Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) for Use of 9-Valent Human Papillomavirus Vaccine (9vHPV) in Females and Males

Methods: GRADE was used to evaluate 9vHPV for routine vaccination of females and males aged 11 or 12 years as well as catch-up vaccination of females aged 13 through 26 years and males aged 13 through 21 years who were not vaccinated previously. Evidence of benefits, harms, values and preferences, and cost-effectiveness were reviewed in accordance with GRADE methods.[1] The policy questions were: "Should 9vHPV be recommended for routine vaccination of 11 or 12 year olds?" and "Should 9vHPV be recommended for females aged 13 through 26 years and males aged 13 through 21 years who have not been vaccinated previously?"

The benefits considered critical outcomes in GRADE were the prevention of cervical intraepithelial neoplasia grade 2 or 3, or adenocarcinoma in situ (≥CIN2), cervical cancer, definitive therapies, oropharyngeal cancer, vaginal/vulvar cancer, and anal cancer in females and anal cancer and oropharyngeal cancer in males (Table 1). Anogenital warts were considered an important outcome for both females and males. The evidence profile included the most prevalent HPV-attributable outcomes for females, ≥CIN2, cervical cancer and anogenital warts, and for males, anal cancer and anogenital warts. Evidence was not available for the critical outcome, oropharyngeal cancer, in females or males; definitive therapies, vaginal/vulvar cancer, and anal cancer in females were not included in the evidence profile for GRADE.

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Data used for the evidence review were from 9vHPV pre-licensure clinical trials as well as the efficacy trials from the quadrivalent HPV vaccine (4vHPV) program (Table 2). The pivotal efficacy trial for 9vHPV was conducted in females aged 16 through 26 years.[2] This was a randomized trial comparing 9vHPV with 4vHPV conducted among approximately 14,000 females aged 16 through 26 years. This trial provided evidence for all policy questions including vaccination of females in the catch-up age group. Evidence used to evaluate efficacy of 9vHPV for prevention of HPV 31, 33, 45, 52, 58-related outcomes was directly from this trial. Evidence used to evaluate efficacy of 9vHPV for prevention of HPV 6, 11, 16, 18-related outcomes was from randomized controlled trials (RCT) of 4vHPV[3] and from immunogenicity studies comparing 9vHPV with 4vHPV;[4] these data were used to infer 9vHPV efficacy for HPV 6, 11, 16, 18-related outcomes.

For HPV vaccination of females in the routine age group, evidence from two immunobridging trials was also used. One trial compared 9vHPV in females aged 9 through 15 years with females aged 16 through 26 years, and another trial compared 9vHPV with 4vHPV in females aged 9 through 15 years.[4] Noninferior immunogenicity of 9vHPV compared with 4vHPV in females aged 9 through 15 years and 9vHPV in females aged 9 through 15 years compared with females aged 16 through 26 years was used to infer efficacy for prevention of HPV 6, 11, 16, 18, 31, 33, 45, 52, 58-related outcomes.

For HPV vaccination of males, evidence used to evaluate efficacy of 9vHPV for prevention of HPV 6, 11, 16, 18-related outcomes was from one RCT of 4vHPV among approximately 4,000 males aged 16 through 26 years, which evaluated anogenital warts; anal precancer outcomes

were evaluated in a subset of approximately 600;[5,6] and an immunogenicity study comparing 9vHPV in males with females aged 16 through 26 years.[4] Noninferior immunogenicity of 9vHPV in males compared with females was used to infer efficacy for prevention of HPV 6, 11, 16, 18-related outcomes.

For HPV vaccination of males in the routine age group, evidence was also from an immunobridging trial, which showed noninferior immunogenicity of 9vHPV in males aged 9 through 15 years compared to females aged 16 through 26 years.[4] These data were used to infer efficacy for prevention of HPV 6, 11, 16, 18-related outcomes. We also compared immunogenicity of 9vHPV in males aged 9 through 15 years with males aged 16 through 26 years.

The critical harms considered were serious adverse events (SAE) and anaphylaxis. Safety of 9vHPV was evaluated based on 6 Phase III studies[*] in the clinical development program.

Immunogenicity and efficacy evidence used was from analyses of the per protocol populations. For the efficacy trials, this included individuals who received all 3 vaccinations within one year of enrollment, did not have major deviations from the study protocol, were naïve (PCR negative and seronegative) to the relevant HPV type(s) prior to dose 1, and who remained PCR negative to the relevant HPV type(s) through one month post-dose 3 (Month 7).[7]

[*] Protocols 001, 002, 003, 005, 007, 009

Evidence type for each considered outcome was derived through a review of study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations.

Table 1. 9vHPV outcome measure ranking and inclusion			
Sex	**Outcome**	**Importance**	**Included in evidence profile**
	Benefits		
Females	≥CIN2	Critical	Yes
	Cervical cancer	Critical	Yes
	Definitive therapies (cervical)[a,b]	Critical	No
	Oropharyngeal cancer[c]	Critical	No
	Vaginal/vulvar cancer[d]	Critical	No
	Anal cancer[d]	Critical	No
	Anogenital warts	Important	Yes
Males	Anal cancer	Critical	Yes
	Oropharyngeal cancer[c]	Critical	No
	Anogenital warts	Important	Yes
	Harms		
Females and males	Serious adverse events	Critical	Yes
	Anaphylaxis	Critical	Yes

[a]Include non-ablative procedures, loop electrosurgical excision procedure, conization
[b]Not considered separately because ≥CIN2 and cervical cancer were included in evidence profile
[c]No data available on outcomes
[d]Not included in evidence profile because of small numbers in trials

Table 2. Characteristics of included studies

Vaccine	Protocol	Design	No. of subjects	Per protocol population	Objectives
4vHPV	007[8]	Randomized, placebo controlled	1106	Females aged 16–26 years	Efficacy, immunogenicity,[f] safety
	013[8]	Randomized, placebo controlled	5759	Females aged 16–26 years	Efficacy, immunogenicity,[f] safety
	015[8]	Randomized, placebo controlled	12167	Females aged 16–26 years	Efficacy, immunogenicity,[f] safety
	020[5]	Randomized, placebo controlled	4065[a]	Males aged 16–26 years	Efficacy, immunogenicity,[f] safety
9vHPV	001[2]	Randomized, 4vHPV comparator	14215	Females aged 16–26 years	Efficacy, immunogenicity,[f] safety
	002[9]	Observational	2999	Females aged 16–26 years, females and males aged 9–15 years	Adult-to-adolescent immunobridging, safety
	003[4]	Observational	2520[b]	Females and males aged 16–26 years	Female-to-male immunobridging, safety
	005[9]	Observational	1241	Females and males aged 11–15 years	Concomitant use: Menactra,[c] Adacel,[d] safety
	007[9]	Observational	1054	Females and males aged 11–15 years	Concomitant use: Repevax,[e] safety
	009[9]	Randomized, 4vHPV comparator	600	Females aged 9–15 years	4vHPV-to-9vHPV immunobridging, safety

[a]Included 3463 heterosexual males (HM) and 602 men who have sex with men (MSM)
[b]Included 1106 HM and 313 MSM
[c]Quadrivalent meningococcal conjugate vaccine (MenACWY-D)
[d]Tetanus, diphtheria, acellular pertussis vaccine (Tdap)
[e]Tdap/polio vaccine
[f]Seroconversion and geometric mean titers; antibody measured by competitive Luminex immunoassay (cLIA) at month 7

Table 3. Available data for females aged 16–26 years from the 9vHPV trials				
	HPV 6, 11, 16, 18-related		**HPV 31, 33, 45, 52, 58-related**	
Outcomes	**Direct**	**Indirect**	**Direct**	**Indirect**
≥CIN2	No[a]	Immunogenicity[b]	Yes	Immunogenicity
Cervical cancer	No	Immunogenicity[b]	No	≥CIN2, immunogenicity
Anogenital warts	No	Immunogenicity[b]	--	--

[a]Active comparator, 4vHPV, used rather than placebo; too few events for efficacy data
[b]Immunogenicity of 9vHPV compared with 4vHPV was used to infer efficacy

Table 4. 4vHPV trials considered for 9vHPV GRADE for HPV 6, 11, 16, 18-related outcomes, per protocol population, females aged 16–26 years				
Protocol	**Population**	**No.**	**Outcome**	**Efficacy**
007, 013, 015	Females aged 16–26 years	15729	≥CIN2[8]	98.2%
		13365	Anogenital warts[3]	99.0%

Table 5. Efficacy of 9vHPV for prevention of HPV 6, 11, 16, 18-related ≥CIN2 and anogenital warts and HPV 31, 33, 45, 52, 58-related ≥CIN2, per protocol population, females aged 16–26 years[a]

Outcome-related HPV type	Outcome	9vHPV		4vHPV		Vaccine efficacy		Absolute risk difference per 1000 (95% CI)	Number needed to vaccinate (95% CI)
		No.	Cases	No.	Cases	%	(95% CI)		
HPV 6, 11, 16, 18	≥CIN2[2]	5823	1	5832	1	--	--	--	--
	Anogenital warts[2]	5876	5	5893	1	--	--	--	--
HPV 31, 33, 45, 52, 58	≥CIN2[7]	5948	1	5943	27	96.3	(79.5, 99.8)	4 fewer per 1000 (3, 5)	250 (200, 333)

[a]Data from Protocol 001

Table 6. Seroconversion and geometric mean titers: 9vHPV compared with 4vHPV, per protocol population, females aged 16–26 years[2a,c]

	9vHPV			4vHPV			
Antibody	n	%	GMT (mMU/mL)	n	%	GMT (mMU/mL)	GMT noninferiority or superiority
Anti-HPV 6	3993	99.8	893	3975	99.8	875	9vHPV noninferior to 4vHPV[b]
Anti-HPV 11	3995	100	666	3982	99.9	830	
Anti-HPV 16	4032	100	3131	4062	100	3157	
Anti-HPV 18	4539	99.8	805	4541	99.7	679	
Anti-HPV 31	4466	99.8	658	4377	50.1	10	9vHPV superior to 4vHPV[b]
Anti-HPV 33	4702	99.7	416	4691	12.7	<4	
Anti-HPV 45	4792	99.6	253	4750	9.2	<3	
Anti-HPV 52	4455	99.8	380	4335	2.6	<3	
Anti-HPV 58	4486	99.8	483	4446	20.4	<4	

GMT = Geometric mean titer; mMU, milli-Merck units

[a]Data from Protocol 001, antibody measured by cLIA at month 7
[b]*P* <0.001
[c]Personal communication, Alain Luxembourg, MD, PhD, September 2014, for anti-HPV 31, 33, 45, 52, 58

Table 7. Evidence type for benefits: 9vHPV vaccination of females in the catch-up age group

Outcome-related HPV type	Benefits	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type
HPV 6, 11, 16, 18	≥CIN2	4vHPV RCT (3)[a] Supportive: 9vHPV Randomized (1), Obs (2)[b]	No serious	No serious	Serious[c]	No serious	2
	Cervical cancer		No serious	No serious	Serious[c,d]	No serious	3
	Anogenital warts		No serious	No serious	Serious[c]	No serious	2
HPV 31, 33, 45, 52, 58	≥CIN2	9vHPV Randomized (1)[e]	No serious	No serious	No serious	No serious	1
	Cervical cancer	Supportive: 9vHPV Obs (2)[f]	No serious	No serious	Serious[d]	No serious	2

[a]Data from Protocols 007, 013, 015
[b]Supportive data from Protocols 001, 002, 003
[c]Downgraded by 1 for indirectness due to use of immunobridging to 4vHPV
[d]Downgraded by 1 for indirectness due to use of ≥CIN2 as surrogate marker for cervical cancer
[e]Data from Protocol 001
[f]Supportive data from Protocols 002, 003

Table 8. Seroconversion and geometric mean titers:9vHPV in females aged 9–15 years compared with females aged 16–26 years, per protocol population[7a]

	9vHPV in females aged 9–15 years			9vHPV in females aged 16–26 years			
Antibody	**n**	**%[c]**	**GMT (mMU/mL)**	**n**	**%**	**GMT (mMU/mL)**	**GMT noninferiority or superiority**
Anti-HPV 6	503	99.8	1703	328	99.7	901	Females aged 9–15 years noninferior to females aged 16–26 years[b]
Anti-HPV 11	503	100	1292	332	100	707	
Anti-HPV 16	513	100	6934	329	100	3523	
Anti-HPV 18	516	99.8	2148	345	99.7	883	
Anti-HPV 31	506	100	1895	340	99.7	754	
Anti-HPV 33	518	100	986	354	99.7	467	
Anti-HPV 45	518	99.8	708	368	99.5	272	
Anti-HPV 52	517	100	962	337	99.7	420	
Anti-HPV 58	516	100	1288	332	100	591	

GMT = Geometric mean titer; mMU, milli-Merck units

[a]Data from Protocol 002, antibody measured by cLIA at month 7
[b]*P* <0.001
[c]Personal communication, Alain Luxembourg, MD, PhD, September 2014

Table 9. Seroconversion and geometric mean titers: 9vHPV compared with 4vHPV, per protocol population, females aged 9–15 years[9a,c]

	9vHPV			4vHPV			
Antibody	**n**	**%**	**GMT (mMU/mL)**	**n**	**%**	**GMT (mMU/mL)**	**GMT noninferiority or superiority**
Anti-HPV 6	273	100	1679	261	100	1566	9vHPV noninferior to 4vHPV[b]
Anti-HPV 11	273	100	1316	261	100	1417	
Anti-HPV 16	276	100	6740	270	100	6887	
Anti-HPV18	276	100	1957	269	100	1796	
Anti-HPV 31	276	100	1770	268	73.5	22	9vHPV superior to 4vHPV[b]
Anti-HPV 33	275	100	937	269	20.4	4	
Anti-HPV 45	275	99.6	622	271	21.0	3	
Anti-HPV 52	276	100	927	269	3.3	2	
Anti-HPV 58	267	100	1349	261	54.8	9	

GMT = Geometric mean titer; mMU, milli-Merck units

[a]Data from Protocol 009, antibody measured by cLIA at month 7
[b]*P* <0.001
[c]Personal communication, Alain Luxembourg, MD, PhD, September 2014, for anti-HPV 31, 33, 45, 52, 58

Table 10. Evidence type for benefits: 9vHPV vaccination of females in the routine age group

Outcome-related HPV type	Benefits	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type
HPV 6, 11, 16, 18	≥CIN2	4vHPV RCT (3)[a]	No serious	No serious	Serious[e]	No serious	2
	Cervical cancer	Supportive: 9vHPV Randomized (2), Obs (4)[b]	No serious	No serious	Serious[e]	No serious	3
	Anogenital warts		No serious	No serious	Serious[e]	No serious	2
HPV 31, 33, 45, 52, 58	≥CIN2	9vHPV Randomized (1)[c]	No serious	No serious	No serious[e]	No serious	1
	Cervical cancer	Supportive: 9vHPV Obs (4)[d]	No serious	No serious	Serious[e]	No serious	2

[a]Data from Protocols 007, 013, 015
[b]Supportive data from Protocols 001, 002, 003, 005, 007, 009
[c]Data from Protocol 001
[d]Supportive data from Protocols 002, 003, 005, 007, 009
[e]Started with evidence type for females in the catch-up age group; not downgraded due to noninferior immunogenicity among females aged 9–15 years compared with females aged 16–26 years, and because efficacy data were from per protocol population

Table 11. 4vHPV RCT considered for 9vHPV GRADE for HPV 6, 11, 16, 18-related outcomes, per protocol population, males aged 16–26 years

Protocol	Population	No.	Outcome	Efficacy
020	Males aged 16–26 years	402	AIN2/3[5]	74.9%
		2798	Anogenital warts[10]	89.3%

AIN2/3 = Anal intraepithelial neoplasia grade 2 or 3

Table 12. Seroconversion and geometric mean titers: 9vHPV in males[a] aged 16–26 years compared with females aged 16–26 years, per protocol population[4b,d]

	9vHPV in males aged 16–26 years			9vHPV in females aged 16–26 years			
Antibody	n	%	GMT (mMU/mL)	n	%	GMT (mMU/mL)	GMT noninferiority or superiority
Anti-HPV 6	847	99.6	782	708	99.6	704	Males noninferior to females[c]
Anti-HPV 11	851	100	617	712	99.9	565	
Anti-HPV 16	899	100	3346	781	99.9	2788	
Anti-HPV 18	906	99.9	808	831	99.8	680	

GMT = Geometric mean titer; mMU, milli-Merck units

[a]Heterosexual males
[b]Data from Protocol 003, antibody measured by cLIA at month 7
[c]*P* <0.001
[d]Personal communication, Alain Luxembourg, MD, PhD, September 2014

Table 13. Evidence type for benefits: 9vHPV vaccination of males in the catch-up age group

Benefits	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type
Anal cancer	4vHPV RCT (1)[a] Supportive: 9vHPV	No serious	No serious	Serious[c,d]	No serious	3
Anogenital warts	Randomized (1), Obs (1)[b]	No serious	No serious	Serious[c]	No serious	2

[a]Data from Protocol 020
[b]Supportive data from Protocols 001, 003
[c]Downgraded by 1 for indirectness due to use of immunobridging to females aged 16–26 years
[d]Downgraded by 1 for indirectness due to use of anal intraepithelial neoplasia grade 2 or 3 as surrogate marker for anal cancer

Table 14. Seroconversion and geometric mean titers: 9vHPV in males aged 9–15 years compared with females aged 16–26 years, per protocol population[7a]

	9vHPV in males aged 9–15 years			9vHPV in females aged 16–26 years			
Antibody	**n**	**%[c]**	**GMT (mMU/mL)**	**n**	**%**	**GMT (mMU/mL)**	**GMT noninferiority or superiority**
Anti-HPV 6	537	99.8	2083	328	99.7	901	Males aged 9–15 years noninferior to females aged 16–26 years[b]
Anti-HPV 11	537	100	1486	332	100	707	
Anti-HPV 16	546	100	8683	329	100	3523	
Anti-HPV 18	544	100	2855	345	99.7	883	

GMT = Geometric mean titer; mMU, milli-Merck units

[a]Data from Protocol 002, antibody measured by cLIA at month 7
[b]*P* <0.001
[c]Personal communication, Alain Luxembourg, MD, PhD, September 2014

Table 15. Seroconversion and geometric mean titers: 9vHPV in males aged 9–15 years[a] compared with males aged 16–26 years,[b] per protocol population[4,7]

	9vHPV in males aged 9–15 years[a]			9vHPV in males aged 16–26 years[b]		
Antibody	**n**	**%[c]**	**GMT (mMU/mL)**	**n**	**%**	**GMT (mMU/mL)**
Anti-HPV 6	537	99.8	2083	847	99.6	782
Anti-HPV 11	537	100	1486	851	100	617
Anti-HPV 16	546	100	8683	899	100	3346
Anti-HPV 18	544	100	2855	906	99.9	808

GMT = Geometric mean titer; mMU, milli-Merck units

[a]Data from Protocol 002, antibody measured by cLIA at month 7
[b]Data from Protocol 003, antibody measured by cLIA at month 7
[c]Personal communication, Alain Luxembourg, MD, PhD, September 2014

Table 16. Evidence type for benefits: 9vHPV vaccination of males in the routine age group

Benefits	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type
Anal cancer	4vHPV RCT (1)[a] Supportive: 9vHPV Randomized (1), Obs (2)[b]	No serious	No serious	Serious[c]	No serious	3
Anogenital warts		No serious	No serious	Serious[c]	No serious	2

[a]Data from Protocol 020
[b]Supportive data from Protocols 001, 002, 003
[c]Started with evidence type for males in the catch-up age group; not downgraded because of noninferior immunogenicity, and because efficacy data were from per protocol population

Table 17. Harms data in females and males[9c]

Harms	Females and males aged 16–26 years			Females and males aged 9–15 years		
	Protocol (Design)	**Incidence in 9vHPV % (n/N)**	**Incidence in 4vHPV % (n/N)**	**Protocol (Design)**	**Incidence in 9vHPV % (n/N)**	**Incidence in 4vHPV % (n/N)**
Serious adverse event day 1–15	001 (Randomized)	0.03 (2/7071)[a]	0.01 (1/7078)	009 (Randomized)	0 (0/299)	0 (0/300)
Serious adverse event any time		0.03 (2/7071)	0.03 (2/7078)		0 (0/299)	0 (0/300)
Anaphylaxis day 1–15		0.01 (1/7071)[b]	0 (0/7078)		0 (0/299)	0 (0/300)
Serious adverse event day 1–15	002, 003 (Obs)	0.03 (1/2930)	--	002, 005, 007 (Obs)	0.02 (1/4793)	--
Serious adverse event any time		0.03 (1/2930)	--		0.02 (1/4793)	--
Anaphylaxis day 1–15		0 (0/2930)	--		0 (0/4793)	--

[a]Determined to be vaccine-related; study medication withdrawn for one case
[b]Determined to be due to non-study medication
[c]Personal communication, Alain Luxembourg, MD, PhD, March 2015

Table 18. Evidence type for harms: 9vHPV in males and females

Harms	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type
Serious adverse event	Randomized (2), Obs (4)[a]	No serious	No serious	No serious	Serious[b]	2
Anaphylaxis		No serious	No serious	No serious	Serious[b]	2

[a]Data from Protocols 001, 002, 003, 005, 007, 009
[b]Downgraded by 1 for imprecision due to small sample size

Table 19. Summary of evidence for 9vHPV vaccination of females in the catch-up age group					
Comparison	**Outcome**	**Design (# studies)**	**Findings**	**Evidence type**	**Overall**
9vHPV vs. 4vHPV	**HPV 6, 11, 16, 18-related: ≥CIN2 Cervical cancer Anogenital warts**	4vHPV RCT (3)[a], 9vHPV Randomized (1), Obs (2)[b]	4vHPV has high efficacy; 9vHPV has noninferior immunogenicity for HPV 6, 11, 16, 18 and comparable risk for outcomes	2–3	2 (Moderate)
	HPV 31, 33, 45, 52, 58-related: ≥CIN2 Cervical cancer	9vHPV Randomized (1)[c], 9vHPV Obs (2)[d]	9vHPV has high efficacy for HPV 31, 33, 45, 52, 58-related outcomes	1–2	
	Serious adverse event	9vHPV Randomized (1), Obs (2)[e]	Few cases	2	
	Anaphylaxis		No vaccine-related cases		

[a]Data from Protocols 007, 013, 015
[b]Supportive data from Protocols 001, 002, 003
[c]Data from Protocol 001
[d]Supportive data from Protocols 002, 003
[e]Data from Protocols 001, 002, 003

Table 20. Summary of evidence for 9vHPV vaccination of females in the routine age group

Comparison	Outcome	Design (# studies)	Findings	Evidence type	Overall
9vHPV vs. 4vHPV	**HPV 6, 11, 16, 18-related:** **Cervical cancer ≥CIN2** **Anogenital warts**	4vHPV RCT (3)[a] 9vHPV Randomized (2), Obs (4)[b]	(See findings in Table 19) Noninferior immunogenicity compared with females in age group in efficacy trials	2–3	2 (Moderate)
	HPV 31, 33, 45, 52, 58-related: **Cervical cancer ≥CIN2**	9vHPV Randomized (1)[c] 9vHPV Randomized (1), Obs (4)[d]	(See findings in Table 19) Noninferior immunogenicity compared with females in age group in efficacy trials	1–2	
	Serious adverse event	9vHPV Randomized (1), Obs (3)[e]	No cases	2	
	Anaphylaxis		No cases		

[a]Data from Protocols 007, 013, 015
[b]Supportive data from Protocols 001, 002, 003, 005, 007, 009
[c]Data from Protocol 001
[d]Supportive data from Protocols 002, 003, 005, 007, 009
[e]Data from Protocols 002, 005, 007, 009

Table 21. Summary of evidence for 9vHPV vaccination of males in the catch-up age group

Comparison	Outcome	Design (# studies)	Findings	Evidence type	Overall
9vHPV vs. 4vHPV	**HPV 6, 11, 16, 18-related:** **Anal cancer** **Anogenital warts**	4vHPV RCT (1)[a] 9vHPV Randomized (1), Obs (1)[b]	4vHPV has high efficacy; 9vHPV has noninferior immunogenicity for HPV 6, 11, 16, 18 and comparable risk for outcomes	2–3	3 (Low)
	Serious adverse event	9vHPV Randomized (1), Obs (2)[c]	Few cases	2	
	Anaphylaxis		No vaccine-related cases		

[a]Data from Protocol 020
[b]Supportive data from Protocols 001, 003
[c]Data from Protocols 001, 002, 003

Table 22. Summary of evidence for 9vHPV vaccination of males in the routine age group

Comparison	Outcome	Design (# studies)	Findings	Evidence type	Overall
9vHPV vs. 4vHPV	**HPV 6, 11, 16, 18-related:** **Anal cancer** **Anogenital warts**	4vHPV RCT (1)[a] 9vHPV Randomized (1), Obs (1)[b]	(See findings in table 21) Noninferior immunogenicity compared with females and males in age group in efficacy trials	2–3	3 (Low)
	Serious adverse event	Randomized (1), Obs (3)[c]	No cases	2	
	Anaphylaxis		No cases		

[a]Data from Protocol 020
[b]Supportive data from Protocols 001, 002
[c]Data from Protocols 002, 005, 007, 009

Table 23. Considerations for formulating recommendations for 9vHPV	
Key factors	**Comments**
Evidence type for benefits and harms	• 9vHPV evidence from a randomized trial comparing 9vHPV with 4vHPV in approximately 14,000 females aged 16–26 years, immunobridging studies, and randomized trials comparing 4vHPV with placebo • Evidence type 2 (moderate) for females • Evidence type 3 (low) for males
Balance of benefits versus harms	• Benefits outweigh harms
Values	• ACIP HPV Work Group placed high value on prevention of outcomes due to HPV 6, 11, 16, 18, 31, 33, 45, 52, 58
Cost-effectiveness	• 9vHPV is cost saving compared to 4vHPV[11]
Summary	• Category A recommendation

References

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