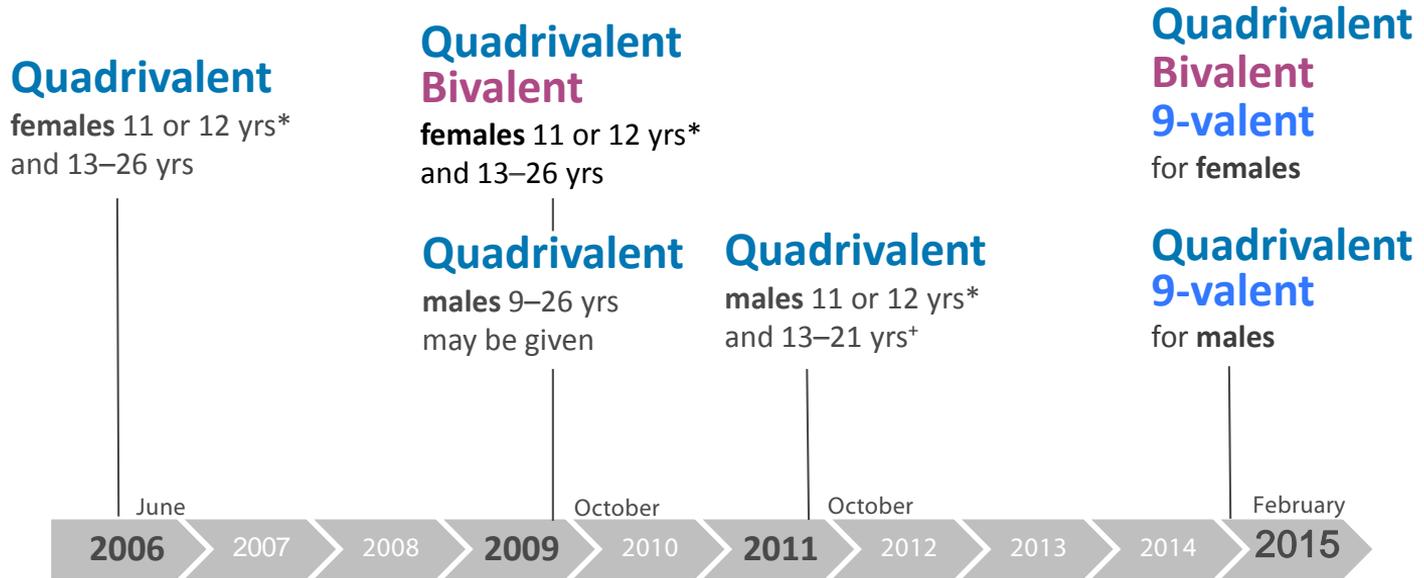
Background

HPV Vaccines Licensed in the United States

	Bivalent 2vHPV (Cervarix)	Quadrivalent 4vHPV (Gardasil)	9-Valent 9vHPV (Gardasil 9)
L1 VLP types	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Manufacturer	GlaxoSmithKline	Merck & Co.	Merck & Co.
Adjuvant	AS04 500 µg aluminum hydroxide 50 µg 3- <i>O</i> -desacyl-4'-monophosphoryl lipid A	AAHS 225 µg amorphous aluminum hydroxyphosphate sulfate	AAHS 500 µg amorphous aluminum hydroxyphosphate sulfate
Licensed	2009	2006	2014

L1, major capsid protein; VLP, virus-like particle

Evolution of Recommendations for HPV Vaccination in the United States through 2015



All vaccines licensed and recommended as 3-dose series

*Can be given starting at 9 years; +Vaccination is also recommended for men who have sex with men through age 26 years and for immunocompromised persons (including those with HIV infection), if not vaccinated previously; May be given to males age 22-26 years

HPV Vaccine Use and Availability, United States

HPV vaccine use

- Through 2014, almost all HPV vaccine used was 4vHPV
- In 2016, almost all HPV vaccine used is 9vHPV

HPV vaccine availability

- Since April 2016, only 9vHPV has been on CDC vaccine contracts
- After the end of October, only 9vHPV will be distributed in the U.S.
- 2vHPV and 4vHPV will continue to be available outside the U.S.

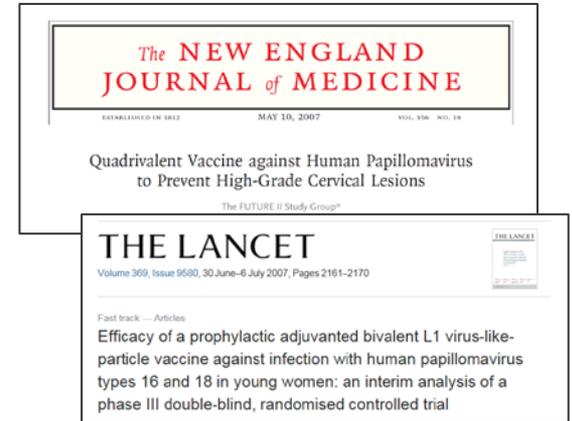
Recommendations for HPV Vaccination in the United States, 2011 - present

- **ACIP recommends routine HPV vaccination at age 11 or 12 years. The vaccination series can be started beginning at age 9 years.**
- **ACIP also recommends HPV vaccination for:**
 - Females through age 26 years, who were not vaccinated previously
 - Males through age 21 years, who were not vaccinated previously (males aged 22 through 26 years may be vaccinated)
 - Men who have sex with men and immunocompromised persons (including those with HIV infection) through age 26 years, who were not vaccinated previously

2-Dose HPV Vaccine Schedules

Efficacy and Immunogenicity Data for Initial Licensure of HPV Vaccines in a 3-Dose Schedule

- **Randomized controlled trials in 15–26 year olds**
 - Trial endpoints were vaccine type HPV infection and cervical precancer lesions*
- **Bridging immunogenicity trials in 9–15 year olds**
 - Licensure in this age group based on non-inferior antibody response compared with young adult women in efficacy trials

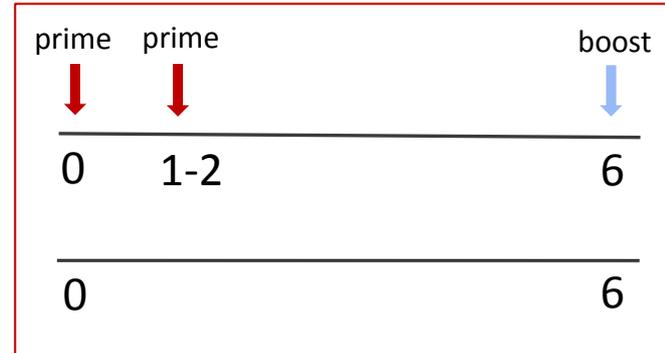


*Future II Study Group, NEJM 2007; Garland, NEJM 2007; Paavonen, Lancet 2007

Quadrivalent vaccine trials had other outcomes as well including anal precancers in males, vulvar, vaginal precancers in females, genital warts in females and male.

Immunologic Basis of HPV Vaccination Schedules

- **3-dose schedule (0, 1-2, 6 months)**
 - Considered “prime-prime-boost”
- **2-dose schedule (0, 6 months)**
 - Considered “prime-boost”



- **Memory B cells require at least 4-6 months to mature and differentiate into high-affinity B cells**
 - ~6 month interval between first and last dose allows last dose to efficiently reactivate memory B cells

Evidence Reviewed on 2-Dose Schedules

- Immunogenicity
- Post hoc analyses of efficacy trials
- Post-licensure effectiveness
- Health economic models
- Duration of protection

Immunogenicity of 2-Dose HPV Vaccination Schedules

- **Immunogenicity trials of 2- vs 3-doses have been conducted for all HPV vaccines**
- **Main analyses are 2 doses in ~9–14 yr olds vs 3 doses in women age ~16–26 yrs**
 - Comparison is the age group and schedule for which efficacy was demonstrated
 - Although the basis of protection after vaccination thought to be neutralizing antibody, there is no established minimum antibody threshold for protection
 - All trials found that antibody response after 2 doses (0,6 months or 0,12 months) in ~9–14 yr olds is non-inferior to the antibody response after 3 doses in older age group
- **Some trials compared 2 vs 3 doses in ~9–14 yr olds**
 - Results vary by trial; antibody titers lower after 2 doses vs 3 dose for some HPV types
- **Based on data from immunogenicity trials, regulatory authorities have approved 2-dose HPV vaccination schedules***

*Only 9vHPV data on 2-dose schedules submitted to FDA

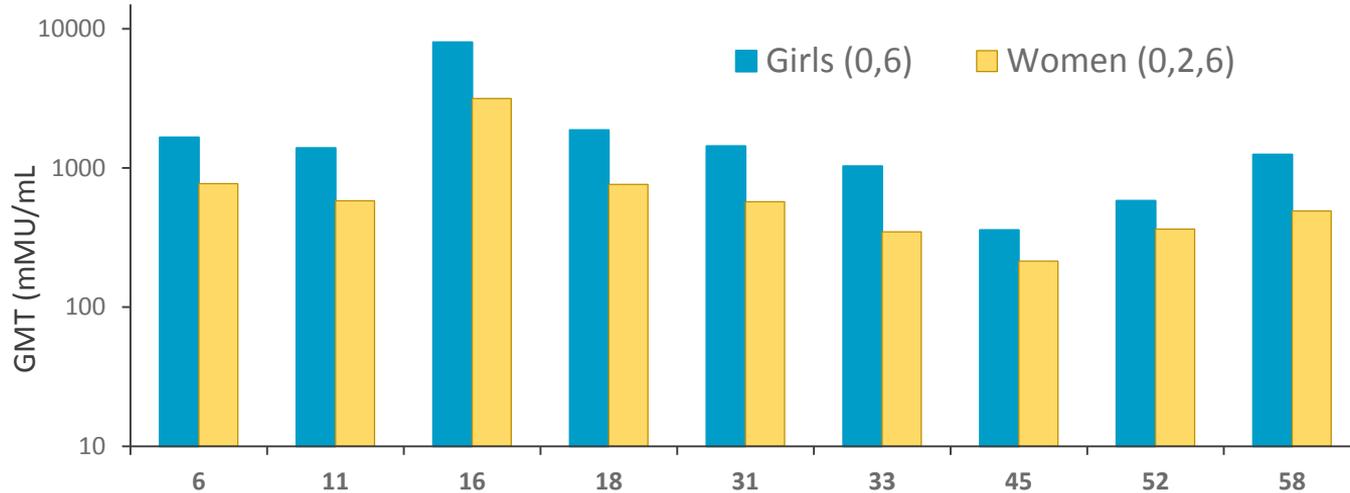
9vHPV 2-Dose Trial: Study Design

Enrollment	Open-label study				
	Cohort	Age (years)	Gender	N	Dosing regimen* (months)
	1	9-14	F	300	0, 6
	2	9-14	M	300	0, 6
	3	9-14	F/M	300	0, 12
	4 (control)	16-26	F	300	0, 2, 6
5 (exploratory)	9-14	F	300	0, 2, 6	
Immunogenicity analyses	<p>Primary analyses at 1 month post-last dose (<i>results presented to ACIP February 2016</i>)</p> <p>Exploratory analyses to assess antibody persistence (<i>Month 12 for cohorts 1, 2, 4, & 5; Months 24 and 36 for all cohorts</i>)</p>				

*interval window included +/- 4 weeks

9vHPV 2-Dose Immunogenicity Trial

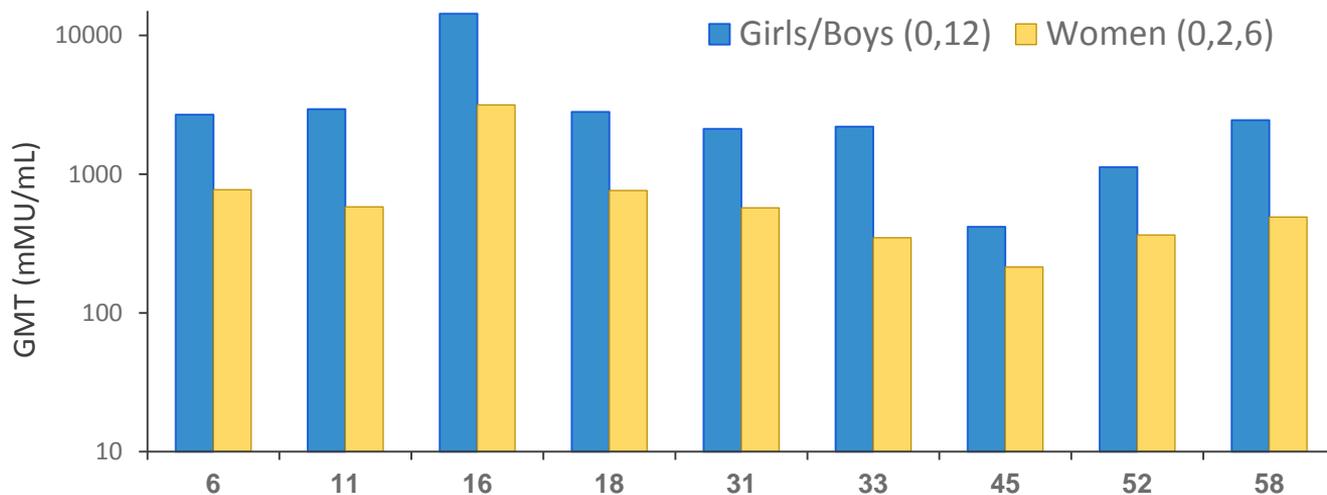
Non-inferior geometric mean antibody titers (GMT) 1 month post-last dose
2-dose girls vs. 3-dose women



Fold difference (girls/women)	2.15	2.39	2.54	2.46	2.51	2.96	1.67	1.60	2.55
<i>95% CI</i>	(1.83, 2.53)	(2.03, 2.82)	(2.14, 3.00)	(2.05, 2.96)	(2.10, 3.00)	(2.50, 3.50)	(1.38, 2.03)	(1.36, 1.87)	(2.15, 3.01)

9vHPV 2-Dose Immunogenicity Trial

Non-inferior geometric mean antibody titers (GMT) 1 month post-last dose
2-dose girls/boys vs. 3-dose women



Fold difference (girls & boys /women)	3.47	5.07	4.54	3.69	3.70	6.31	1.96	3.08	4.98
<i>95% CI</i>	(2.93, 4.11)	(4.32, 5.94)	(3.84, 5.37)	(3.06, 4.45)	(3.08, 4.45)	(5.36, 7.43)	(1.61, 2.37)	(2.64, 3.61)	(4.23, 5.86)

9vHPV 2-Dose Immunogenicity Trial Overview

- **97.8% – 100% seropositive to all 9 types, 1 month after last dose**
- **Compared with 3 doses in 16–26 year olds, antibody titers after**
 - 2 doses in 9–14 year olds (0,6 months or 0,12 months) were non-inferior, and significantly higher, 1 month after last dose
 - 2 doses in 9–14 year olds (0,6 months) remained non-inferior, and higher, 6 months after last dose
- **Follow-up of trial participants will continue through 36 months**
- **Based on data from trial, on October 7, 2016, FDA approved a 9vHPV 2-dose series for persons age 9–14 years***

*<http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf>

Immunogenicity Data on 2-Dose Schedules for 2vHPV and 4vHPV

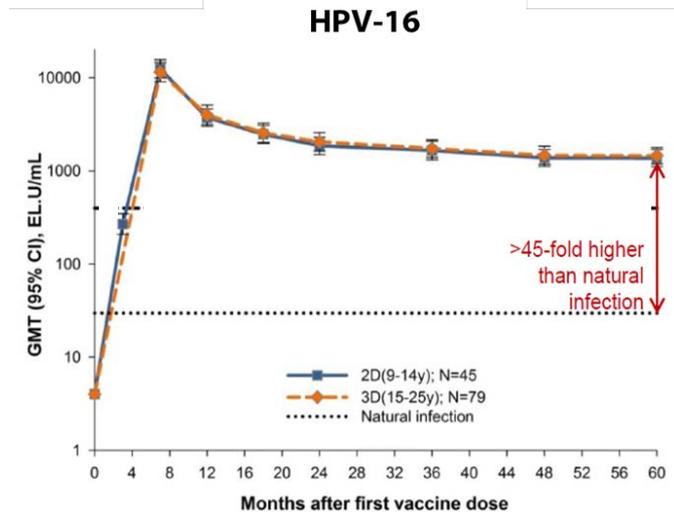
- **Longer follow-up in 2vHPV and 4vHPV than 9vHPV 2-dose trials**
 - 2vHPV: 60 months
 - 4vHPV: 36 months
 - 9vHPV: 12 months
- **Many individuals have received 4vHPV in the U.S. and some have not completed a 3-dose series**

Immunogenicity Data on 2-Dose Schedules for 2vHPV and 4vHPV

- 2 trials of 4vHPV and 3 trials of 2vHPV compared 2 doses (0,6 months or 0,12 months) in ~9–14 year olds with 3 doses in 15-26 year olds
- >97% seroconversion in all vaccine groups
- Antibody titers non-inferior after 2 doses in persons aged 9–14 years compared with 3 doses in age group in which clinical efficacy demonstrated
- 2vHPV and 4vHPV immunogenicity studies included in GRADE evidence review for ACIP

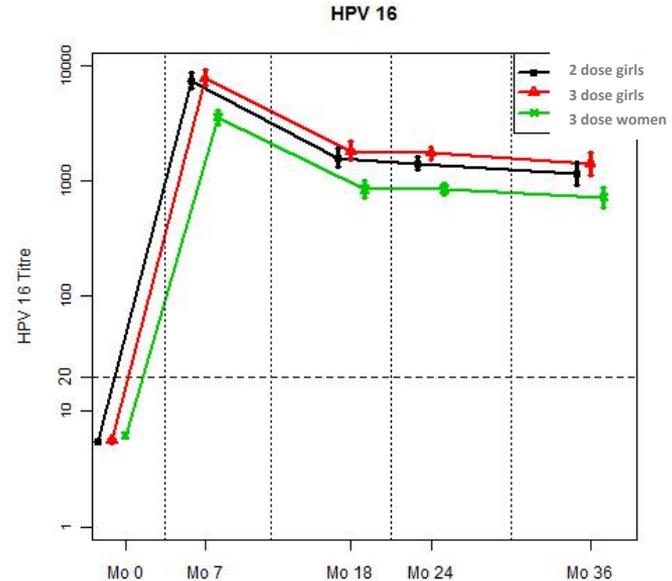
2vHPV 2- vs 3-Dose Immunogenicity Trial

- **Follow-up through month 60**
 - 2 doses (0,6 months) in 9–14 yr olds
 - 3 doses (0,1,6 months) in 15–25 yr olds
- **Antibody kinetics similar in 2 groups**



4vHPV 2- vs 3-Dose Immunogenicity Trial

- **Follow-up through month 36**
 - 2 doses (0,6 months) in 9–13 yr olds
 - 3 doses 0,2,6 months in 9–13 yr olds
 - 3 doses (0,1,6 months) in 16–26 yr olds
- **Antibody kinetics similar in 3 groups**



2-Dose Schedules for 2vHPV and 4vHPV

- **Regulatory approval in other countries**
 - Based on immunobridging data
 - European Medicines Agency approved a 2-dose schedule for young adolescents in 2014
- **Recommendations and implementation**
 - In 2014, World Health Organization recommended a 2-dose schedule, if vaccination series started at <15 years*
 - Many countries are using a 2-dose schedule for this age group

Efficacy Data for 2-Dose Schedules

- **No data from randomized controlled trials of 2 doses of HPV vaccines evaluating efficacy against infection or disease endpoints**
- **2vHPV: data from post hoc analyses of 3-dose efficacy trials**
- **4vHPV: data from analysis of interrupted 2- vs 3-dose efficacy trial that that was analyzed as an observational study**
- **Data from these analyses suggest efficacy with less than a 3-dose schedule**

Post-Licensure HPV Vaccine Effectiveness Evaluations

- **10 studies evaluated effectiveness by number of doses**
 - In setting of a recommended 3-dose schedule for 2vHPV or 4vHPV
 - Most found 2 doses were not as effective as 3 doses
- **Limitations of post-licensure effectiveness studies**
 - 2-dose vaccinees received vaccine at a 0,1 or 0,2 month interval
 - Persons who only received 2 doses differed from those completing series
 - Older, earlier cervical screening: differences in HPV exposure prior to vaccination
- **One study evaluated different intervals between 2 doses**
 - Effectiveness increased as interval between doses increased
- **Data from post-licensure effectiveness studies conducted to date may not inform 2-dose (0, 6-12 month) vaccination schedules**

Duration of Protection after HPV Vaccination

No evidence of waning protection after a 3-dose schedule

- Data available through ~ 10 years for 2vHPV and 4vHPV

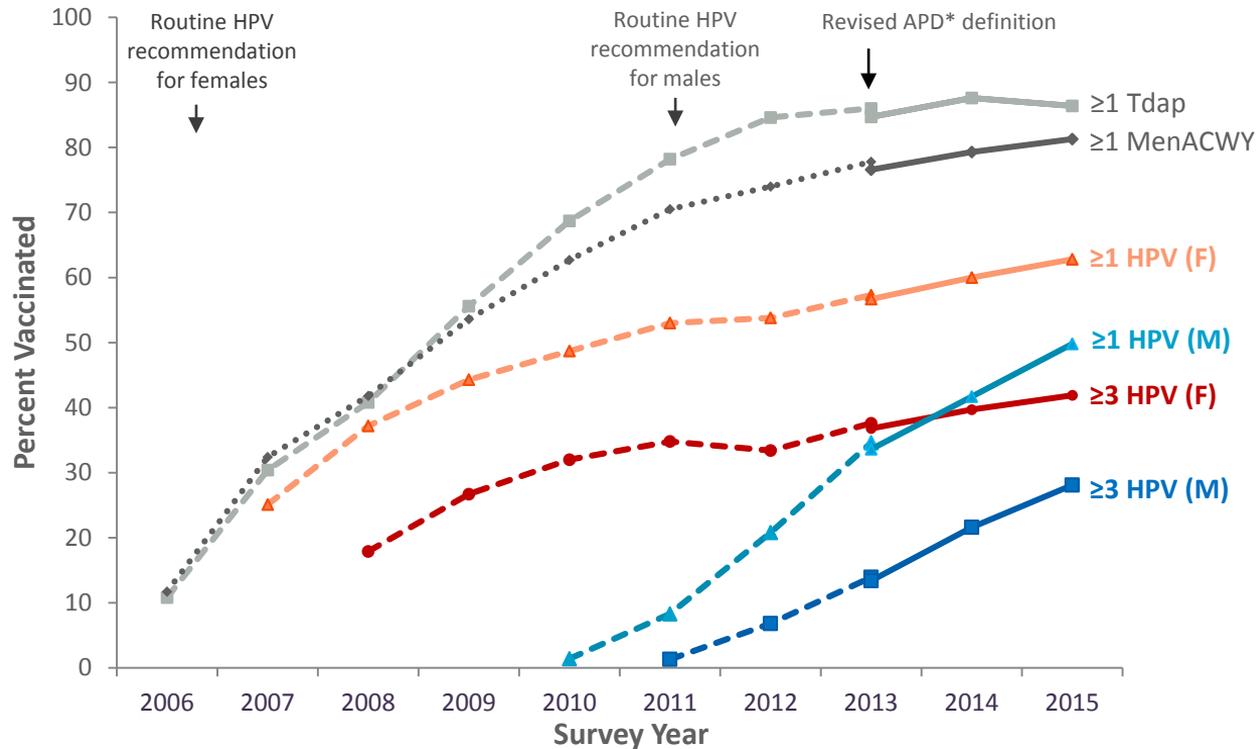
Antibody responses maintained over time after a 3-dose schedule

- Data available through ~10 years for 2vHPV and 4vHPV
- Waning of detectable antibody to HPV 18 (by cLIA) in 4vHPV vaccinees not associated with loss of protection

2-dose schedules

- Long term protection data not available from 2-dose trials
- Antibody kinetics similar with 2-dose and 3-dose schedules, suggesting duration of protection after 2 doses also will be long lasting

Estimated Vaccination Coverage among Adolescents Aged 13–17 Years, NIS-Teen, United States, 2006-2015



Programmatic Considerations

- **Unknown if 2-dose recommendation will impact vaccination initiation or series completion**
- **A 2-dose schedule considered easier to implement and more acceptable**
- **Although other countries have switched to a 2-dose schedule, most have school-based vaccination and many already had high coverage**
- **In United States, a 2-dose (0, 6-12 month) schedule would allow flexibility and vaccinations could coincide with preventive health care visits**

Summary (1)

- **Although three HPV vaccines are licensed for use in the United States, after the end of 2016 only 9vHPV will be available in the United States**
- **In October 2016, FDA approved 9vHPV as a 2-dose series for persons age 9 through 14 years**
- **During 2016, ACIP reviewed data related to 2-dose HPV vaccine schedules**
- **Trials of all HPV vaccines found antibody response after 2 doses (0,6 months or 0,12 months) in 9–14 year olds non-inferior to the response after 3 doses in the age group in which efficacy demonstrated**

Summary (2)

- **Post-licensure studies examining HPV vaccine effectiveness by number of doses are difficult to interpret at this time in the vaccination program**
- **Data from follow-up of 3-dose vaccine trials show that duration of protection after HPV vaccination is long lasting; antibody data suggest duration of protection will be the same after 2-dose and 3-dose schedules**
- **ACIP used GRADE to evaluate evidence on 2-dose HPV vaccination schedules and made a *Category A* recommendation for a 2-dose schedule for persons initiating the series at age 9 through 14 years**
- **A 2-dose HPV vaccination schedule might facilitate vaccine initiation and series completion in the United States**

HPV Vaccination Recommendations

Updated Recommendations for HPV vaccination

Recommendations

- Routine and catch-up age groups (no changes)
- **Dosing schedules**
- **Evaluating persons with prior vaccination**
- Interrupted schedules
- Medical conditions

Routine and catch-up age groups (no changes)

- **ACIP recommends routine HPV vaccination at age 11 or 12 years. Vaccination can be given starting at age 9 years.**
- **ACIP also recommends vaccination for females through age 26 years and for males through age 21 years who were not previously adequately vaccinated. Males aged 22 through 26 years may be vaccinated.**

Updated Recommendations for HPV vaccination

Dosing schedules

- **For persons initiating vaccination before the 15th birthday**
 - Recommended immunization schedule is 2 doses of HPV vaccine. The second dose should be administered 6–12 months after the first dose (0, 6–12 month schedule).
- **For persons initiating vaccination on or after the 15th birthday**
 - Recommended immunization schedule is 3 doses of HPV vaccine. The second dose should be administered 1–2 months after the first dose, and the third dose should be administered 6 months after the first dose (0, 1–2, 6 month schedule).

Updated Recommendations for HPV vaccination

Persons with prior vaccination

- **Persons who initiated vaccination with 9vHPV, 4vHPV, or 2vHPV before the 15th birthday, and received 2 doses of any vaccine at the recommended dosing schedule*, or 3 doses of any vaccine at the recommended dosing schedule, are considered adequately vaccinated.**
- **Persons who initiated vaccination with 9vHPV, 4vHPV, or 2vHPV on or after the 15th birthday, and received 3 doses of any vaccine at the recommended dosing schedule, are considered adequately vaccinated.**

*Minimum interval between dose 1 and dose 2 in 2-dose schedule is 5 months

Updated Recommendations for HPV vaccination

Interrupted schedules

- **If the vaccine schedule is interrupted, the vaccination series does not need to be restarted.**
- **Number of recommended doses is based on age at administration of the first dose.**

Updated Recommendations for HPV vaccination

Medical conditions

- **ACIP recommends HPV vaccination for immunocompromised persons aged 9 through 26 years with 3 doses of HPV vaccine (0, 1–2, 6 months).**
- **Persons who should receive 3 doses are those with primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity**
 - B lymphocyte antibody deficiencies, T lymphocyte complete or partial defects, HIV infection, malignant neoplasm, transplantation, autoimmune disease, or immunosuppressive therapy, since immune response to vaccination may be attenuated.*

* The recommendation for a 3-dose schedule for immunocompromised persons does not apply to children with asplenia, asthma, chronic granulomatous disease, chronic liver disease, chronic lung disease, chronic renal disease, CNS anatomic barrier defects (e.g., cochlear implant), complement deficiency, diabetes, heart disease, persistent complement component deficiencies, or sickle cell disease.

Case examples

Case example - 1

- A 15 year old is starting the HPV vaccine series. How many doses does she need?

This adolescent needs 3 doses (0, 1-2, 6 months schedule) because she is starting the series on or after the 15th birthday.

Case example - 2

- A 13 year old has a history of 2 doses of HPV vaccine: 4vHPV given at age 12 years and 9vHPV given 6 months later. How many doses are needed to complete the vaccination series?

No further doses are recommended because she initiated vaccination before the 15th birthday and received 2 doses of vaccine 6 months apart.



Case example - 3

- A 13 year old has a history of 2 doses of HPV vaccine: 4vHPV given at age 11 years and 9vHPV given 2 months later. Are any more HPV vaccine doses needed to complete the vaccination series?

Yes, although she initiated the vaccination series before her 15th birthday, she needs a third dose because the 2 HPV vaccine doses were administered less than 5 months apart.

Case example - 4

- A 13 year old received of 1 dose of 4vHPV at age 10 years. Does she need 1 or 2 more HPV vaccine doses to complete the series?

This adolescent needs 1 more dose to complete the series, because she initiated vaccination before the 15th birthday.

She received the first dose more than a year ago; the second dose can be given as soon as possible.



Questions?

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Thank you

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