Grading of Recommendations Assessment, Development and Evaluation (GRADE) for use of HPV vaccine in adults ages 27 through 45 years

Introduction

Three HPV vaccines are licensed for use in the United States: 9-valent and quadrivalent HPV vaccines (9vHPV and 4vHPV, Gardasil 9 and Gardasil, Merck & Co., Inc., Kenilworth, NJ) and bivalent HPV vaccine (2vHPV, Cervarix, GlaxoSmithKline, Rixensart, Belgium).[1-3] Until October 2018, all were licensed for use in persons aged 9 through 25 or 26 years. Since late 2016, only 9vHPV has been available in the United States. In October 2018, FDA approved an expansion of the age indication through age 45 years for 9vHPV. HPV vaccination of adults in the United States was considered using Grading of Recommendations Assessment, Development and Evaluation (GRADE). The main policy question was, "Should catch-up HPV vaccination be recommended for primary prevention of HPV infection and HPV-related disease for all persons aged 27 through 45 years?"

Methods

The population of interest was adults aged 27 through 45 years at initiation of vaccination; intervention was catch-up vaccination with a complete 3-dose series of HPV vaccine (9vHPV, 4vHPV, or 2vHPV); comparison was persons through age 45 years with no catch-up HPV vaccination; and outcome was primary prevention of HPV infection and HPV-related disease.

Scientific literature was searched from January 1, 2006 through October 18, 2018 using five databases: Medline, Embase, CINAHL, Cochrane library, and ClinicalTrials.gov. Search terms used to identify clinical trials of efficacy for primary prevention of HPV-associated health outcomes and safety of 3 doses of any licensed HPV vaccine in adults (age 27–45 years at initiation of vaccination) are listed in the appendix. These searches identified 1,388 references.

Trials were excluded if they did not report original data on the relevant population, outcome, or intervention. Benefits were based on per-protocol analyses of HPV vaccine efficacy; immunogenicity data were also considered. Harms were any vaccine-related serious adverse events including deaths.

After reviewing titles and abstracts, we selected 100 references mentioning age 27 and older for detailed review. Of these, 16 publications were selected for inclusion, and 84 were excluded, 50 because they included duplicate data, and the others because they did not address the policy question: 15 did not report data on population of interest (not age-stratified), 11 did not report data on outcome of interest (not primary prevention), and 8 did not report data on intervention of interest (no HPV vaccination).

GRADE tables reference these 16 publications; [4] [5] [6] [7] [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] [18] [19]; personal communication from the vaccine manufacturer providing additional age-limited analyses for previously published studies [20]; and a June 2018 ACIP presentation on clinical data submitted to FDA supporting 9vHPV use in adults [21]. In June 2019, GRADE tables were updated to include new results from a 9vHPV immunogenicity and safety trial in women age 16 through 45 years.[22]

Supplemental data may not directly address the policy question, and is not included in the formal GRADE scoring, but may be helpful for decision making. Supplemental GRADE tables include data from the 9vHPV trial [22], an additional four studies reporting bridging immunogenicity and efficacy data from young adults; [23] [24] [25] [26] two presentations on 9vHPV safety [23] [24]; and the updated FDA label for 9vHPV.[1]

Results

Outcomes of interest included individual benefits and harms. Benefits of interest were per-protocol analyses of HPV vaccine efficacy against persistent HPV infections; anogenital warts; HPV-related precancers including cervical or anal intraepithelial neoplasias (CIN or AIN); or HPV-related cancers including cervical, anal, penile, vaginal, vulvar, and/or oropharyngeal cancers. Immunogenicity to HPV vaccine types was also considered. Harms of interest were vaccine-related serious adverse events including deaths. (Table 1)

Included trials involved 9vHPV, 4vHPV, or 2vHPV (Table 2A), as well as supplemental immunobridging data (Table 2B). For 9vHPV, there was 1 included observational trial. For 4vHPV, there were 7 included trials: 3 randomized placebo-controlled trials, and 4 observational trials. For 2vHPV, there were 4 included trials: 2 randomized placebo-controlled trials, and 2 observational trials. Supplemental data included 4 trials providing bridging immunogenicity data, and 2 surveillance reports of post-licensure safety data for 9vHPV in the United States.

In per-protocol analyses, HPV vaccines showed significant efficacy against a combined endpoint of persistent vaccine-type HPV infections, anogenital warts, and/or cervical intraepithelial neoplasia (CIN) grade 1 or worse (Table 3A). For immunogenicity, post-vaccination seroconversion rates were high, and antibody geometric mean titers (GMTs) tended to be higher than those after natural infection. Seropositivity rates were still high at 3 to 10 years post-initial vaccination, although noticeably lower for HPV type 18 (Table 3B).

For serious adverse events, numbers were comparable among the vaccine group and the placebo group across 8 studies; there were no vaccine-related deaths (Table 3C).

GRADE was used to evaluate evidence for use of 9vHPV in adults. Initial evidence level was 1 for each outcome based on data from randomized controlled trials (Table 4). All were downgraded for indirectness since no randomized placebo-controlled trials were conducted on use of 9vHPV in this age range, and extrapolation from 4vHPV efficacy was based on immunobridging data. Outcomes for which the 95% confidence interval crossed 1 were further downgraded for imprecision. For men, evidence type for each outcome could be further downgraded for indirectness, since most trials enrolled women only.

In summary, evidence level for efficacy is 2 in women and 3 in men, and evidence level for immunogenicity is 2. Overall evidence type for benefits is level 2 (Table 5A). Overall evidence type for harms is also level 2 (Table 5B).

Supplemental immunobridging data showed non-inferior immunogenicity comparing HPV vaccination in mid-adults with HPV vaccination in young adults (Supplemental table 1), and comparing 9vHPV in young adults with 4vHPV in young adults (Supplemental table 2). Supplemental data on harms summarize U.S. postlicensure safety data for over 29 million doses of HPV vaccine (Supplemental table 3).

Abbreviations

HPV, human papillomavirus

2vHPV, bivalent HPV vaccine (Cervarix)

4vHPV, quadrivalent HPV vaccine (Gardasil)

9vHPV, 9-valent HPV vaccine (Gardasil 9)

EGL, external genital lesions

CIN, cervical intraepithelial neoplasia

AIN, anal intraepithelial neoplasia

CI, confidence interval

M, months

GMT, geometric mean titer

mMU/mL, milliMerck Units per milliliter

EU/mL, ELISA units per milliliter

ED_{50}, effective dose producing 50% response

RCT, randomized controlled trial

Obs, observational trial

TABLE 1: Important and critical outcomes related to HPV vaccination

Outcome	Importance	Included in evidence profile
Benefits		
≥6-month persistent vaccine-type HPV infection	Important	Yes
Anogenital warts/condyloma/external genital lesions (EGL)	Important	Yes
Cervical or anal intraepithelial neoplasia (CIN or AIN) 1+	Important	Yes
Cervical or anal intraepithelial neoplasia (CIN or AIN) 2+	Critical	Yes
Combined endpoint: persistent infection, EGL, and/or CIN 1+	Important	Yes
HPV-related cancer (anal, cervical, oropharyngeal, penile, and/or vaginal/vulvar)	Critical	No*
Immunogenicity (seropositivity and GMTs to vaccine types, early or late)	Important	Yes
Harms		
Serious adverse events, any or vaccine-related	Important	Yes
Death, any or vaccine-related	Critical	Yes

* No HPV-related cancers were reported in per-protocol analyses from any of the studies reviewed; data on these outcomes not necessarily expected in clinical trials of current duration/size

TABLE 2A: Characteristics of included studies

Vaccine	Author, year [reference]	Clinical trial number (name)	Design	Participants (N=total enrolled)	Follow-up time	Main outcomes related to HPV vaccine types**
9vHPV	Luxembourg, 2019 [22]	NCT03158220 (Protocol 004)	Observational trial in 6 countries	Women age 27–45 years (N=642)	7 months	• Immunogenicity • Harms
4vHPV	Muñoz, 2009 [4]* Castellsagué, 2011 [5]* Luxembourg, 2018 [21]	NCT00090220 (Future III)	Randomized, placebo-controlled trial in 7 countries (through M48); observational trial in Colombia (through M120)	Women age 24–45 years (N=3819)	7 months; 48 months; 120 months	• Immunogenicity • Persistent HPV infection • External genital lesions (warts) • CIN 1+, CIN 2+ • Combined endpoint • Harms
	Wei, 2018 [6]*	NCT00834106	Randomized, placebo-controlled trial in China	Women age 20–45 years (N=3006, including 1166 women age 27–45 years)	78 months	• Persistent HPV infection • External genital lesions (warts) • CIN 1+, CIN 2+ • Combined endpoint • Harms

	Einstein, 2009 [7] Einstein, 2014 [8]	NCT00423046	Observational trial in the USA	Women age 18–45 years in the USA (N=1106)	60 months	• Immunogenicity • Harms
	Huang, 2018 [9]	NCT01427777	Observational trial in China	Women age 9–45 years (N=468, including <250 age 27–45 years)	42 months	• Immunogenicity
	Giuliano, 2015 [10]	NCT01432574 (MAM)	Observational trial in the USA and Brazil	Men 27–45 years (N=150)	7 months	• Immunogenicity • Harms
	Money, 2016 [11]	None (CTN 236)	Observational trial in Canada	HIV+ women age 15–45 years (N=372, including 98 women age 24–45 years)	24 months	• Immunogenicity
	Wilkin, 2018 [12]	NCT01461096 (ACTG A5298)	Randomized, placebo-controlled trial in the USA and Brazil	HIV+ people age ≥27 years (N=575, including 472 men and 103 women)	12 months (trial halted; no per-protocol analysis)	• Harms
2vHPV	Skinner, 2014 [13] Wheeler, 2016 [14]	NCT00294047 (VIVIANE)	Randomized, placebo-controlled trial in 12 countries	Women age ≥26 years (N=4407, including 3916 women age 26–45 years)	48 months; 84 months	• Immunogenicity • Persistent HPV infection • CIN 1+ • CIN 2+ • Combined endpoint • Harms
	Schwarz, 2009 [15] Schwarz, 2011 [16] Schwarz, 2015 [17]	NCT00196937; NCT00947115	Observational trial in	Women age 15–55 years (N=667, including 226 women age 26–45 years)	1 month; 48 months;	• Immunogenicity • Harms

	Schwarz, 2017 [18]		Germany and Poland		72 months; 120 months	
	Einstein, 2009 [7] Einstein, 2014 [8]	NCT00423046	Observational trial in the United States	Women age 18–45 years (N=1106)	24 months; 60 months	• Immunogenicity • Harms
	Zhu, 2014 [19]	NCT01277042 (protocol HPV-069)	Randomized, placebo-controlled trial in China	Women age 9–45 years (N=1962, including 1212 women age 26-45 years)	7 months	• Immunogenicity • Harms

* Age-restricted data obtained from Luxembourg, 2018 [20]

** Per-protocol results for benefits; intention-to-treat results for harms

TABLE 2B: Characteristics of included studies, supplemental

Vaccine	Author, year [reference]	Clinical trial number (name)	Design	Participants (N=total enrolled)	Follow-up time	Main outcomes related to HPV vaccine types*
9vHPV	Luxembourg, 2019 [22]	NCT03158220 (Protocol 004)	Observational trial in 6 countries	Women age 16–26 years (N=570)	7 months	• Immunogenicity • Harms
4vHPV	Hillman, 2012 [23] Giuliano, 2011 [24] Palefsky, 2011 [25]	NCT00090285	Randomized, placebo-controlled trial in 18 countries	Men age 16–26 years (N=4065)	7 months	• Supplemental, immunogenicity (bridging of age groups: 4vHPV immunogenicity and clinical efficacy in young adult males)
	Luxembourg, 2018 [21]	NCT00092521 (Future I); NCT00092534 (Future II); NCT00090220 (Future III)	Post hoc analysis of data from randomized, placebo-controlled trials	Women age 16–26 years	7 months	• Supplemental, immunogenicity (bridging of age groups: 4vHPV immunogenicity in young adult females)
9vHPV	Joura, 2015 [26] Huh, 2017 [27]	NCT00543543	Randomized, placebo-controlled trial in 18 countries	Women age 16–26 years (N=14215)	7 months; 42 months	• Supplemental, immunogenicity (bridging of vaccines: 9vHPV in young adult females)

	Van Damme, 2016 [28]	NCT02114385	Randomized, placebo-controlled trial in Belgium, Netherlands, and Germany	Men age 16–26 years (N=500)	7 months	• Supplemental, immunogenicity (bridging of vaccines: 9vHPV in young adult males)
	Donahue [29]	N/A	Observational data from Vaccine Safety Datalink (VSD)	U.S. enrollees age 9–26 years		• Supplemental, harms
	Arana [30]	N/A	Observational data from Vaccine Adverse Events Reporting System (VAERS)	Reports of potential adverse events following 9vHPV (N=8529 in the USA; n=73 age 26–45)		• Supplemental, harms

* Per-protocol results for benefits; intention-to-treat results for harms

TABLE 3A: Efficacy outcomes

Vaccine	Reference	Outcome (number of months)	Vaccine group N (%)	Placebo group N (%)	Observed Efficacy** (95% CI)
Persistent (≥6M) HPV infection					
4vHPV	Castellsagué, 2011 [5]*	6M-persistent cervical HPV 6/11/16/18 (M48)	8/1358 (0.6)	71/1372 (5.2)	88.8% (76.8–95.4)
	Wei, 2018 [6]*	12M-persistent cervical HPV 6/11/16/18 (M78)	3/521 (0.6)	29/515 (5.6)	90.0% (67.6–98.0)
2vHPV	Wheeler, 2016 [14]	6M-persistent cervical HPV 6/11 (M84)	6/1815 (0.06)	67/1786 (0.7)	91.4% (79.4–97.1)
Anogenital warts/condyloma					
4vHPV	Castellsagué, 2011 [5]* Luxembourg, 2018 [21]	Condyloma (M48)	0/1376 (0.0)	5/1384 (0.4)	100% (-9.8–100)
		Condyloma (M120)	0/527 (0.0)	-	-
	Wei, 2018 [6]*	Condyloma (M48)	0/521 (0.0)	0/516 (0.0)	-
Cervical Intraepithelial Neoplasia (CIN), any grade (1+)					
4vHPV	Castellsagué, 2011 [5]*	CIN 1+ (M48)	1/1358 (0.0)	16/1370 (1.2)	93.7% (59.5–99.9)
	Luxembourg, 2018 [21]	CIN 1+ (M120)	0/527 (0.0)	-	-
	Wei, 2018 [6]*	CIN 1+ (M78)	0/520 (0.0)	6/515 (1.2)	100% (15.5–100)
2vHPV	Wheeler, 2016 [14]	CIN 1+ (M84)	2/1852 (0.02)	12/1818 (0.1)	83.7% (21.9–98.5)
Cervical Intraepithelial Neoplasia [CIN] 2+					
4vHPV	Castellsagué, 2011 [5]*	CIN 2+ (M48)	1/1358 (0.0)	5/1370 (0.4)	79.8% (-80.1–99.6)
	Luxembourg, 2018 [21]	CIN 2+ (M120)	0/527 (0.0)	-	-

	Wei, 2018 [6]*	CIN 2+ (M78)	0/520 (0.0)	4/515 (0.8)	100% (-51.0–100)
2vHPV	Wheeler, 2016 [14]	CIN 2+ (M84)	1/1852 (0.01)	6/1818 (0.06)	83.7% (-46.5–99.7)
Combined endpoint: persistent infection, CIN 1+, and/or EGL					
4vHPV	Castellsagué, 2011 [5] * Luxembourg, 2018 [21]	Combined endpoint: persistent infection, CIN 1+, and/or EGL (M48)	9/1376 (0.7)	72/1384 (5.2)	87.7% (75.4–94.6)
		Combined endpoint: CIN or condyloma (M72–120)	0/527 (0.0)	-	-
	Wei, 2018 [6]*	Combined endpoint: persistent infection, CIN 1+, and/or EGL (M78)	3/521 (0.6)	31/516 (6.0)	90.6% (69.9–98.2)
2vHPV	Wheeler, 2016 [14]	Combined endpoint: persistent infection, CIN 1+ (M84)	7/1852 (0.07)	71/1818 (0.7)	90.5% (78.6–96.5)

* Age-restricted data obtained fromLuxembourg, 2018 [20]

** Per-protocol results

TABLE 3B: Immunogenicity outcomes

Vaccine	Reference	Antibody	Months	Post-vaccination**		
				Seropositive n	Seropositive %	GMTs (95% CI)
Immunogenicity, early (7 months post first vaccination dose)						
9vHPV	Luxembourg, 2019 [22]	anti-HPV6	M7	448	100	638 (595–685) mMu/mL
		anti-HPV11		447	99.8	454 (424—485) mMu/mL
		anti-HPV16		448	100	2148 (2001–2305) mMu/mL
		anti-HPV18		469	99.6	532 (492–576) mMu/mL
		anti-HPV31		487	99.8	396 (367–427) mMu/mL
		anti-HPV33		492	99.8	259 (243–276) mMu/mL
		anti-HPV45		511	99.2	146 (134–158) mMu/mL
		anti-HPV52		496	100	245 (229–261) mMu/mL
		anti-HPV58		477	99.8	296 (277–317) mMu/mL
4vHPV	Muñoz, 2009 [4]*	anti-HPV6	M7	1083	98.2	412 (386–440) mMU/mL
		anti-HPV11		1083	97.9	538 (506–573) mMU/mL
		anti-HPV16		1092	98.6	2212 (2076–2357) mMU/mL
		anti-HPV18		1223	97.1	348 (326–372) mMU/mL
	Einstein, 2009 [7]	anti-HPV16	M7	186	100	20605 (16259–26112) ED_{50}
		anti-HPV18		212	100	9674 (7677–18194) ED_{50}
	Huang, 2018 [9]	anti-HPV6	M7		98.1	
		anti-HPV11			100	
		anti-HPV16			100	

		anti-HPV18			99.2	
	Giuliano, 2015 [10]	anti-HPV6	M7	145	100	365 mMU/mL
		anti-HPV11		145	100	490 mMU/mL
		anti-HPV16		145	100	2178 mMU/mL
		anti-HPV18		145	100	296 mMU/mL
	Money, 2016 [11]	anti-HPV6	M7	61	99.0	426 (324–561) mMU/mL
		anti-HPV11		98	98.7	540 (436–668) mMU/mL
		anti-HPV16		66	98.1	1495 (1046–2137) mMU/mL
		anti-HPV18		94	93.6	295 (223–391) mMU/mL
2vHPV	Skinner, 2014 [13]	anti-HPV16	M7	406	100	5413 (4934–5938) EU/mL
		anti-HPV18		405	100	2568 (2340–2818) EU/mL
	Schwarz, 2009; [15]	anti-HPV16	M7	164	100	4060 (3511–4695) EU/mL
		anti-HPV18		185	100	1881 (1661–2130) EU/mL
	Einstein, 2009 [7]	anti-HPV16	M7	168	100	6296 (4906–8082) ED_{50}
		anti-HPV18		190/192	99.0	1241 (947–1626) ED_{50}
	Zhu, 2014 [19]	anti-HPV16	M7	596	100	6440 (6040–6866) EU/mL
		anti-HPV18		363/365	99.5	3563 (3310–3836) EU/mL
Immunogenicity, later (up to 120 months post first vaccination dose)						
4vHPV	Castellsagué, 2011 [5]*	anti-HPV6	M48	1007	85.3	61 (57–65) mMU/mL
		anti-HPV11		1007	91.8	64 (61–69) mMU/mL
		anti-HPV16		1022	97.3	200 (186–214) mMU/mL
		anti-HPV18		1132	47.5	23 (21–25) mMU/mL
	Einstein, 2014 [8]	anti-HPV16	M60	73/76	96.1	555 (341–904) ED_{50}
		anti-HPV18		60/87	69.0	89 (59–136) ED_{50}
	Huang, 2018 [9]	anti-HPV6	M42		91.2	

		anti-HPV11			88.3	
		anti-HPV16			96.8	
		anti-HPV18			37.6	
	Money, 2016 [11]	anti-HPV6	M24	53		129 (93–179) mMU/mL
		anti-HPV11		78		125 (125–160) mMU/mL
		anti-HPV16		54		459 (341–618) mMU/mL
		anti-HPV18		72		54 (39–74) mMU/mL
2vHPV	Skinner, 2014 [13]	anti-HPV16	M48	345/345	100	546 (490–608) EU/mL
		anti-HPV18		336/338	99.4	228 (202–259 EU/mL)
	Schwarz, 2017 [18]	anti-HPV16	M120	120/121	99.2	334 (270-414) EU/mL
		anti-HPV18		133/142	93.7	115 (94-142) EU/mL
	Einstein, 2014 [8]	anti-HPV16	M60	89	100	1855 (1267–2715) ED_{50}
		anti-HPV18		109	100	892 (759–1268) ED_{50}

* Age-restricted data obtained fromLuxembourg, 2018 [20]

** Per-protocol results

TABLE 3C: Harms

Vaccine	Reference	Outcome**	Months	Vaccine group n/N (%)	Placebo group n/N (%)
Serious adverse events, any					
9vHPV	Luxembourg, 2019 [22]	Serious adverse events	M7	8/640 (0.1)	6/570 (0.1)
4vHPV	Castellsagué, 2011 [5]*	Serious adverse events	M48	14/1908 (0.7)	16/1902 (0.8)
	Wei, 2018 [6]*	Serious adverse events	M78	20/580 (3.4)	23/586 (3.9)
	Einstein, 2014 [8]	Serious adverse events	M60	44/553 (8.0)	No placebo group
2vHPV	Einstein, 2014 [8]	Serious adverse events	M60	37/553 (6.7)	No placebo group
	Wheeler, 2016 [14]	Serious adverse events	M48	286/2877 (9.9)	266/2870 (9.3)
	Schwarz, 2017 [18]	Serious adverse events	M48	8/226 (3.5)	No placebo group
Vaccine-related serious adverse events					
9vHPV	Luxembourg, 2019 [22]	Vaccine-related serious adverse events	M7	0/640 (0.0)	0/570 (0.0)
4vHPV	Castellsagué, 2011 [5]*	Vaccine-related serious adverse events	M48	0/1908 (0.0)	0/1902 (0.0)
	Wei, 2018 [6]*	Vaccine-related serious adverse events	M78	0/580 (0.0)	1/586 (0.2)
	Giuliano, 2015 [10]	Vaccine-related serious adverse events (grade 3+)	M7	1/150 (0.7)	No placebo group
2vHPV	Wheeler, 2016 [14]	Vaccine-related serious adverse events	M84	5/2877 (0.2)	8/2870 (0.3)

	Schwarz, 2017 [18]	Vaccine-related serious adverse events	M48	1/226 (0.4) Cervical dysplasia (resolved)	No placebo group
	Zhu, 2014 [19]	Vaccine-related serious adverse events	M12	0/606 (0.0)	0/606 (0.0)
Deaths, any					
9vHPV	Luxembourg, 2019 [22]	Death	M7	0/640 (0.0)	0/570 (0.0)
4vHPV	Castellsagué, 2011 [5]*	Death	M48	7/1908 (0.4) Acute liver disease secondary to nasopharyngeal cancer; Breast cancer; Cardiac arrest secondary to breast cancer metastasis; Cardiac arrest secondary to cerebrovascular accident; Pulmonary embolism; Pericarditis; Tuberculosis	1/1902 (0.1) Pulmonary embolism
	Wei, 2018 [6]*	Death	M78	2/580 (0.3) Ovarian cancer; Road traffic crash	0/586 (0.0)
	Einstein, 2014 [8]	Death	M60	1/553 (0.2) Metastatic renal cell carcinoma	No placebo group
	Giuliano, 2015 [10]	Death	M7	0/150 (0.0)	No placebo group
	Wilkin, 2018 [12]	Death	M12	3/276 (1.1)	6/277 (2.2)
2vHPV	Wheeler, 2016 [14]	Death	M84	13/2877 (0.5) Acute myocardial infarction; Acute renal failure; Breast cancer; Cervix cancer; Glioblastoma multiforme; Homicide; Interstitial lung disease; Lung cancer;	5/2870 (0.2) Anaplastic astrocytoma; Cardiac valve disease and liver disorder; Cardiorespiratory arrest; Lower respiratory tract

				Pneumonia; Pulmonary embolism; Suicide (x3)	infection and sepsis; Nasopharyngeal cancer
	Schwarz, 2017 [18]	Death	M48	2/226 (0.9) Chronic lymphocytic leukemia; Lung cancer	No placebo group
Vaccine-related deaths					
9vHPV	Luxembourg, 2019 [22]	Death, vaccine-related	M7	0/640 (0.0)	0/570 (0.0)
4vHPV	Castellsagué, 2011 [5]*	Death, vaccine-related	M48	0/1908 (0.0)	0/1902 (0.0)
	Wei, 2018 [6]*	Death, vaccine-related	M78	0/580 (0.0)	0/586 (0.0)
	Einstein, 2014 [8]	Death, vaccine-related	M60	0/553 (0.0)	No placebo group
	Giuliano, 2015 [10]	Death, vaccine-related	M7	0/150 (0.0)	No placebo group
	Wilkin, 2018 [12]	Death, vaccine-related	M12	0/276 (0.0)	0/277 (0.0)
2vHPV	Wheeler, 2016 [14]	Death, vaccine-related	M84	0/2877 (0.0)	0/2870 (0.0)
	Schwarz, 2017 [18]	Death, vaccine-related	M48	0/226 (0.0)	No placebo group
	Zhu, 2014 [19]	Death, vaccine-related	M12	0/606 (0.0)	0/606 (0.0)

* Age-restricted data obtained from Luxembourg, 2018 [20]

** Intention-to-treat results

TABLE 4: Evidence for use of 9vHPV in adults ages 27 through 45 years

Outcome	Finding	Design (number of studies)	Initial evidence level*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations **	Evidence type*
9vHPV Benefits									
Persistent HPV infection	Prevents ≥6M-persistent HPV infection	RCTs (3) + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**2**
Anogenital warts	Prevents anogenital warts	RCTs (2) + supplemental	1	Not serious	Not serious	Serious[1]	Serious[2]	None	**3**
CIN 1+	Prevents CIN 1+	RCTs (3) + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**2**
CIN 2+	Prevents CIN 2+	RCTs (3) + supplemental	1	Not serious	Not serious	Serious[1]	Serious[2]	None	**3**
Combined endpoint	Prevents the above HPV-related outcomes	RCTs (3) + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**2**
Immunogenicity	Immunogenic	RCTs (3), Obs (6) + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**2**
9vHPV Harms									
Serious Adverse Events	Similar numbers of serious adverse events with 9vHPV vs placebo	RCTs (3), Obs (3) + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**2**

Vaccine-related Serious Adverse Events	Few vaccine-related serious adverse events	RCTs (4), Obs (3) + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**2**
Death	Similar numbers of deaths with 9vHPV vs placebo	RCTs (4), Obs (4) + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**2**
Vaccine-related Death	No vaccine-related deaths	RCTs (5), Obs (4) + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**2**

RCT, randomized controlled trial; Obs, observational study

* Evidence levels: 1) High, 2) Moderate, 3) Low, 4) Very Low

** Strength of association, dose-response, plausible residual confounding, publication bias

1. Downgraded for indirectness since no randomized placebo-controlled trials were conducted on use of 9vHPV in adults aged 27 through 45 years, and there are no 4vHPV efficacy trials in males aged 27 through 45 years; extrapolation of efficacy from 4vHPV across age and genders is based on supplemental bridging immunogenicity data

2. Downgraded for imprecision since 95% confidence interval for efficacy includes 1

TABLE 5A: Summary of evidence for benefits

Comparison	Outcome	Design (number of studies)	Findings	Evidence type	Overall evidence type*
HPV vaccination (adults age 27–45 years) versus no HPV vaccination	**Efficacy**	RCTs (3)	9vHPV is more efficacious against HPV-related outcomes than no vaccination	2	**2**
	Immunogenicity	RCTs (3), Obs (6)	9vHPV is immunogenic	2	

* Evidence levels: 1) High, 2) Moderate, 3) Low, 4) Very Low

TABLE 5B: Summary of evidence for harms

Comparison	Outcome	Design (number of studies)	Findings	Evidence type	Overall evidence type*
HPV vaccination (adults age 27–45 years) versus no HPV vaccination	**Harms, any**	RCTs (4), Obs (4)	Similar adverse events among participants receiving placebo versus 9vHPV	2	**2**
	Vaccine-related harms	RCTs (5), Obs (4)	Few vaccine-related serious adverse events, and no vaccine-related deaths	2	

* Evidence levels: 1) High, 2) Moderate, 3) Low, 4) Very Low

SUPPLEMENTAL DATA

SUPPLEMENTAL TABLE 1: Immunobridging comparing HPV vaccination in mid-adults with HPV vaccination in young adults

Group	Reference; population	Antibody	Months	Mid-adult vaccination (27–45 years)			Young adult vaccination (16–26 years)			Comparison
				Sero-positive n/N	Sero-positive %	GMTs (95% CI) mMU/mL	Sero-positive n/N	Sero-positive %	GMTs (95% CI) mMU/mL	GMT ratio (95% CI)
9vHPV	Luxembourg, 2019 [22]; age 16–26 and 27–45 years	anti-HPV6	M7	448/448	100	638 (595–685)	420/421	99.8	788 (733–847)	Not done
		anti-HPV11		447/448	99.8	454 (424—485)	421/421	100	599 (559–642)	Not done
		anti-HPV16		448/448	100	2148 (2001–2305)	436/436	100	3076 (2863–3304)	0.7 (0.6–0.8)
		anti-HPV18		469/471	99.6	532 (492–576)	421/421	100	745 (685–809)	0.7 (0.6–0.8)
		anti-HPV31		487/488	99.8	396 (367–427)	447/447	100	596 (551–645)	0.7 (0.6–0.7)
		anti-HPV33		492/493	99.8	259 (243–276)	457/457	100	355 (332–379)	0.7 (0.7–0.8)
		anti-HPV45		511/515	99.2	146 (134–158)	468/470	99.6	215 (198–234)	0.7 (0.6–0.8)
		anti-HPV52		496/496	100	245 (229–261)	456/456	100	347 (324–371)	0.7 (0.6–0.8)
		anti-HPV58		477/478	99.8	296 (277–317)	451/451	100	428 (399–459)	0.7 (0.6–0.8)
4vHPV, females	Muñoz, 2009 [4]; age 27–45 years	anti-HPV6	M7	1083/	98.2	412				
		anti-HPV11		1083/	97.9	538				
		anti-HPV16		1092/	98.6	2212				
		anti-HPV18		1223/	97.1	348				
	Luxembourg, 2018 [21]; age 16–26 years	anti-HPV6	M7				2800		536.2	0.8 (0.7–0.8)
		anti-HPV11					2824		754.3	0.7 (0.7–0.8)
		anti-HPV16					2749		2297.6	1.0 (0.9–1.1)
		anti-HPV18					3006		458.1	0.8 (0.7–0.8)
4vHPV, males	Giuliano, 2015 [10];	anti-HPV6	M7	145/145	100	419 (363–484)				
		anti-HPV11		145/145	100	517 (455–587)				
		anti-HPV16		145/145	100	2229 (2004–2448)				

	age 27–45 years	anti-HPV18		145/145	100	300 (259–347)				
	Hillman, 2012 [23]; age 16–26 years	anti-HPV6	M7				1080/1092	98.9	448 (423–474)	
		anti-HPV11					1083/1092	99.2	624 (594–655)	
		anti-HPV16					1121/1135	98.8	2404 (2272–2544)	
		anti-HPV18					1143/1174	97.4	402 (380–426)	
	Luxembourg, 2018 [21]; age 27–45 years	anti-HPV6	M7							0.8 (0.6–1.0)
		anti-HPV11								0.8 (0.7–0.9)
		anti-HPV16								0.9 (0.7–1.1)
		anti-HPV18								0.7 (0.6–0.9)

SUPPLEMENTAL TABLE 2: Immunobridging comparing 9vHPV in young adults with 4vHPV in young adults

Vaccine	Reference; population	Antibody	Months	Vaccination with 9vHPV			Vaccination with 4vHPV			Comparison
				Sero-positive n/N	Sero-positive %	GMTs (95% CI) mMU/mL	Sero-positive n/N	Sero-positive %	GMTs (95% CI) mMU/mL	GMT ratio (95% CI)
9vHPV	Joura [26]; females age 16–26 years	anti-HPV6	M7	3985/3993	99.8	893	3969/3975	99.8	875	1.0 (0.9–1.1)
		anti-HPV11		3994/3995	100	666	3980/3982	99.9	830	0.8 (0.8–0.8)
		anti-HPV16		4031/4032	100	3131	4060/4062	100	3157	1.0 (1.0–1.0)
		anti-HPV18		4532/4539	99.8	805	4528/4541	99.7	679	1.2 (1.1–1.2)
	Huh [27]; females age 16–26 years	anti-HPV6	M42	692	95.5	147 (137-158)	675	94.5	144 (134–155)	1.0 (0.9–1.1)
		anti-HPV11		696	95.4	85 (79-91)	677	96.8	104 (97–112)	0.8 (0.7–0.9)
		anti-HPV16		709	98.4	347 (319-377)	690	98.6	363 (334–395)	1.0 (0.8–1.1)
		anti-HPV18		806	81.6	71 (65-77)	770	77.0	60 (55–66)	1.2 (1.0–1.3)
		anti-HPV31		783	93.6	70 (65-76)	730	13.0	<4	-
		anti-HPV33		835	94.6	44 (42-47)	789	7.6	<4	-
		anti-HPV45		846	78.8	21 (20-23)	802	1.2	<3	-
		anti-HPV52		791	95.2	43 (41-46)	735	5.6	<3	-
		anti-HPV58		784	94.4	52 (49-56)	756	5.6	<4	-
	Van Damme [28]; males age 16–26 years	anti-HPV6	M7	224/228	98.2	758 (666–863)	223/226	98.7	618 (554–690)	1.2 (1.0–1.5)
		anti-HPV11		228/228	100	682 (609–763)	226/226	100	769 (683–865)	0.9 (0.8–1.0)
		anti-HPV16		234/234	100	3924 (3514–4382)	237/237	100	3788 (3378–4247)	1.0 (0.9–1.2)
		anti-HPV18		233/234	99.6	884 (766–1020)	235/236	99.6	791 (683–916)	1.1 (0.9–1.4)
		anti-HPV31		234/234	100	794 (694–909)	146/237	61.6	15 (12–18)	-

		anti-HPV33		236/236	100	460 (411–516)	40/236	16.9	3 (3–4)	-
		anti-HPV45		232/232	100	263 (226–306)	22/236	9.3	2 (2–3)	-
		anti-HPV52		235/235	100	431 (378–491)	6/236	2.5	2 (2–2)	-
		anti-HPV58		232/232	100	691 (615–777)	84/233	36.1	6 (5–7)	-

SUPPLEMENTAL TABLE 3: 9vHPV post-licensure safety data

Vaccine	Reference	Outcome	Months	Vaccine group n/N (%)	Placebo group n/N (%)
9vHPV	Donahue, 2018 [23], Vaccine Safety Datalink	Pre-specified adverse events	Any	Signal detected: Syncope, injection site reactions Signal not confirmed: Allergic reactions, appendicitis (no increased risk in further analysis) No signal detected: Anaphylaxis, Guillain-Barré syndrome, pancreatitis, seizures, stroke, venous thromboembolism, chronic inflammatory demyelinating polyneuropathy	-
	Arana, 2018 [24],* Vaccine Adverse Event Reporting System	Serious adverse events Deaths	Any Any	3/73 (4.1) 0/73 (0.0)	- -

Summary

After reviewing the available data including the GRADE analysis, in June 2019, ACIP recommended catch-up HPV vaccination for all adults through age 26 years. ACIP did not recommend catch-up vaccination of adults aged 27–45 years, but recognized that some adults who are not previously vaccinated may be at risk for new HPV infection and might benefit from vaccination in this age range; therefore, ACIP recommended shared clinical decision making regarding potential HPV vaccination for these individuals. See 2019 policy note Update: Recommendations of the Advisory Committee on Immunization Practices (ACIP) for Human Papillomavirus (HPV) Vaccination of Adults.

APPENDIX: Search Methods

Database	Strategy	Run Date	Records
Medline (OVID) 1946-	*Papillomavirus Vaccines/ OR Human Papillomavirus Recombinant Vaccine Quadrivalent, Types 6, 11, 16, 18 / OR (human papillomavirus ADJ2 vaccin*) OR (human papillomavirus ADJ2 immunization*) OR (human papillomavirus ADJ2 immunisation*) OR (human papilloma virus ADJ2 vaccin*) OR (human papilloma virus ADJ2 immunization*) OR (human papilloma virus ADJ2 immunisation*) OR (HPV ADJ2 vaccin*) OR (HPV ADJ2 immunization*) OR (HPV ADJ2 immunisation*) OR Gardasil OR Cervarix OR silgard AND Adult/ OR (older ADJ2 26) OR 27 years OR >26 OR =>27 OR age 27 OR aged 27 OR ages 27* OR mid-adult OR older women OR older men AND ((randomized controlled trial.pt. or controlled clinical trial.pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)) Limit 2006- ;	8/6/2018	798
Embase (OVID) 1947-	*Wart virus vaccine/ OR (human papillomavirus ADJ2 vaccin*) OR (human papillomavirus ADJ2 immunization*) OR (human papillomavirus ADJ2 immunisation*) OR (human papilloma virus ADJ2 vaccin*) OR (human papilloma virus ADJ2 immunization*) OR (human papilloma virus ADJ2 immunisation*) OR (HPV ADJ2 vaccin*) OR (HPV ADJ2 immunization*) OR (HPV ADJ2 immunisation*) OR Gardasil OR Cervarix OR silgard AND Adult/ OR (older ADJ2 26) OR 27 years OR >26 OR =>27 OR age 27 OR aged 27 OR ages 27* OR mid-adult OR older women OR older men AND crossover procedure.sh. OR double-blind procedure.sh. OR randomized controlled trial.sh. OR single-blind procedure.sh. OR (random* OR factorial* OR crossover* OR (cross ADJ1 over*) OR placebo* OR (doubl* ADJ1 blind*) OR (singl* ADJ1 blind*) OR assign* OR allocat* OR volunteer*).sh,ab,ti. Limit 2006- ; not pubmed/medline ;	8/6/2018	611 -285 duplicates =327 unique items
CINAHL (Ebsco)	(MM "Papillomavirus Vaccine") OR (“human papillomavirus” N2 vaccin*) OR (“human papillomavirus” N2 immunization*) OR (“human papillomavirus” N2 immunisation*) OR (“human papilloma virus” N2 vaccin*) OR (“human papilloma virus” N2 immunization*) OR (“human papilloma virus” N2 immunisation*) OR (HPV N2 vaccin*) OR (HPV N2 immunization*) OR (HPV N2 immunisation*) OR Gardasil OR Cervarix OR silgard AND (MH "Adult") OR (older N2 26) OR 27 years OR >26 OR =>27 OR “age 27” OR “aged 27” OR “ages 27*” OR mid-adult OR “older women” OR “older men” AND	8/6/2018	71 -11 duplicates =60 unique items

	(TX allocat* random*) OR (MH "Quantitative Studies") OR (MH "Placebos") OR (TX placebo*) OR (TX random* allocat*) OR (MH "Random Assignment") OR (TX randomi* control* trial*) OR (TX ((singl* N1 blind*) OR (singl* N1 mask*))) OR (TX ((doubl* N1 blind*) OR (doubl* N1 mask*))) OR (TX ((tripl* N1 blind*) OR (tripl* N1 mask*))) OR (TX ((trebl* N1 blind*) OR (trebl* N1 mask*))) OR (TX clinic* N1 trial*) OR (PT "Clinical trial") OR (MH "Clinical Trials+") Limit 2006- ; exclude Medline records ;		
Cochrane Library	[mh "Papillomavirus Vaccine"] OR (("human papillomavirus" NEAR/2 vaccin*) OR ("human papillomavirus" NEAR/2 immunization*) OR ("human papillomavirus" NEAR/2 immunisation*) OR ("human papilloma virus" NEAR/2 vaccin*) OR ("human papilloma virus" NEAR/2 immunization*) OR ("human papilloma virus" NEAR/2 immunisation*) OR (HPV NEAR/2 vaccin*) OR (HPV NEAR/2 immunization*) OR (HPV NEAR/2 immunisation*) OR Gardasil OR Cervarix OR silgard):ti,ab AND [mh "Adult"] OR ((older NEAR/2 26) OR 27 years OR >26 OR =>27 OR "age 27" OR "aged 27" OR "ages 27*" OR mid-adult OR "older women" OR "older men"):ti,ab Limit to database *Central Register of Controlled Trials*	8/6/2018	148 -110 duplicates =38 unique items
Clinicaltrials.gov	Interventional Studies | "human papillomavirus vaccine" OR "human papilloma virus vaccine" OR "HPV vaccine" OR Gardasil OR Cervarix OR silgard | Adult	8/6/2018	128

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