Background: Application for expanded age indication for 9-valent HPV vaccine

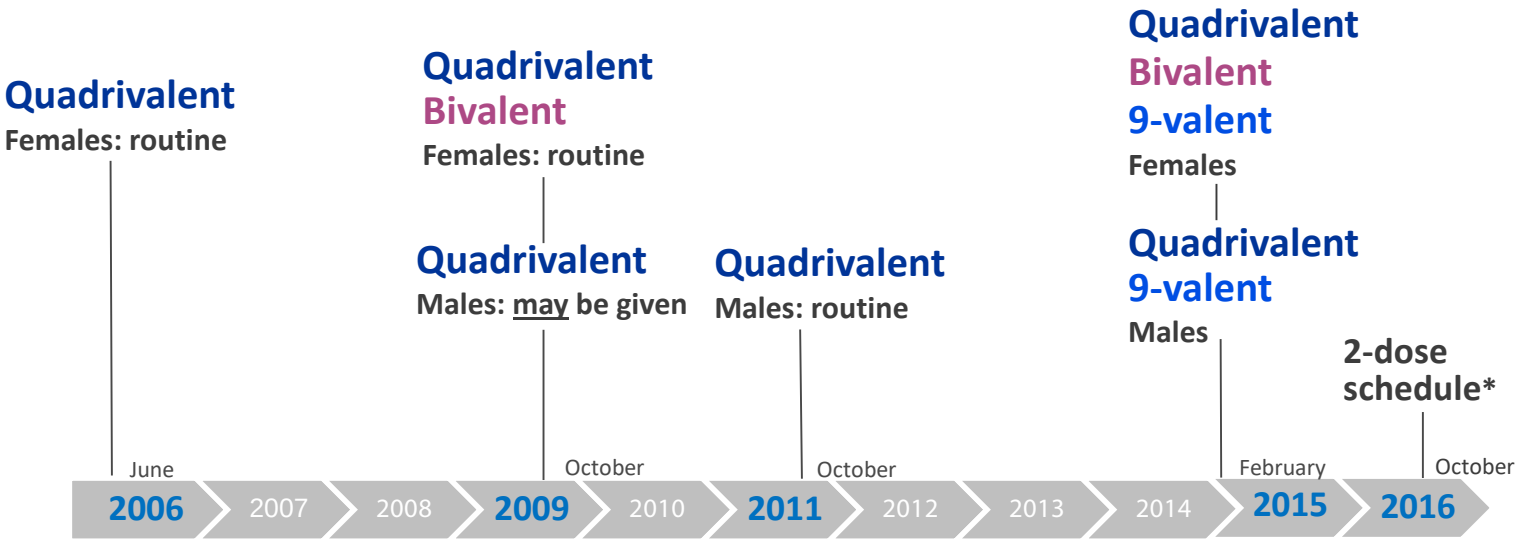
Lauri Markowitz, MD
Division of Viral Diseases

Advisory Committee on Immunization Practices
June 20, 2018

Outline

- Background: U.S. program and HPV vaccine licensure
- Overview of clinical trials in persons over age 26 years

Evolution of recommendations for HPV vaccination in the United States



*For persons starting series before age 15 years

HPV vaccine licensure and availability, United States

Licensure

Vaccine	Types	Manufacturer	Licensure ages
Bivalent (2vHPV)	16,18	GSK	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	

Availability

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

https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094042.htm;https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm186957.htm; https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm426445.htm

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
  - Men who have sex with men*, transgender persons, or persons with certain immunocompromising conditions, through age 26 years
  - Males aged 22 through 26 years may be vaccinated

MMWR 2014;63 (RR05) MMWR 2015;64:300-4

*including men who identify as gay or bisexual, or who intend to have sex with men

Application for expanded age indication

- Manufacturer filed a sBLA in April 2018 to expand age indication for 9vHPV through age 45 years for females and males
- FDA accepted the application in June and will give this a priority review
- Review expected to be complete by early October 2018

sBLA, Supplemental Biologics License Application

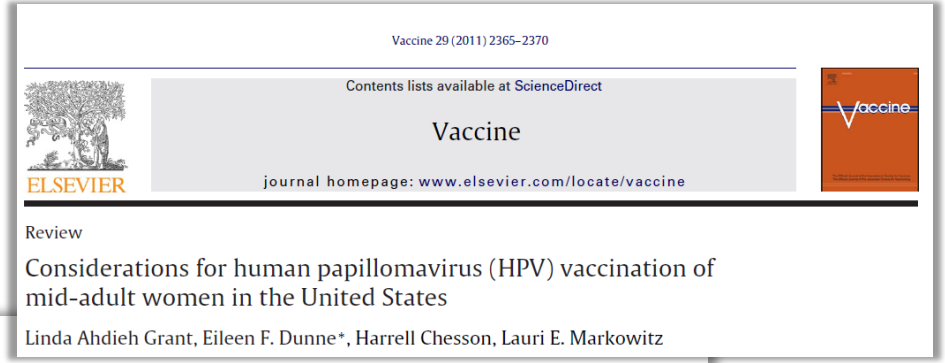
Data from 4vHPV efficacy trials contribute to evidence for 9vHPV

- **4vHPV efficacy trials in females aged 16–26 years**
  - Data from these trials, along with immunogenicity data in 9–15 year-olds, led to licensure in 2006 in females aged 9–26 years
- **4vHPV efficacy trial in females aged 24–45 years**
  - In 2008, Merck submitted an application to FDA for an expanded age indication for females through age 45 years
  - FDA did not approve an expanded age indication but allowed data from the trial to be included in the vaccine label
    - Lack of statistically significant efficacy for vaccine-type CIN2+
    - More cases in vaccine than control group in an intention-to-treat analysis regardless of type – imbalance at randomization

CIN2+, cervical intraepithelial neoplasia grade 2 or worse

Background: Consideration of 4vHPV in mid-adult women

- In 2009–2010, while FDA was reviewing application for 4vHPV in mid-adult women, ACIP HPV Vaccine Work Group considered options for use



Vaccine 29 (2011) 2365–2370

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Considerations for human papillomavirus (HPV) vaccination of mid-adult women in the United States

Linda Ahdieh Grant, Eileen F. Dunne*, Harrell Chesson, Lauri E. Markowitz

Contents

Grant et al. Vaccine 2011

4vHPV (Gardasil) label

Safety in Women 27 Through 45 Years of Age

The adverse reaction profile in women 27 through 45 years of age was comparable to the profile seen in girls and women 9 through 26 years of age.

https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/Approv

14.7 Studies in Women 27 through 45 Years of Age

Study 6 evaluated efficacy in 3253 women 27 through 45 years of age based on a combined endpoint of HPV 6-, 11-, 16- or 18-related persistent infection, genital warts, vulvar and vaginal dysplastic lesions of any grade, CIN of any grade, AIS, and cervical cancer. These women were randomized 1:1 to receive either GARDASIL or AAHS control. The efficacy for the combined endpoint was driven primarily by prevention of persistent infection. There was no statistically significant efficacy demonstrated for CIN 2/3, AIS, or cervical cancer. In post hoc analyses conducted to assess the impact of GARDASIL on the individual components of the combined endpoint, the results in the population of women naïve to the relevant HPV type at baseline were as follows: prevention of HPV 6-, 11-, 16- or 18-related persistent infection (80.5% [95% CI: 68.3, 88.6]), prevention of HPV 6-, 11-, 16- or 18-related CIN (any grade) (85.8% [95% CI: 52.4, 97.3]), and prevention of HPV 6-, 11-, 16- or 18-related genital warts (87.6% [95% CI: 7.3, 99.7]).

4vHPV (Gardasil) label

of injection site swelling adverse experiences were reported as being mild to moderate in intensity.

Safety in Women 27 Through 45 Years of Age

The adverse reaction profile in women 27 through 45 years of age was comparable to the profile seen in girls and women 9 through 26 years of age.

- https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/Approv

14.7 Studies in Women 27 through 45 Years of Age

Study 6 evaluated efficacy in 3253 women 27 through 45 years of age based on a combined endpoint of HPV 6-, 11-, 16- or 18-related persistent infection, genital warts, vulvar and vaginal dysplastic lesions of any grade, CIN of any grade, AIS, and cervical cancer. These women were randomized 1:1 to receive either GARDASIL or AAHS control. The efficacy for the combined endpoint was driven primarily by prevention of persistent infection. There was no statistically significant efficacy demonstrated for CIN 2/3, AIS, or cervical cancer. In post hoc analyses conducted to assess the impact of GARDASIL on the individual components of the combined endpoint, the results in the population of women naïve to the relevant HPV type at baseline were as follows: prevention of HPV 6-, 11-, 16- or 18-related persistent infection (80.5% [95% CI: 68.3, 88.6]), prevention of HPV 6-, 11-, 16- or 18-related CIN (any grade) (85.8% [95% CI: 52.4, 97.3]), and prevention of HPV 6-, 11-, 16- or 18-related genital warts (87.6% [95% CI: 7.3, 99.7]).

9vHPV (Gardasil 9) label

Women 27 through 45 Years of Age

A clinical trial evaluated efficacy of GARDASIL in 3,253 women 27 through 45 years of age, based on a combined endpoint of HPV 6-, 11-, 16- or 18-related persistent infection, genital warts, vulvar and vaginal dysplastic lesions of any grade, CIN of any grade, AIS, and cervical cancer. These women were randomized 1:1 to receive either GARDASIL or AAHS control. The efficacy estimate for the combined endpoint was driven primarily by prevention of persistent infection. No statistically significant efficacy was demonstrated for GARDASIL in prevention of cervical intraepithelial neoplasia grades 2 and 3 (CIN 2/3), adenocarcinoma *in situ* (AIS) or cervical cancer related to HPV types 16 and 18.

Regulatory approval in other countries

HPV vaccines are licensed for use in persons >26 years by some other regulatory agencies

Examples:

- **Canada and Australia**
  - 2vHPV, 4vHPV and 9vHPV approved for use in females aged 9–45 years
  - 4vHPV and 9vHPV approved for use in males aged 9–26 years
- **European Medicines Agency**
  - 2vHPV, 4vHPV and 9vHPV approved for use “from the age of 9 years”

https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-9-human-papillomavirus-vaccine.html#p4c8a5_b
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003852/WC500189113.pdf

Overview of HPV vaccine clinical trials in mid-adults

HPV vaccine randomized controlled efficacy, safety and immunogenicity trials in mid-adult women

	4vHPV (FUTURE III) Munoz et al. Lancet 2009 Castellsagué et al. Br J Cancer 2011	**2vHPV** (VIVIANE) Skinner et al. Lancet 2014 Wheeler et al. Lancet ID 2016
Population	Women aged 24–45 years	Women aged >25 years
Number enrolled	3,819	5,752
Primary endpoint	Vaccine type 6-month persistent infection or vaccine-type related CIN1 or worse, external genital lesions	Vaccine type 6-month persistent infection or vaccine-type related CIN1 or worse

CIN1, cervical intraepithelial neoplasia, grade 1

HPV vaccine randomized controlled efficacy, safety and immunogenicity trials in mid-adult women

Per-protocol efficacy results

HPV 16,18-related	4vHPV Castellsagué et al. Br J Cancer 2011				2vHPV Wheeler et al. Lancet ID 2016			
	Cases				Cases			
	Vaccine	Control	Efficacy	(95% CI)	Vaccine	Control	Efficacy	(96.2% CI)
Persistent infection, CIN, EGL*	8	51	**84.7%**	(67.5, 93.7)	7	71	**90.5%**	(78.6, 96.5)
CIN2+	1	6	**83.4%**	(-36.7, 99.6)	1	6	**83.7%**	(-46.5, 99.7)

Per protocol: PCR negative and seronegative to relevant vaccine type, received 3 doses
CIN, cervical intraepithelial neoplasia, EGL, external genital lesions; CIN2+: CIN grade 2 or worse
Mean follow-up time 46 months for 4vHPV, 5.9 years for 2vHPV
*EGL included for 4vHPV endpoint

4vHPV vaccine safety and immunogenicity in mid-adult men (aged 27–45 years) — MAM Study

- Open label, single arm trial, 3 doses of 4vHPV
- Men recruited from ongoing natural history study of HPV infection from sites in Florida and Mexico
- 150 men enrolled
- Results:
  - 100% seropositive to all 4 vaccine types one month after dose 3*
  - Antibody titers >10 fold higher than prevaccination titers, among those seropositive on day 1

Giuliano et al. Vaccine 2015

* By competitive Luminex immunoassay

Summary

- Since end of 2016, 9vHPV is only HPV vaccine available in the United States
  - 9vHPV is licensed for use in males and females aged 9–26 years
- A Biologics License Application to expand the age indication for 9vHPV in males and females through age 45 years is being reviewed by FDA
- 4vHPV efficacy trial was conducted in females aged 24–45 years showing high, statistically significant, efficacy against persistent infection, CIN and external genital lesions due to vaccine types
- No 9vHPV efficacy trial has been conducted in males or females among persons >26 years; no 4vHPV efficacy trial among males in this age group
- Bridging efficacy and immunogenicity data, accepted for other HPV vaccine approvals, will inform consideration of the expanded age application

ACIP HPV Vaccines Work Group

ACIP Members
Peter Szilagyi (Chair)
Cynthia Pellegrini
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

CDC Contributors

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

Thank You

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov