2-dose HPV Vaccination Schedules Background

Lauri E. Markowitz, MD

Centers for Disease Control and Prevention

Advisory Committee on Immunization Practices

February 24, 2016

Overview

- Background on HPV vaccines
- Previous ACIP considerations of 2-dose schedules

HPV vaccines licensed in the United States

	Bivalent 2vHPV (Cervarix)	Quadrivalent 4vHPV (Gardasil)	9-valent 9vHPV (Gardasil 9)
VLP types	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Adjuvant	**AS04** 500 µg aluminum hydroxide 50 µg 3-*O*-desacyl-4'-monophosphoryl lipid A	**AAHS** 225 µg amorphous aluminum hydroxyphosphate sulfate	**AAHS** 500 µg amorphous aluminum hydroxyphosphate sulfate
FDA Licensed	**2009**	**2006**	**2014**
Sex/age groups	**Females** 9-25	**Females and males** 9-26	**Females and males** 9-26
Schedule	**3 doses** (0,1,6 months)	**3 doses** (0,2,6 months)	**3 doses** (0,2,6 months)

VLP, virus like particle

4vHPV licensed in 2006 for females and 2009 for males

Background
Efficacy and immunogenicity data for licensure of HPV vaccines

- **Efficacy trials in 15-26 year olds**
  - Trial endpoints – 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

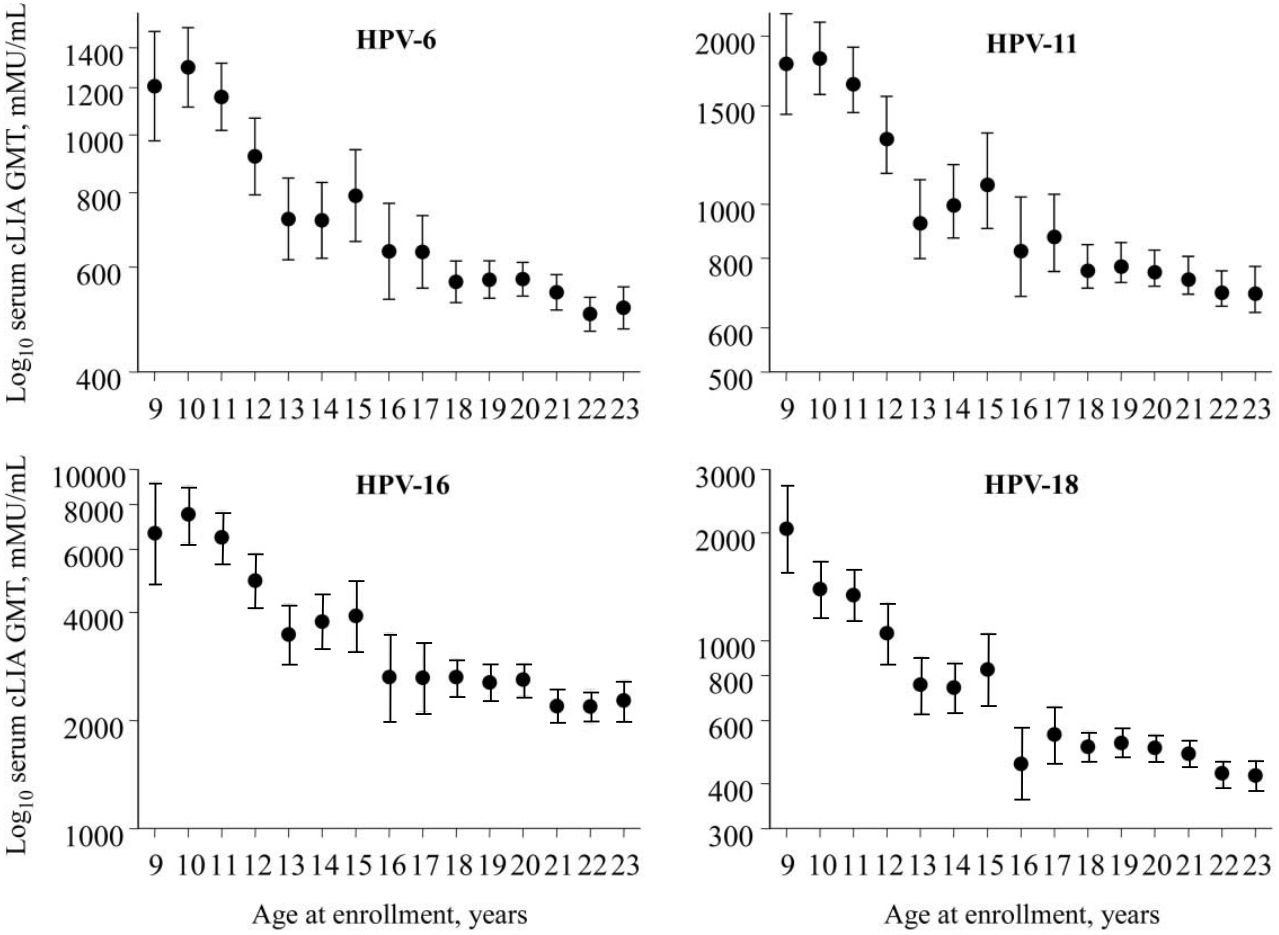
*Quadrivalent vaccine trials had other outcomes as well, including anal precancers in males; vulvar, vaginal precancers in females; genital warts in females and males

Background
Immunogenicity of HPV vaccines

- **High seroconversion after vaccination (>98%)**
- **Vaccines induce higher antibody titers than natural infection**
- **Main basis of protection is neutralizing antibody**
  - The minimum protective antibody threshold not known
- **Clinical trials used different serologic assays**
  - Results cannot be compared across studies or between types
  - In prelicensure clinical trials, some 4vHPV vaccinees lost detectable HPV 18 antibody* but no loss of protection
- **Vaccination at younger ages results in higher antibody titers**

*by competitive Luminex immunoassay (cLIA)

GMTs one month after 3rd dose of 4vHPV by age at vaccination



Giuliano, et al. JID 2007

HPV vaccine 2-dose or alternative schedules

- **Global interest in simplified schedules for HPV vaccine**
- **Could facilitate implementation**
  - Reduce logistical challenges
  - Decrease resource needs
- **Might increase acceptability**
  - For providers, parents and vaccinees
- **Interest in evaluating 2-dose schedules in young adolescents stimulated by data from clinical trials with 3 doses**
  - High efficacy
  - High serologic response to vaccination
  - Higher antibody titers achieved in the younger age groups

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

Siegrist. Chapter 2. Vaccine Immunology. In Vaccines 2013; Stanley et al. Expert Reviews 2014

2-dose HPV vaccination schedules bivalent and quadrivalent HPV vaccines

- **Regulatory approval in other countries**
  - Based on immunobridging data: non-inferior antibody response with 2 doses (0,6 months) in adolescents compared with 3 doses in women
  - 2014: European Medicines Agency approved a 2-dose schedule (age 9-14 years for 2vHPV; 9-13 years for 4vHPV)
  - Regulatory approval also obtained in other countries
- **Recommendations and implementation**
  - 2014: World Health Organization changed recommendation to 2-dose schedule for those starting the vaccination series before age 15*
  - Many countries have changed to or introduced a 2-dose schedule for this age group

*Weekly Epidemiologic Record 2014; 89: 221-236

June 2014 ACIP meeting

- **Data on 2-dose schedules for bivalent and quadrivalent HPV vaccines reviewed by ACIP**
- **Considerations**
  - No FDA indication for a 2-dose schedule for any HPV vaccine
  - No plans by manufacturers for submission of 2-dose data to FDA for 2vHPV or 4vHPV
  - 9vHPV was being considered by ACIP; no data on 2-dose schedules in the initial 9vHPV BLA under review by FDA at that time
    - 2- vs 3-dose trial had been initiated by manufacturer
- **ACIP decision**
  - Continue to review 9vHPV as 3-dose series
  - Consider 2-dose schedules after data from 2- vs 3-dose trial of 9vHPV available

BLA, Biologics License Application

9-valent HPV vaccine, United States

- **Licensed by FDA (as 3-dose schedule), December 2014**
- **Recommended by ACIP, February 2015**
  - MMWR Policy Note published, March 2015
- **Available through Vaccines For Children Program, April 2015**
- **Doses distributed in United States**
  - 7M doses through December 2015
- **9vHPV 2-vs 3-dose trial data**
  - Will be reviewed by ACIP along with other data on 2-dose schedules