GRADE for HPV vaccination of mid-adults

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OUTLINE

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- Evidence Retrieval
- Included Studies
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- Outcomes: Immunogenicity and Immunobridging
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PICO QUESTION

PICO QUESTION

- Should catch-up vaccination with HPV vaccine be recommended for primary prevention of HPV infection and HPV-related disease in U.S. adults age 27–45 years who were not vaccinated previously at the routinely recommended age?

- Population: U.S. adults age 27–45 years (“mid-adult” age range)
- Intervention: Vaccination with 3 doses of HPV vaccine*
- Comparison: No HPV vaccination
- Outcome: Important and critical HPV vaccine-related benefits and harms

* Data considered for all licensed HPV vaccines, but only 9vHPV is available in the United States

CRITICAL OUTCOMES

Benefits	Importance	Include in evidence profile
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, Vaginal, Vulvar)	Critical	No*
Immunogenicity (Seroconversion and GMTs to vaccine types)	Important	Yes

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

CRITICAL OUTCOMES

Harms	Importance	Include in evidence profile
Serious adverse events, any or vaccine-related	Important	Yes
Death, any or vaccine-related	Critical	Yes

EVIDENCE RETRIEVAL

- Systematic review of HPV vaccine clinical trials in Medline, Embase, CINAHL, Cochrane Library, and clinicaltrials.gov published between 2006, when HPV vaccine was first licensed, and October 18, 2018
  - Trials of HPV vaccination in 27–45 year-olds
  - Search terms listed on next slide
- Efforts made to obtain unpublished or other relevant data
  - Previous ACIP presentations
  - Cochrane reviews for SAGE
  - FDA label for 9vHPV updated October 5, 2018
  - Clarification of data from vaccine manufacturer

EVIDENCE RETRIEVAL

Database	Strategy	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- ;	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 ;	611 -285 duplicates =327 unique items

Database	Strategy	Records
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 (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 ;	71 -11 duplicates =60 unique items
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	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	128

EVIDENCE RETRIEVAL

- Search identified 1388 references:
- Selected 100 references mentioning age ≥27 years for detailed review:
  - 16 trials selected for inclusion
  - 84 papers excluded
    - 50 included duplicate data
    - 15 did not report data on population of interest (not age-stratified)
    - 11 did not report data on outcome of interest (not primary prevention)
    - 8 did not report data on intervention of interest (no vaccination)
- Evidence tables included:
  - 16 trials, 1 ACIP presentation, and 1 personal communication
  - Supplemental data included an additional 6 articles and 2 ACIP presentations

EVIDENCE TYPES

Initial evidence type	Study design
1	Randomized controlled trials (RCTs) or overwhelming evidence from observational studies
2	RCTs with important limitations, or exceptionally strong evidence from observational studies
3	Observational studies (Obs), or RCTs with notable limitations
4	Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

INCLUDED STUDIES

CHARACTERISTICS OF INCLUDED STUDIES, 4vHPV

Author, year	Clinical trial number	Design	Participants (N=total enrolled)	Follow-up time	Main outcomes related to HPV vaccine types**
Muñoz, 2009 [1]* Castellsagué, 2011 [2]* Luxembourg, 2018 [4]	NCT00090220 (Future III)	RCT, 7 countries (through month 48), then Obs, Colombia (through month 120)	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 [5]*	NCT00834106	RCT, China	Women age 20–45 years (N=3006, including 1166 women age 27–45 years)	78 months	Immunogenicity Persistent HPV infection External genital lesions (warts) CIN 1+, CIN 2+ Combined endpoint Harms
Einstein, 2009 [6] Einstein, 2014 [7]	NCT00423046	Obs, USA	Women age 18–45 years in the USA (N=1106)	60 months	Immunogenicity Harms
Huang, 2018 [8]	NCT01427777	Obs, China	Women age 9–45 years (N=468, including <250 age 27–45 years)	42 months	Immunogenicity
Giuliano, 2015 [9]	NCT01432574 (MAM)	Obs, USA and Brazil	Men 27–45 years (N=150)	7 months	Immunogenicity Harms
Money, 2016 [10]	None (CTN 236)	Obs, Canada	HIV+ women age 15–45 years (N=372, including 98 women age 24–45 years)	24 months	Immunogenicity
Wilkin, 2018 [11]	NCT01461096 (ACTG A5298)	RCT, 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

* Age-restricted data obtained from Merck, 2018 [3]
** Per-protocol results for benefits; intention-to-treat results for harms

CHARACTERISTICS OF INCLUDED STUDIES, 2vHPV

Author, year	Clinical trial number	Design	Participants (N=total enrolled)	Follow-up time	Main outcomes related to HPV vaccine types*
Skinner, 2014 [12] Wheeler, 2016 [13]	NCT00294047 (VIVIANE)	RCT, 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 [14] Schwarz, 2011 [15] Schwarz, 2015 [16] Schwarz, 2017 [17]	NCT00196937; NCT00947115	Obs, Germany and Poland	Women age 15–55 years (N=667, including 226 women age 26–45 years)	1 month; 48 months; 72 months; 120 months	Immunogenicity Harms
Einstein, 2009 [6] Einstein, 2014 [7]	NCT00423046	Obs, USA	Women age 18–45 years (N=1106)	24 months; 60 months	Immunogenicity Harms
Zhu, 2014 [18]	NCT01277042	RCT, China	Women age 9–45 years (N=1962, including 1212 women age 26-45 years)	7 months	Immunogenicity Harms

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

CHARACTERISTICS OF INCLUDED STUDIES, SUPPLEMENTAL

Vaccine	Author, year	Clinical trial number	Design	Participants (N=total enrolled)	Follow-up time	Main outcomes related to HPV vaccine types*
4vHPV	Hillman, 2012 [19] Giuliano, 2011 [20] Palefsky, 2011 [21]	NCT00090285	RCT, 18 countries	Males 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 [4]	NCT00092521 (Future I); NCT00092534 (Future II); NCT00090220 (Future III)	Post hoc analysis of data from RCTs	Females age 16–26 years	7 months	Supplemental Immunogenicity (bridging of age groups: 4vHPV immunogenicity in young adult females)
9vHPV	Joura, 2015 [22] Huh, 2017 [23]	NCT00543543	RCT, 18 countries	Females age 16–26 years (N=14215)	7 months; 42 months	Supplemental Immunogenicity (bridging of vaccines: 9vHPV in young adult females)
	Van Damme, 2016 [24]	NCT02114385	RCT, Belgium, Netherlands, and Germany	Males age 16–26 years (N=500)	7 months	Supplemental Immunogenicity (bridging of vaccines: 9vHPV in young adult males)
	Donahue, 2018 [25]	N/A	Obs, Vaccine Safety Datalink (VSD)	U.S. enrollees age 9–26 years	-	Supplemental Harms
	Arana, 2018 [26]	N/A	Obs, Vaccine Adverse Events Reporting System (VAERS)	Reports of potential adverse events following 9vHPV (N=8529 in the USA; n=73 age 27–45)	-	Supplemental Harms

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

BENEFITS: EFFICACY

BENEFITS: PERSISTENT HPV INFECTION

Vaccine	Reference	Outcome (months)	Vaccine group n/N (%)	Placebo group n/N (%)	Observed Efficacy** (95% CI)
Persistent (≥6M) HPV infection					
4vHPV	Castellsagué, 2011 [2]*	6M-persistent cervical HPV 6/11/16/18 (48)	8/1358 (0.6)	71/1372 (5.2)	**88.8% (76.8–95.4)**
	Wei, 2018 [5]*	12M-persistent cervical HPV 6/11/16/18 (78)	3/521 (0.6)	29/515 (5.6)	**90.0% (67.6–98.0)**
2vHPV	Wheeler, 2016 [13]	6M-persistent cervical HPV 6/11 (84)	6/1815 (0.06)	67/1786 (0.7)	**91.4% (79.4–97.1)**

* Age-restricted data obtained from Merck, 2018 [3]
** Per-protocol results

BENEFITS: WARTS

Vaccine	Reference	Outcome (months)	Vaccine group n/N (%)	Placebo group n/N (%)	Observed Efficacy** (95% CI)
Anogenital warts/condyloma/EGL					
4vHPV	Castellsagué, 2011 [2]*	Condyloma (48)	0/1376 (0.0)	5/1384 (0.4)	**100% (-9.8–100)**
	Luxembourg, 2018 [4]	Condyloma (120)	0/527 (0.0)	-	-
	Wei, 2018 [5]*	Condyloma (48)	0/521 (0.0)	0/516 (0.0)	-

* Age-restricted data obtained from Merck, 2018 [3]
** Per-protocol results

BENEFITS: CIN

Vaccine	Reference	Outcome (months)	Vaccine group n/N (%)	Placebo group n/N (%)	Observed Efficacy** (95% CI)
Cervical Intraepithelial Neoplasia (CIN), any grade (1+)					
4vHPV	Castellsagué, 2011 [2]*	HPV 6/11/16/18-related CIN 1+ (48)	1/1358 (0.0)	16/1370 (1.2)	**93.7% (59.5–99.9)**
	Luxembourg, 2018 [4]	CIN 1+ (120)	0/527 (0.0)	-	-
	Wei, 2018 [5]*	HPV 6/11/16/18-related CIN 1+ (78)	0/520 (0.0)	6/515 (1.2)	**100% (15.5–100)**
2vHPV	Wheeler, 2016 [13]	HPV 16/18-related CIN 1+ (84)	2/1852 (0.02)	12/1818 (0.1)	**83.7% (21.9–98.5)**

* Age-restricted data obtained from Merck, 2018 [3]
** Per-protocol results

BENEFITS: CIN 2+

Vaccine	Reference	Outcome (months)	Vaccine group n/N (%)	Placebo group n/N (%)	Observed Efficacy** (95% CI)
Cervical Intraepithelial Neoplasia (CIN) 2+					
4vHPV	Castellsagué, 2011 [2]*	HPV 6/11/16/18-related CIN 2/3 or worse (48)	1/1358 (0.0)	5/1370 (0.4)	**79.8% (-80.1–99.6)**
	Luxembourg, 2018 [4]	HPV 6/11/16/18-related CIN 2 or worse (120)	0/527 (0.0)	-	-
	Wei, 2018 [5]*	HPV 6/11/16/18-related CIN 2+ (78)	0/520 (0.0)	4/515 (0.8)	**100% (-51.0–100)**
2vHPV	Wheeler, 2016 [13]	HPV 16/18-related CIN 2+ (84)	1/1852 (0.01)	6/1818 (0.06)	**83.7% (-46.5–99.7)**

* Age-restricted data obtained from Merck, 2018 [3]
** Per-protocol results

BENEFITS: COMBINED ENDPOINT

Vaccine	Reference	Outcome (months)	Vaccine group n/N (%)	Placebo group n/N (%)	Observed Efficacy** (95% CI)
Combined endpoint: persistent infection, CIN 1+, and/or EGL					
4vHPV	Castellsagué, 2011 [2]*	Combined endpoint: persistent infection, CIN 1+, and/or EGL (48)	9/1376 (0.7)	72/1384 (5.2)	**87.7% (75.4–94.6)**
	Luxembourg, 2018 [4]	Combined endpoint: CIN or condyloma (72–120)	0/527 (0.0)	-	-
	Wei, 2018 [5]*	Combined endpoint: persistent infection, CIN 1+, and/or EGL (78)	3/521 (0.6)	31/516 (6.0)	**90.6% (69.9–98.2)**
2vHPV	Wheeler, 2016 [13]	Combined endpoint: persistent infection, CIN 1+ (84)	7/1852 (0.07)	71/1818 (0.7)	**90.5% (78.6–96.5)**

* Age-restricted data obtained from Merck, 2018 [3]
** Per-protocol results

BENEFITS: IMMUNOGENICITY

BENEFITS: IMMUNOGENICITY, EARLY

Vaccine	Reference	Antibody	Months	Post-vaccination**		
				Seropositive n/N	Seropositive %	GMTs (95% CI)
Immunogenicity, early (7 months post first vaccination dose)						
4vHPV	Muñoz, 2009 [1]*	HPV 6	7	1083/	**98.2**	412 (386–440) mMU/mL
		HPV 11		1083/	**97.9**	538 (506–573) mMU/mL
		HPV 16		1092/	**98.6**	2212 (2076–2357) mMU/mL
		HPV 18		1223/	**97.1**	348 (326–372) mMU/mL
	Einstein, 2009 [6]	HPV 16	7	186/186	**100**	20605 (16259–26112) ED_{50}
		HPV 18		212/212	**100**	9674 (7677–18194) ED_{50}
	Huang, 2018 [8]	HPV 6	7		**98.1**	
		HPV 11			**100**	
		HPV 16			**100**	
		HPV 18			**99.2**	
	Giuliano, 2015 [9]	HPV 6	7	115/115	**100**	365 mMU/mL
		HPV 11		136/136	**100**	490 mMU/mL
		HPV 16		111/111	**100**	2178 mMU/mL
		HPV 18		135/135	**100**	296 mMU/mL
	Money, 2016 [10]	HPV 6	7	61/	**99.0**	426 (324–561) mMU/mL
		HPV 11		98/	**98.7**	540 (436–668) mMU/mL
		HPV 16		66/	**98.1**	1495 (1046–2137) mMU/mL
		HPV 18		94/	**93.6**	295 (223–391) mMU/mL

* Age-restricted data obtained from Merck, 2018 [3]
** Per-protocol results

BENEFITS: IMMUNOGENICITY, EARLY

Vaccine	Reference	Antibody	Months	Post-vaccination*		
				Seropositive n/N	Seropositive %	GMTs (95% CI)
Immunogenicity, early (7 months post first vaccination dose)						
2vHPV	Skinner, 2014 [12]	HPV 16	7	406/406	**100**	5413 (4934–5938) EU/mL
		HPV 18		405/405	**100**	2568 (2340–2818) EU/mL
	Schwarz, 2009 [14]	HPV 16	7	164/164	**100**	4060 (3511–4695) EU/mL
		HPV 18		185185	**100**	1881 (1661–2130) EU/mL
	Einstein, 2009 [6]	HPV 16	7	168/168	**100**	6296 (4906–8082) ED_{50}
		HPV 18		190/192	**99.0**	1241 (947–1626) ED_{50}
	Zhu, 2014 [18]	HPV 16	7	596/596	**100**	6440 (6040–6866) EU/mL
		HPV 18		363/365	**99.5**	3563 (3310–3836) EU/mL

*Per-protocol results

BENEFITS: IMMUNOGENICITY, LATER

Vaccine	Reference	Antibody	Months	Post-vaccination**			
				Seropositive n/N	Seropositive %	GMTs (95% CI)	
Immunogenicity, later (up to 120 months post first vaccination dose)							
4vHPV	Castellsagué, 2011 [2]*	HPV 6	48	1007	**85.3**	61 (57–65)	mMU/mL
		HPV 11		1007	**91.8**	64 (61–69)	mMU/mL
		HPV 16		1022	**97.3**	200 (186–214)	mMU/mL
		HPV 18		1132	**47.5**	23 (21–25)	mMU/mL
	Einstein, 2014 [7]	HPV 16	60	73/76	**96.1**	555 (341–904)	ED_{50}
		HPV 18		60/87	**69.0**	89 (59–136)	ED_{50}
	Huang, 2018 [8]	HPV 6	42		**91.2**		
		HPV 11			**88.3**		
		HPV 16			**96.8**		
		HPV 18			**37.6**		
	Money, 2016 [10]	HPV 6	24	53		129 (93–179)	mMU/mL
		HPV 11		78		125 (125–160)	mMU/mL
		HPV 16		54		459 (341–618)	mMU/mL
		HPV 18		72		54 (39–74)	mMU/mL

* Age-restricted data obtained from Merck, 2018 [3]
** Per-protocol results

BENEFITS: IMMUNOGENICITY, LATER

Vaccine	Reference	Antibody	Months	Post-vaccination*		
				Seropositive n/N	Seropositive %	GMTs (95% CI)
Immunogenicity, later (up to 120 months post first vaccination dose)						
2vHPV	Skinner, 2014 [12]	HPV 16 HPV 18	48	345/345 336/338	**100** **99.4**	546 (490–608) EU/mL 228 (202–259) EU/mL
	Schwarz, 2017 [17]	HPV 16 HPV 18	120	120/121 133/142	**99.2** **93.7**	334 (270-414) EU/mL 115 (94-142) EU/mL
	Einstein, 2014 [7]	HPV 16 HPV 18	60	89/89 109/100	**100** **100**	1855 (1267–2715) ED_{50} 892 (759–1268) ED_{50}

*Per-protocol results

IMMUNOBRIDGING STUDIES

- The minimum threshold level of HPV antibodies required for protection has not been established, and might vary depending on the assay
- Data from clinical trials suggest minimum level of antibody needed for protection is below that detected by current assays
- Immunobridging studies are used to compare immunogenicity in a group of interest (e.g., age 27–45 years) with a comparison group in which efficacy has been demonstrated (e.g., age 16–26 years)
- Non-inferiority criteria met when the lower bound of the 95% CI for the ratio comparing the groups is not less than a preset value (e.g., 0.5)
- Immunobridging data contributed to 9vHPV licensure

SUPPLEMENTAL: IMMUNOBRIDGING, OF AGE GROUPS

Group	Reference; population	Antibody	Mo	Mid-adult vaccination (27–45 years)			Young adult vaccination (16–26 years)			Comparison
				Seropositive n/N	%	GMTs** (95% CI)	Seropositive n/N	%	GMTs** (95% CI)	GMT ratio (95% CI)
4vHPV, Females	Muñoz, 2009 [1], age 27–45 years Luxembourg, 2018 [4], age 16–26 years*	HPV 6 HPV 11 HPV 16 HPV 18	7	1083/ 1083/ 1092/ 1223/	98.2 97.9 98.6 97.1	412 538 2212 348	2800/ 2824/ 2749/ 3006/		536.2 754.3 2297.6 458.1	**0.8 (0.7–0.8)** **0.7 (0.7–0.8)** **1.0 (0.9–1.1)** **0.8 (0.7–0.8)**
4vHPV, Males	Giuliano, 2015 [9], age 27–45 years Hillman, 2012 [19], age 16–26 years*	HPV 6 HPV 11 HPV 16 HPV 18	7	115/115 136/136 111/111 135/135	100 100 100 100	365 490 2178 296	1080/1092 1083/1092 1121/1135 1143/1174	98.9 99.2 98.8 97.4	448 (423–474) 624 (594–655) 2404 (2272–2544) 402 (380–426)	**0.8 (0.6–1.0)** **0.8 (0.7–0.9)** **0.9 (0.7–1.1)** **0.7 (0.6–0.9)**

* Age-restricted data obtained from Merck, 2018 [3]
** Mmu/mL

SUPPLEMENTAL: EFFICACY, YOUNG ADULT MALES

Vaccine	Reference	Outcome (months)	Vaccine group n/N (%)	Placebo group n/N (%)	Observed Efficacy** (95% CI)
4vHPV	**Persistent (≥6M) HPV infection**				
	Giuliano, 2011 [20]	Persistent HPV infection (36)	3/1275 (0.2)	36/1270 (2.8)	**83.8% (61.2–94.4)**
	Anogenital warts/condyloma/EGL				
	Giuliano, 2011 [20]	Condyloma (36)	3/1397 (0.2)	28/ 1408 (2.0)	**89.4% (65.5–97.9)**
	AIN 1+				
	Palefsky, 2011 [21]	AIN grade 1 (36)	4/194 (2.1)	16/208 (7.7)	**73.0% (16.3–93.4)**
	AIN 2+				
	Palefsky, 2011 [21]	AIN grade 2 or 3 (36)	3/194 (1.5)	13/208 (6.2)	**74.9% (8.8–95.4)**

GRADE for use of 9vHPV in females and males: https://www.cdc.gov/vaccines/acip/recs/grade/hpv-9v.pdf

SUPPLEMENTAL: IMMUNOBRIDGING TO 9vHPV

Vaccine	Reference; population	Antibody	Mo	Vaccination with 9vHPV			Vaccination with 4vHPV			Comparison
				Seropositive n/N	Seropositive %	GMTs* (95% CI)	Seropositive n/N	Seropositive %	GMTs* (95% CI)	GMT ratio (95% CI)
9vHPV	Joura [22], females age 16–26 years	HPV 6	7	3985/3993	99.8	893	3969/3975	99.8	875	**1.0 (0.9–1.1)**
		HPV 11		3994/3995	100	666	3980/3982	99.9	830	**0.8 (0.8–0.8)**
		HPV 16		4031/4032	100	3131	4060/4062	100	3157	**1.0 (1.0–1.0)**
		HPV 18		4532/4539	99.8	805	4528/4541	99.7	679	**1.2 (1.1–1.2)**
	Huh [23], females age 16–26 years	HPV 6	42	692	95.5	147 (137-158)	675	94.5	144 (134–155)	**1.0 (0.9–1.1)**
		HPV 11		696	95.4	85 (79-91)	677	96.8	104 (97–112)	**0.8 (0.7–0.9)**
		HPV 16		709	98.4	347 (319-377)	690	98.6	362.9 (334–395)	**1.0 (0.8–1.1)**
		HPV 18		806	81.6	71 (65-77)	770	77.0	60 (55–66)	**1.2 (1.0–1.3)**
		HPV 31		783	93.6	70 (65-76)	730	13.0	<4	-
		HPV 33		835	94.6	44 (42-47)	789	7.6	<4	-
		HPV 45		846	78.8	21 (20-23)	802	1.2	<3	-
		HPV 52		791	95.2	43 (41-46)	735	5.6	<3	-
		HPV 58		784		52 (49-56)	756		<4	-
	Van Damme [24], males age 16–26 years	HPV 6	7	224/228	98.2	758 (666–863)	223/226	98.7	618 (554–690)	**1.2 (1.0–1.5)**
		HPV 11		228/228	100	682 (609–763)	226/226	100	769 (683–865)	**0.9 (0.8–1.0)**
		HPV 16		234/234	100	3924 (3514–4382)	237/237	100	3788 (3378–4247)	**1.0 (0.9–1.2)**
		HPV 18		233/234	99.6	884 (766–1020)	235/236	99.6	791 (683–916)	**1.1 (0.9–1.4)**
		HPV 31		234/234	100	794 (694–909)	146/237	61.6	15 (12–18)	-
		HPV 33		236/236	100	460 (411–516)	40/236	16.9	3 (3–4)	-
		HPV 45		232/232	100	263 (226–306)	22/236	9.3	2 (2–3)	-
		HPV 52		235/235	100	431 (378–491)	6/236	2.5	2 (2–2)	-
		HPV 58		232/232	100	691 (615–777)	84/233	36.1	6 (5–7)	-

* Mmu/mL

HARMS

HARMS: SERIOUS ADVERSE EVENTS, ANY

Vaccine	Reference	Outcome**	Months	Vaccine group n/N (%)	Placebo group n/N (%)
4vHPV	Castellsagué, 2011 [2]*	Serious adverse events	48	14/1908 (0.7)	16/1902 (0.8)
	Wei, 2018 [5]*	Serious adverse events	78	20/580 (3.4)	23/586 (3.9)
	Einstein, 2014 [7]	Serious adverse events	60	44/553 (8.0)	No placebo group
2vHPV	Einstein, 2014 [7]	Serious adverse events	60	37/553 (6.7)	No placebo group
	Wheeler, 2016 [13]	Serious adverse events	48	286/2877 (9.9)	266/2870 (9.3)
	Schwarz, 2017 [17]	Serious adverse events	48	8/226 (3.5)	No placebo group

* Age-restricted data obtained from Merck, 2018 [3]
** Intention-to-treat results

HARMS: SERIOUS ADVERSE EVENTS, VACCINE-RELATED

Vaccine	Reference	Outcome**	Months	Vaccine group n/N (%)	Placebo group n/N (%)
4vHPV	Castellsagué, 2011 [2]* Luxembourg, 2018 [4]*	Vaccine-related serious adverse events	48 120	**0/1908 (0.0)** **0/527 (0.0)**	**0/1902 (0.0)** No placebo group
	Wei, 2018 [5]*	Vaccine-related serious adverse events	78	**0/580 (0.0)**	**1/586 (0.2)**
	Giuliano, 2015 [9]	Vaccine-related serious adverse events (grade 3+)	7	**1/150 (0.7)**	No placebo group
2vHPV	Wheeler, 2016 [13]	Vaccine-related serious adverse events	84	**5/2877 (0.2)**	**8/2870 (0.3)**
	Schwarz, 2017 [17]	Vaccine-related serious adverse events	48	**1/226 (0.4)** - Cervical dysplasia (resolved)	No placebo group
	Zhu, 2014 [18]	Vaccine-related serious adverse events	12	**0/606 (0.0)**	**0/606 (0.0)**

* Age-restricted or updated data obtained from Merck, 2018 [3]
** Intention-to-treat results

HARMS: DEATHS, ANY

Vaccine	Reference	Outcome**	Months	Vaccine group n/N (%)	Placebo group n/N (%)
4vHPV	Castellsagué, 2011 [2]*	Death	48	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
	Luxembourg, 2018 [4]*	Death	120	2/527 (0.4) Leiomyosarcoma; Ventricular tachycardia	No placebo group
	Wei, 2018 [5]*	Death	78	2/580 (0.3) Ovarian cancer; Road traffic crash	0/586 (0.0)
	Einstein, 2014 [7]	Death	60	1/553 (0.2) Metastatic renal cell carcinoma	No placebo group
	Giuliano, 2015 [9]	Death	7	0/150 (0.0)	No placebo group
	Wilkin, 2018 [11]	Death	12	3/276 (1.1)	6/277 (2.2)
2vHPV	Wheeler, 2016 [13]	Death	84	13/2877 (0.5) Acute myocardial infarction; Acute renal failure; Breast cancer; Cervix cancer; Glioblastoma multiforme; Homicide; Interstitial lung disease; Lung cancer; Pneumonia; Pulmonary embolism; Suicide (x3)	5/2870 (0.2) Anaplastic astrocytoma; Cardiac valve disease and liver disorder; Cardiorespiratory arrest; Lower respiratory tract infection and sepsis; Nasopharyngeal cancer
	Schwarz, 2017 [17]	Death	48	2/226 (0.9) Chronic lymphocytic leukemia; Lung cancer	No placebo group

* Age-restricted or updated data obtained from Merck, 2018 [3]
** Intention-to-treat results

HARMS: DEATHS, VACCINE-RELATED

Vaccine	Reference	Outcome**	Months	Vaccine group n/N (%)	Placebo group n/N (%)
4vHPV	Castellsagué, 2011 [2]* Luxembourg, 2018 [4]*	Death, vaccine-related	48	**0/1908 (0.0)** **0/527 (0.0)**	**0/1902 (0.0)** No placebo group
	Wei, 2018 [5]*	Death, vaccine-related	78	**0/580 (0.0)**	**0/586 (0.0)**
	Einstein, 2014 [7]	Death, vaccine-related	60	**0/553 (0.0)**	No placebo group
	Giuliano, 2015 [9]	Death, vaccine-related	7	**0/150 (0.0)**	No placebo group
	Wilkin, 2018 [11]	Death, vaccine-related	12	**0/276 (0.0)**	**0/277 (0.0)**
2vHPV	Wheeler, 2016 [13]	Death, vaccine-related	84	**0/2877 (0.0)**	**0/2870 (0.0)**
	Schwarz, 2017 [17]	Death, vaccine-related	48	**0/226 (0.0)**	No placebo group
	Zhu, 2014 [18]	Death, vaccine-related	12	**0/606 (0.0)**	**0/606 (0.0)**

* Age-restricted data or updated obtained from Merck, 2018 [3]
** Intention-to-treat results

SUPPLEMENTAL: HARMS

Vaccine	Reference	Outcome	Months	Vaccine group n/N (%)	Placebo group n/N (%)
9vHPV*	Donahue, 2018 [23], age 9–26 years in VSD	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],*** age 27–45 years in VAERS	Serious adverse events**	Any	**3/73 (4.1)**	-
		Deaths**	Any	**0/73 (0.0)**	-

* >29 million doses of 9vHPV have been distributed in the U.S. since 2014
** 8,529 U.S. reports of potential adverse events following 9vHPV at any age, in the United States since licensure
*** Updated August 21, 2018, CDC unpublished data

EVIDENCE TYPE

EVIDENCE TYPE, 9vHPV BENEFITS, MID-ADULTS

Finding	Design (number of studies)	Initial evidence level*	Risk of bias	Inconsis-tency	Indirect-ness	Imprecision	Other consider-ations**	Evidence type*
Prevents ≥6M-persistent HPV infection	RCTS (3) + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**2**
Prevents anogenital warts	RCTs (2) + supplemental	1	Not serious	Not serious	Serious[1]	Serious[2]	None	**3**
Prevents CIN 1+	RCTs (3) + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**2**
Prevents CIN 2+	RCTs (3) + supplemental	1	Not serious	Not serious	Serious[1]	Serious[2]	None	**3**
Prevents the above HPV-related outcomes	RCTs (3) + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**2**
Immunogenic	RCTs (3), Obs (6) + 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 studies report data on use of 9vHPV in the mid-adult age range; extrapolation to 9vHPV from 4vHPV based on immunobridging data
2. Downgraded for imprecision since 95% confidence interval for efficacy includes 1

EVIDENCE TYPE, 9vHPV BENEFITS, MID-ADULT WOMEN

Finding	Design (number of studies)	Initial evidence level*	Risk of bias	Inconsis-tency	Indirect-ness	Imprecision	Other consider-ations**	Evidence type*
Prevents ≥6M-persistent HPV infection	RCTS (3) in women + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**2**
Prevents anogenital warts	RCTs (2) in women + supplemental	1	Not serious	Not serious	Serious[1]	Serious[2]	None	**3**
Prevents CIN 1+	RCTs (3) in women + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**2**
Prevents CIN 2+	RCTs (3) in women + supplemental	1	Not serious	Not serious	Serious[1]	Serious[2]	None	**3**
Prevents the above HPV-related outcomes	RCTs (3) in women + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**2**
Immunogenic	RCTs (3) in women Obs (5) in women + 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 studies report data on use of 9vHPV in the mid-adult age range; extrapolation to 9vHPV from 4vHPV based on immunobridging data
2. Downgraded for imprecision since 95% confidence interval for efficacy includes 1

EVIDENCE TYPE, 9vHPV BENEFITS, MID-ADULT MEN

Finding	Design (number of studies)	Initial evidence level*	Risk of bias	Inconsis-tency	Indirect-ness	Imprecision	Other consider-ations**	Evidence type*
Prevents ≥6M-persistent HPV infection	RCTS (3) in women + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**3**
Prevents anogenital warts	RCTs (2) in women + supplemental	1	Not serious	Not serious	Serious[1]	Serious[2]	None	**4**
Prevents CIN 1+	RCTs (3) in women + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**3**
Prevents CIN 2+	RCTs (3) in women + supplemental	1	Not serious	Not serious	Serious[1]	Serious[2]	None	**4**
Prevents the above HPV-related outcomes	RCTs (3) in women + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**3**
Immunogenic	RCTs (3) in women Obs (1) in men + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**3**

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 studies report data on use of 9vHPV in the mid-adult age range; extrapolation to 9vHPV from 4vHPV based on immunobridging data
2. Downgraded for imprecision since 95% confidence interval for efficacy includes 1

EVIDENCE TYPE, 9vHPV HARMS, MID-ADULTS

Finding	Design (number of studies)	Initial evidence level*	Risk of bias	Inconsis-tency	Indirect-ness	Imprecision	Other consider-ations**	Evidence type*
Similar numbers of severe adverse events with 9vHPV vs placebo	RCTs (3), Obs (2) + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**2**
Few vaccine-related severe adverse events	RCTs (4), Obs (2) + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**2**
Similar numbers of deaths with 9vHPV vs placebo	RCTs (4), Obs (3) + supplemental	1	Not serious	Not serious	Serious[1]	Not serious	None	**2**
No vaccine-related deaths	RCTs (5), Obs (3) + 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 studies directly report data on use of 9vHPV use in the mid-adult age range, and there are no 4vHPV efficacy trials in mid-adult males; extrapolation to 9vHPV from 4vHPV across age and genders is based on supplemental bridging immunogenicity data

SUMMARY

GRADE SUMMARY, BENEFITS

Comparison	Outcome	Design (number of studies)	Findings	Evidence type	Overall evidence type
HPV vaccination (mid-adults age 27–45 years) versus no HPV vaccination	Efficacy in women	RCTs (3) + supplemental	**9vHPV is more efficacious against HPV-related outcomes than no vaccination**	**2**	**2**
	Efficacy in men	Obs (1) + supplemental	**9vHPV is more efficacious against HPV-related outcomes than no vaccination**	**3**	
	Immunogenicity	RCTs (3), Obs (6) + supplemental	**9vHPV is immunogenic**	**2**	

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

GRADE SUMMARY, HARMS

Comparison	Outcome	Design (number of studies)	Findings	Evidence type	Overall evidence type
HPV vaccination (mid-adults age 27–45 years) versus no HPV vaccination	Harms, any	RCTs (4), Obs (3)	**Similar harms among people receiving placebo versus 9vHPV**	2	**2**
	Vaccine-related harms	RCTs (5), Obs (3)	**Few vaccine-related serious adverse events, and no vaccine-related deaths**	2	

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

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