

# Overview of issues and considerations: HPV vaccination recommendation options

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# Policy issues for HPV vaccine

## □ Impacted by

- Expected licensure of 9-valent HPV vaccine (HPV9)
- Status of data on 2-dose schedules

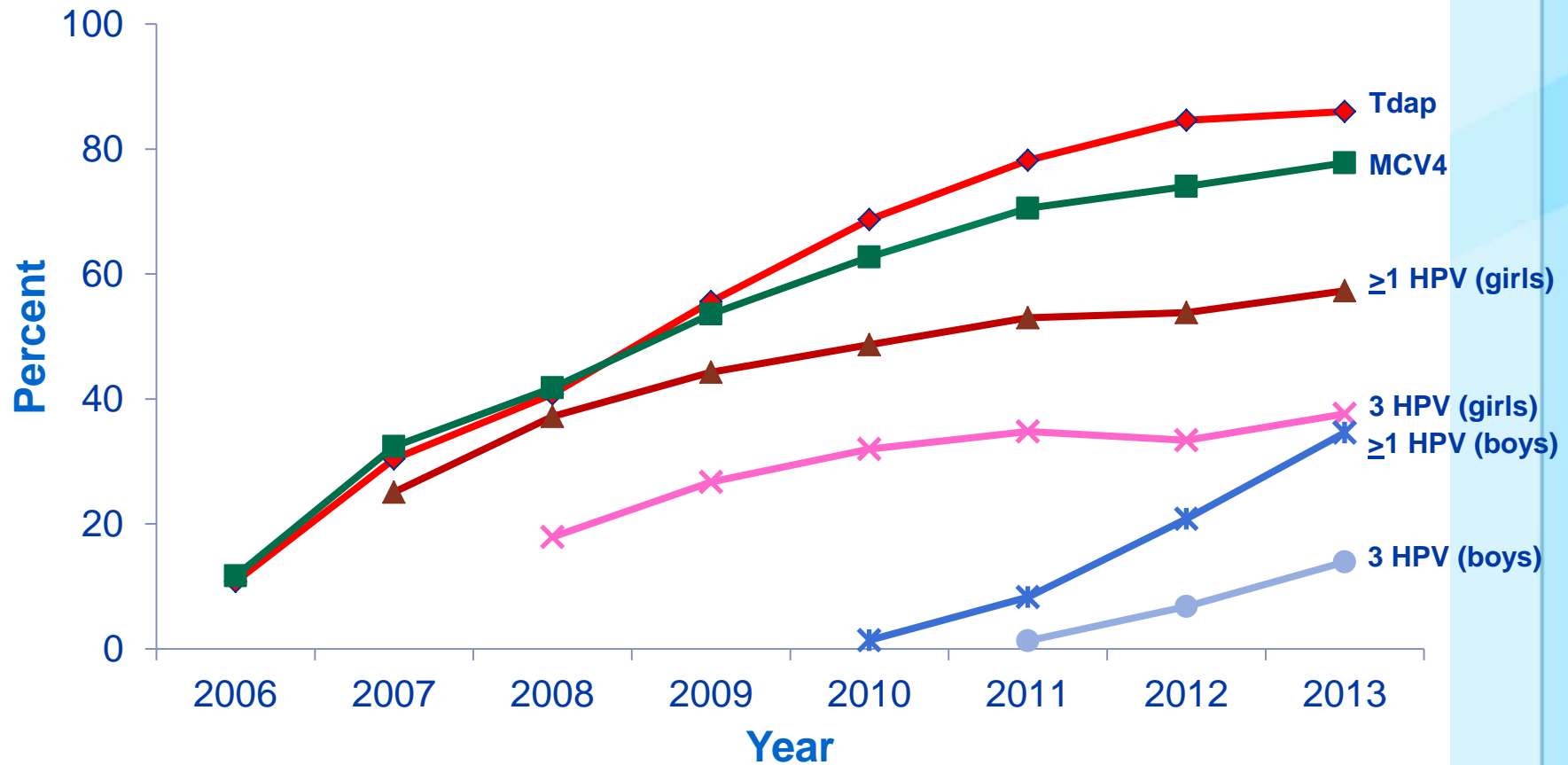
## □ Issues for consideration

- Evidence base
- Programmatic
- Regulatory

## Overview of presentation

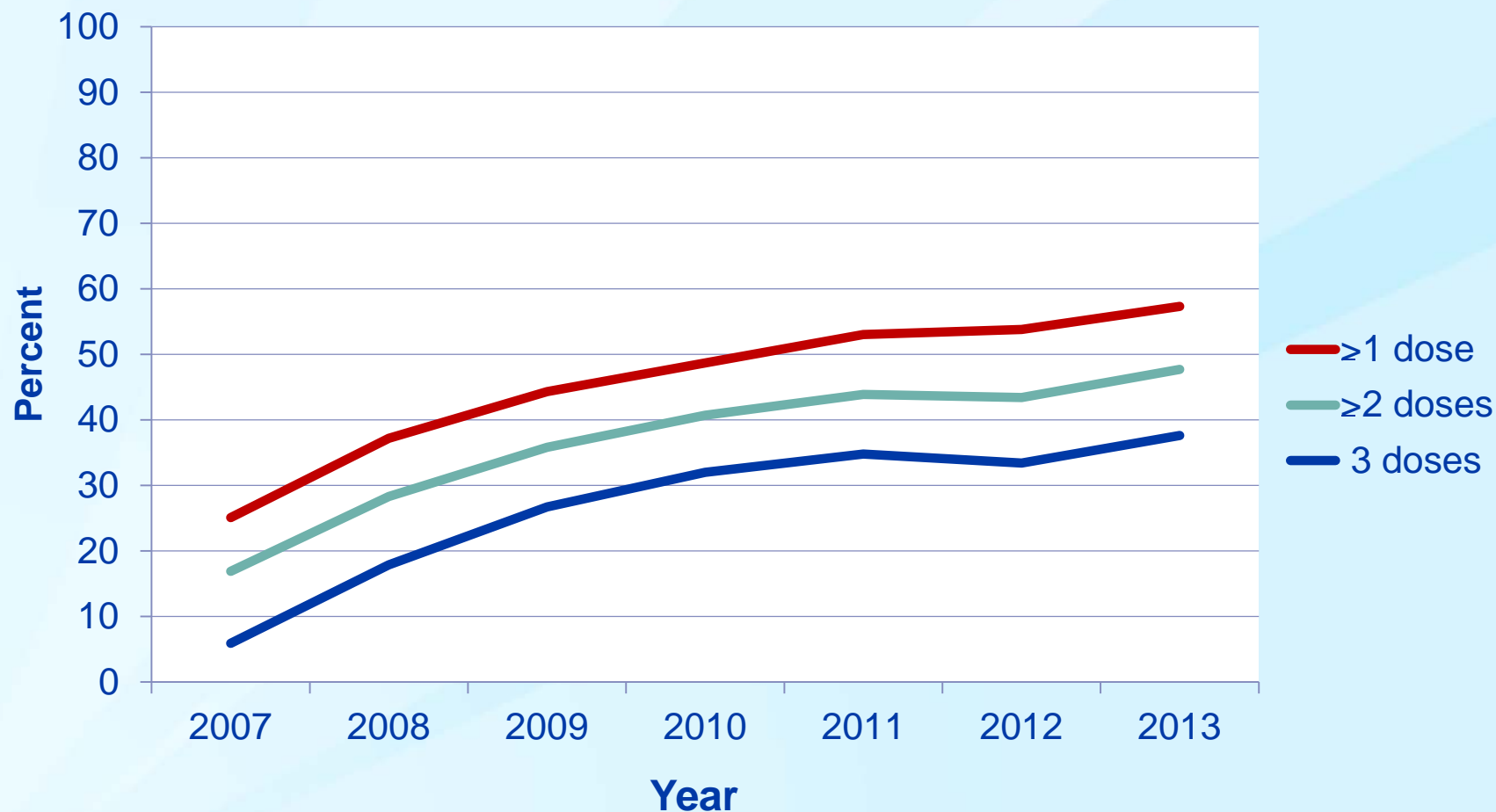
- ❑ **HPV vaccine coverage**
  - National Immunization Survey - Teen
- ❑ **2-dose schedules**
  - Brief overview of data presented at June 2014 ACIP
- ❑ **Recommendation considerations and options**
  - Discussed by the ACIP Workgroup

# National estimated vaccination coverage levels among adolescents 13-17 years NIS-Teen, 2006-2013



NIS-Teen = National Immunization Survey-Teen  
MMWR 2014;63:625-33

# National estimated HPV vaccination coverage by number of doses among females 13-17 years NIS-Teen 2007-2013



NIS-Teen = National Immunization Survey-Teen  
Source: MMWR. 2014;63:625-33

# Ongoing efforts to increase HPV vaccine coverage

**HPV CANCER PREVENTION**

- 1 HPV VACCINE IS CANCER PREVENTION**  
HPV vaccine protects against HPV types that most commonly cause anal, cervical, oropharyngeal, penile, vaginal, and vulvar cancers.  
Every year in the U.S., 27,000 people get cancer caused by HPV. That's 1 person every 20 minutes of every day, all year long.  
Most of these cancers can be prevented by HPV vaccine.
- 2 HPV VACCINE IS RECOMMENDED AT THE SAME TIME AS OTHER TEEN VACCINES**  
Teens need three vaccines at 11 or 12. They protect against whooping cough, cancers caused by HPV, and meningitis.  
Vaccinate for your 11-12 year old:  
• Shingles  
• HPV  
• Meningococcal
- 3 HPV VACCINE IS BEST AT 11-12 YEARS**  
Teens have a higher immune response to HPV vaccine than older teens.  
While there is very little risk of exposure to HPV before age 13, the risk of exposure increases thereafter.

Parents and healthcare professionals are the key to protecting adolescents from HPV cancers.

**VACCINATE YOUR 11-12 YEAR OLDS.**

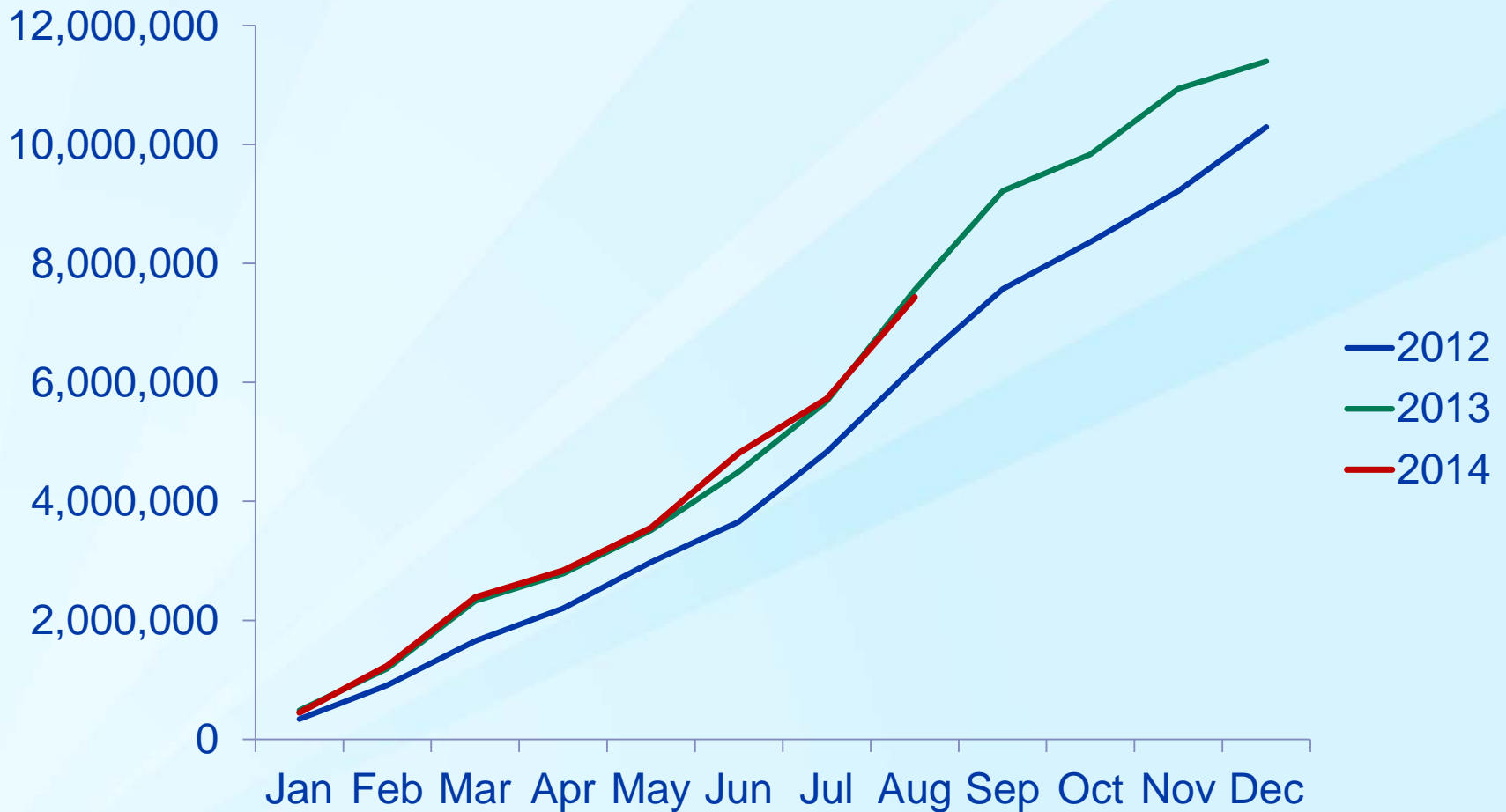
[www.cdc.gov/vaccines/teens](http://www.cdc.gov/vaccines/teens)

**YOU ARE THE KEY TO HPV CANCER PREVENTION**

U.S. Department of Health and Human Services  
Centers for Disease Control and Prevention

- **Materials to assist providers**
- **Increased funding to 22 project areas**
  - Communication
  - Education
  - Elimination of missed opportunities
- **Partnerships with other organizations**

# Total HPV doses distributed – Year-to-date (2012-2014)



## 2-dose HPV vaccination schedules

- **Information on 2-dose schedules presented to ACIP at June 2014 meeting**
  - Data from trials of alternative and 2-dose schedules
  - Regulatory approvals/recommendations
  - Countries using 2-dose schedules
  - Considerations for the US



# Summary: data on 2-dose schedules

## □ Immunogenicity<sup>1</sup>

- GMTs non-inferior after 2 doses (0,6 mos) in females in ~9-14 yrs compared with 3 doses (0,1-2, 6 mos) in females ~16-26 yrs

## □ Efficacy<sup>2</sup>

- Post-hoc analysis of 3 dose RTC (HPV2) found high efficacy for 2 doses

## □ Effectiveness<sup>3</sup>

- Post-licensure studies found lower effectiveness for 2 vs 3 doses (HPV prevalence, cervical precancers, genital warts)
- Many limitations of post licensure effectiveness evaluation:
  - 2-dose recipients did not receive 0,6 month schedule
  - Differences between 2-dose and 3-dose recipients

# Immunogenicity studies comparing 2 and 3 doses of HPV vaccine

Study	Country	Vaccine	Design Age and doses		Schedules	Longest followup
Romanowski Hum Vaccin 2011* Hum Vaccin 2014	Canada/ Germany	HPV2	9-14	2 doses	0, 6	24 mos
			9-14	3 doses	0, 1, 6	48 mos
			15-25	3 doses	0, 1, 6	
Puthanakit EUROGIN 2013 ESPID 2014	Multi- national	HPV2	9-14	2 doses	0, 6	~12 mos
			9-14	2 doses	0, 12	
			15-25	3 doses	0, 1, 6	
Lazcano-Ponce Vaccine 2014	Mexico	HPV2	9-10	2 doses	0, 6	21 mos
			9-10	3 doses	0, 1, 6	
			18-24	3 doses	0, 1, 6	
Dobson JAMA 2013	Canada	HPV4	9-13	2 doses	0, 6	36 mos
			9-13	3 doses	0, 2, 6	
			16-26	3 doses	0, 2, 6	
Sankaranarayanan EUROGIN 2013	India	HPV4	10-18	2 doses	0, 6	18 mos
			10-18	3 doses	0, 2, 6	

\*dose ranging study: included other groups as well

# HPV4: 2-dose vs 3-dose immunogenicity trial

Number of doses	Dose interval (mos)	Age group
2	0,6	9-13 yr old girls
3	0,2,6	9-13 yr old girls
3	0,2,6	16-26 yr old women

- ❑ **Main analysis: 2-dose in 9-13 yr old group compared with 3-dose in 16-26 yr old group**
  - Non-inferiority criteria met
  - Antibody response higher in 2-dose 9-13 yr old group
- ❑ **Analysis comparing 2-dose and 3-dose in 9-13 yr old group**
  - Non-inferiority lost for HPV 18 by 24 mos and HPV 6 by 36 mos

# Regulatory approval and recommendations for HPV vaccine 2-dose schedules

- HPV2 and HPV4 have regulatory approval for use in a 2-dose schedule in young adolescents from EMA and a variety of countries
- WHO changed vaccination recommendations in 2014\*
  - 2-dose schedule, if vaccination initiated prior to 15 years; minimal interval of 6 months between doses
  - 3-dose schedule (0,1-2,6 months), if vaccination initiated on or after 15 years
- Several countries recommended 2-dose schedules before WHO recommendation/regulatory approvals and more are changing to 2-dose schedules

# Regulatory considerations for 2-dose HPV vaccination schedules in the U.S.

- ❑ **HPV2** – no plans for submission to FDA
- ❑ **HPV4** – no plans for submission to FDA
- ❑ **HPV9**
  - No data on 2-dose schedules in BLA currently under consideration by FDA
  - Trial comparing 2-dose and 3-dose schedules initiated by manufacturer

# 9-valent HPV vaccine 2- vs 3-dose trial

- ❑ Immunogenicity trial
- ❑ Start date: Dec 2013; last visit: July 2015
- ❑ 5 arms (N=1500)

Number of doses	Dose interval (mos)	Age groups
2	0,6	9-14 yr old girls
2	0,6	9-14 yr old boys
2	0,12	9-14 yr old girls and boys
3	0,2,6	9-14 yr old girls and boys
3	0,2,6	16-26 yr old women

## **RECOMMENDATIONS: ISSUES AND OPTIONS**

## **Recommendation options given expected licensure of HPV9 and status of data on 2-dose schedules**

- 1) Consider HPV9 as 3-dose schedule and wait to consider 2-dose schedules when HPV9 2- vs 3-dose trial data available\***
- 2) Consider 2-dose schedules for HPV2 and HPV4 in 9 through 14 year olds based on available data**

\*Q4 2015



## Considerations: 9-valent HPV vaccine (HPV9)

- **BLA submitted to FDA in Dec 2013; expected licensure in 2014**
  - Data from 3-dose schedule in females 9-26 yrs and males 9-15 yrs
- **HPV4 likely will continue to be available for 12-18 months after HPV9 licensed** (differs from PCV7/PCV13 transition)
- **Workgroup discussed HPV9 for currently recommended ages**
  - Use in males older than age 15 would be off-label initially
    - Immunogenicity data in males 16-26 yrs presented to ACIP today
  - Compared with HPV4, HPV9 would provide little additional benefit for males
  - Programmatic issues considered for age group for male recommendations

## **Recommendation options given expected licensure of HPV9 and status of data on 2-dose schedules**

- 1) Consider HPV9 as 3-dose schedule and wait to consider 2-dose schedules when HPV9 2- vs 3-dose trial data available\***
- 2) Consider 2-dose schedules for HPV2 and HPV4 in 9 through 14 year olds based on current data**

\*Q4 2015

# Option 1

## HPV9 as 3-dose schedule; wait to consider 2-dose schedules

- ❑ ACIP recommends routine HPV vaccination at age 11 or 12 years for females and males. The vaccination schedule can be started beginning at age 9 years.
- ❑ Vaccination is also recommended for females aged 13 through 26 years and for males aged 13 through 21 years who have not been previously vaccinated. Males aged 22 through 26 years may be vaccinated.
- ❑ **Vaccination of females is recommended with HPV2, HPV4 (as long as this formulation is available) or HPV9. Vaccination of males is recommended with HPV4 (as long as this formulation is available) or HPV9.**
- ❑ A 3-dose schedule is recommended with the second dose 1-2 months after the first dose and the third dose 6 months after the first dose.

## Table for Option 1

### HPV9 as 3-dose schedule and wait to consider 2-dose schedules

Routine	Those not previously vaccinated
<p><b>Females and males 11-12 years</b></p> <p>3-dose schedule (0,1-2, 6 mos)</p>	<p><b>Females 13-26 years</b> <b>Males 13-21 years</b></p> <p>3-dose schedule (0,1-2, 6 mos)</p>

**Females:** HPV2, HPV4 or HPV9

**Males:** HPV4 or HPV9

- *HPV9 off-label for males older than age 15; data available*

## ***Draft proposed wording for any option***

- ❑ HPV2, HPV4 and HPV9 all protect against HPV types 16 and 18, types that cause about 66% of cervical cancers and the majority of other HPV-attributable cancers in the United States. HPV9 targets 5 additional cancer causing types, which account for about 15% of cervical cancers in the United States. HPV4 and HPV9 also protect against HPV types 6 and 11, types that cause genital warts.
- ❑ For protection against genital warts in addition to cancer causing HPV types, vaccination is recommended with HPV4 or HPV9. When HPV4 is no longer available, HPV9 can be used to complete a series begun with HPV4.

## **Recommendation options given expected licensure of HPV9 and status of data on 2-dose schedules**

- 1) Consider HPV9 as 3-dose schedule and wait to consider 2-dose schedules when HPV9 2- vs 3-dose trial data available\*
- 2) Consider 2-dose schedules for HPV2 and HPV4 in 9 through 14 year olds based on available data

ACIP GRADE for 2 doses not yet conducted

WHO GRADE: [http://www.who.int/immunization/position\\_papers/hpv\\_grad\\_immunogenicity\\_2vs3\\_immunocompetent.pdf](http://www.who.int/immunization/position_papers/hpv_grad_immunogenicity_2vs3_immunocompetent.pdf)

## Recommendation options given expected licensure of HPV9 and status of data on 2-dose schedules

- 1) Consider HPV9 as 3-dose schedule and wait to consider 2-dose schedules when HPV9 2- vs 3-dose trial data available\*
  
- 2) Consider 2-dose schedules for HPV2 and HPV4 in 9 through 14 year olds based on available data
  - If a 2-dose schedule is recommended, options for HPV9:
    - Recommend HPV9 as 3-dose schedule
    - Recommend HPV9 as 2-dose schedule (no data available)
    - Postpone recommendation for HPV9 until 2-dose trial results are available (Q4 2015)

## Option 2

### 2-dose schedule for HPV2, HPV4 in 9-14 year olds, and 3-dose schedule for HPV9

- ❑ Vaccination of females is recommended with HPV2, HPV4 (as long as this formulation is available) or HPV9. Vaccination of males is recommended with HPV4 (as long as this formulation is available) or HPV9.
- ❑ If the vaccination series is started with HPV2 or HPV4 before age 15 years a 2-dose schedule is recommended (0,6 months). If the vaccination series is started with HPV9 before age 15 years, a 3-dose schedule is recommended (0,2,6 months).
- ❑ If the vaccination series is started at age 15 years or older with any HPV vaccine a 3-dose schedule is recommended (0,1-2 and 6 months).



## Table for Option 2

### 2-dose schedule for HPV2, HPV4 in 9-14 year olds, and 3-dose schedule for HPV9

Routine	For those not previously vaccinated
<p><b>Females and males 11-12 years</b></p> <p>HPV2 or HPV4: 2-doses (0,6 mos) HPV9: 3-doses (0,2,6 mos)</p>	<p><b>Females and males 13-14 years</b></p> <p>HPV2 or HPV4: 2-doses (0,6 mos) HPV9: 3-doses (0,2,6 mos)</p> <p><b>Females 15-26 years and males 15-21 years</b></p> <p>HPV2, HPV4, HPV9: 3-doses (0,1-2, 6 mos)</p>

**Females:** HPV2, HPV4 or HPV9

**Males:** HPV4 or HPV9

- *Off-label for 2-dose schedules for HPV2, HPV4; HPV9 for males 16-21 years*
- *Data available for all schedules and vaccines*

## Table for Option 2a

### 2-dose schedule for HPV2, HPV4 in 9-14 year olds, and 3-dose schedule for HPV9

Routine	For those not previously vaccinated
<p><b>Females and males 11-12 years</b></p> <p>HPV2 or HPV4: 2-doses (0,6 mos)                      HPV9: 3-doses <b>(0,6,12 mos)</b></p>	<p><b>Females and males 13-14 years</b></p> <p>HPV2 or HPV4: 2-doses (0,6 mos)                      HPV9: 3-doses <b>(0,6,12 mos)</b></p> <p><b>Females 15-26 years and males 15-21 years</b></p> <p>HPV2, HPV4, HPV9: 3-doses (0,1-2, 6 mos)</p>

**Females:** HPV2, HPV4 or HPV9

**Males:** HPV4 or HPV9

- *Off-label for HPV2, HPV4 and HPV9 delayed schedule; HPV9 males 16-21 yrs*
- *No data available for HPV9 delayed schedule*

# **Considerations for Option 1 (HPV9 as 3-dose schedule and wait to consider 2-dose schedules)**

- ❑ Less confusion for providers and public
- ❑ Consider 2-dose schedules when 2-dose trial data available from HPV9

## **Considerations for Option 2 (consider 2-dose schedules for HPV2 and HPV4)**

- ❑ 2-dose schedules would facilitate delivery, decrease resources
- ❑ Concerns about potential confusion for providers and public
  - Different schedules for different vaccines and frequent recommendation changes
- ❑ Potential differences in duration of protection for 2 vs 3 doses
- ❑ 2-dose schedule would be off-label for HPV2 and HPV4 and manufacturers have no plans for submission to FDA

## Questions for ACIP members

- ❑ Are there other recommendation options that ACIP members want to consider?
- ❑ What other data would ACIP members want to see before February or at the February ACIP meeting?
- ❑ Which option do ACIP members prefer?

# Acknowledgements

## ACIP Members

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## Ex Officio Members

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# Thank you

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