GRADE for 9-valent HPV vaccine

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ACIP meeting

October 30, 2014

Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process

- **Develop policy questions**
- Consider critical outcomes
- Review and summarize evidence of benefits and harms
- Evaluate quality of evidence
- Assess population benefit
- Evaluate values and preferences
- Review health economic data
- Considerations for formulating recommendations
- ACIP recommendations and GRADE category

HPV9 policy questions for GRADE

- Should HPV9 be recommended routinely for 11–12 year olds?
- Should HPV9 be recommended for females aged 13–26 years and males aged 13–21 years who have not been previously vaccinated?

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HPV9 outcome measure ranking and inclusion

Benefits	Importance	Include in evidence profile
Females		
Cervical precancer[a]	Critical	Yes
Cervical cancer	Critical	Yes
Definitive therapies[b] **(cervical)**	Critical	No[c]
Oropharyngeal cancer	Critical	No[d]
Vaginal/vulvar cancer	Critical	No
Anal cancer	Critical	No
Anogenital warts	Important	Yes
Males		
Anal cancer	Critical	Yes
Oropharyngeal cancer	Critical	No[d]
Anogenital warts	Important	Yes
Harms (both females and males)		
Serious adverse events	Critical	Yes
Anaphylaxis	Critical	Yes

[a]Cervical intraepithelial neoplasia (CIN) 2/3 or adenocarcinoma in situ (AIS) 2/3
[b]Includes non-ablative procedures, loop electrosurgical excision procedure, conization
[c]Represented by cervical precancer and cervical cancer
[d]No data available on outcomes

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HPV9 clinical development program

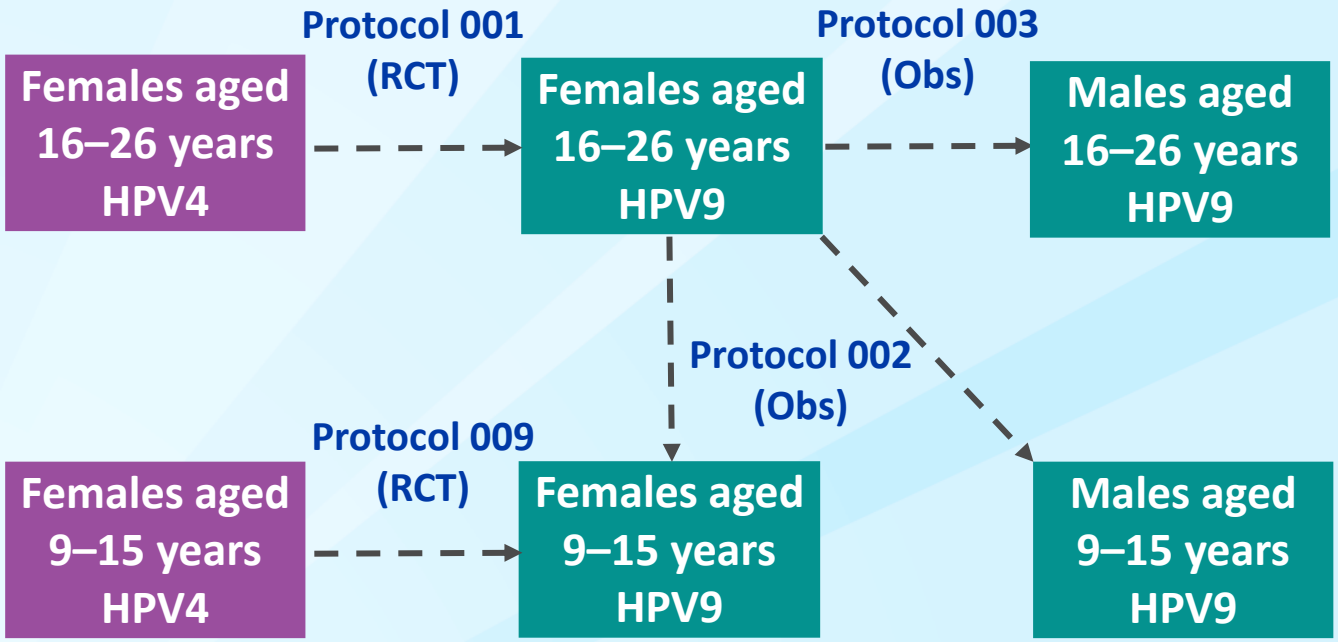
- **HPV9 and HPV4**
  - Recombinant HPV virus-like particle (VLP) vaccines
  - Same HPV 6/11/16/18 VLPs
  - HPV9 contains 5 additional HPV 31/33/45/52/58 VLPs
- **Active comparator (HPV4)**
  - Highly efficacious
  - Few disease endpoints (cannot assess efficacy against HPV 6/11/16/18)
- **HPV9 immunobridged to HPV4**
  - To demonstrate non-inferior immunogenicity and comparable efficacy
  - HPV4 data considered for HPV 6/11/16/18 for HPV9 GRADE
- **Neutralizing antibody is considered mechanism of protection**
  - HPV vaccines induce high antibody titers
  - No minimum level of protective antibody has been identified

HPV4 phase II and III efficacy RCTs considered for HPV9 GRADE for HPV 6/11/16/18-related outcomes

Per protocol population	Protocol	Outcomes
Females aged 16–26 years	007, 013, 015	CIN 2/3 or AIS Anogenital warts
Males aged 16–26 years	020	AIN 2/3 Anogenital warts

CIN = Cervical intraepithelial neoplasia
AIS = Adenocarcinoma in situ
AIN = Anal intraepithelial neoplasia

HPV9 studies* considered for HPV9 GRADE



Per protocol population

*Includes concomitant use observational Protocols 005 and 007 (not shown)

Population, Intervention, Comparison, Outcome (PICO)

- Population: Females aged 13–26 years
- Intervention: HPV9
- Comparison: HPV4
- Outcome:
  - HPV 6/11/16/18
  - HPV 31/33/45/52/58

HPV4 phase II and III efficacy RCTs considered for HPV9 GRADE for HPV 6/11/16/18-related outcomes

Per protocol population	Protocol	n	Outcome	Efficacy
Females aged 16–26 years	007	15729	CIN 2/3 or AIS[a]	98.2%
	013	13365	Anogenital warts[b,c]	98.9%
	015			

CIN = Cervical intraepithelial neoplasia
AIS = Adenocarcinoma in situ

[a]Kjær SK, Sigurdsson K, Iversen OE, et al. Cancer Prev Res 2009;2:868–78.
[b]Dillner J, Kjær SK, Wheeler CM, et al. BMJ 2010;341:c3493.
[c]Data from protocols 013 and 015

GRADE for HPV9 in females

HPV9 outcome data in females aged 16–26 years[a]

HPV vaccine type	Outcome	No. of subjects (# studies)	Incidence[d] in HPV9 (n/N)	Incidence[d] in HPV4 (n/N)	Vaccine efficacy % (95% CI)	Absolute risk difference per 1000 (95% CI)	Number needed to vaccinate (95% CI)
6/11/16/18	Cervical precancer[b]	11447 (1)	1 / 5715	0 / 5732	--	--	--
	Anogenital warts[c]	9549 (1)	4 / 4744	0 / 4805	--	--	--
31/33/45/52/58	Cervical precancer	11891 (1)	1 / 5948	27 / 5943	96.3% (79.5, 99.8)	4 fewer per 1000 (3, 5)	250 (200, 333)

[a]Data from Protocol 001 (RCT)
[b]HPV 16/18-related
[c]HPV 6/11-related
[d]Incidence over up to 54 months of follow-up

Based on a dynamic model of HPV vaccination, 1 case of CIN 2/3 due to the 5 additional types is prevented for every 51–76 females vaccinated with HPV9 instead of HPV4 (over a period of 70 years).

GRADE for HPV9 in females

Seroconversion in females aged 16–26 years

HPV9 compared with HPV4[a,b]

	Outcome	HPV9 n	HPV9 %	HPV4 n	HPV4 %	Estimated % Difference (95% CI)
4 original types	**Anti-HPV 6**	3993	**99.8**	3975	**99.8**	0.0 (-0.3, 0.2)
	Anti-HPV 11	3995	**100**	3982	**99.9**	0.1 (-0.1, 0.2)
	Anti-HPV 16	4032	**100**	4062	**100**	0.0 (-0.1, 0.2)
	Anti-HPV 18	4539	**99.8**	4541	**99.7**	0.1 (-0.1, 0.4)
5 additional types	**Anti-HPV 31**	4466	**99.8**	4377	**50.1**	49.7 (48.2, 51.2)
	Anti-HPV 33	4702	**99.7**	4691	**12.7**	87.0 (86.0, 88.0)
	Anti-HPV 45	4792	**99.6**	4750	**9.2**	90.4 (89.6, 91.2)
	Anti-HPV 52	4455	**99.8**	4335	**2.6**	97.2 (96.7, 97.7)
	Anti-HPV 58	4486	**99.8**	4446	**20.4**	79.4 (78.2, 80.6)

[a]Data from Protocol 001 (RCT), as measured by competitive Luminex immunoassay (cLIA) at month 7
[b]Protocols 002 (Obs), 003 (Obs) demonstrated supportive evidence (data not shown)

GRADE for HPV9 in females

Geometric mean titers (GMTs) in females aged 16–26 years HPV9 compared with HPV4[a,b]

Outcome	HPV9 n	HPV9 GMTs	HPV4 n	HPV4 GMTs	*P* for non-inferiority or superiority	
Anti-HPV 6	3993	**893**	3975	**875**	<0.001	**HPV9 non-inferior to HPV4**
Anti-HPV 11	3995	**666**	3982	**830**	<0.001	
Anti-HPV 16	4032	**3131**	4062	**3157**	<0.001	
Anti-HPV 18	4539	**805**	4541	**679**	<0.001	
Anti-HPV 31	4466	**658**	4377	**10**	<0.001	**HPV9 superior to HPV4**
Anti-HPV 33	4702	**416**	4691	**<4**	<0.001	
Anti-HPV 45	4792	**253**	4750	**<3**	<0.001	
Anti-HPV 52	4455	**380**	4335	**<3**	<0.001	
Anti-HPV 58	4486	**483**	4446	**<4**	<0.001	

[a]Data from Protocol 001 (RCT), as measured by cLIA at month 7
[b]Protocols 002 (Obs), 003 (Obs) demonstrated supportive evidence (data not shown)

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Initial evidence type

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, or RCTs with notable limitations
4	Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

GRADE for HPV9 in females
Evidence type for HPV 6/11/16/18-related benefits

Benefits	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type
Cervical precancer	HPV4 RCT (3)[a]	No serious	No serious	Serious[c]	No serious	2
Supportive data	HPV9 RCT (1), Obs (2)[b]					
Cervical cancer	HPV4 RCT (3)[a]	No serious	No serious	Serious[c,d]	No serious	3
Supportive data	HPV9 RCT (1), Obs (2)[b]					
Anogenital warts	HPV4 RCT (3)[a]	No serious	No serious	Serious[c]	No serious	2
Supportive data	HPV9 RCT (1), Obs (2)[b]					

[a]Data from HPV4 Protocols 007 (RCT), 013 (RCT), 015 (RCT)
[b]Supportive HPV9 Protocols 001 (RCT), 002 (Obs), 003 (Obs)
[c]Downgrade by 1 for indirectness due to use of immunobridging to HPV4
[d]Downgrade by 1 for indirectness due to use of cervical precancer as surrogate marker for cervical cancer

GRADE for HPV9 in females
Evidence type for HPV 31/33/45/52/58-related benefits

Benefits	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type
Cervical precancer	HPV9 RCT (1)[a]	No serious	No serious	No serious	No serious	1
Supportive data	HPV9 Obs (2)[b]					
Cervical cancer	HPV9 RCT (1)[a]	No serious	No serious	Serious[b]	No serious	2
Supportive data	HPV9 Obs (2)[b]					

[a]Data from HPV9 Protocol 001 (RCT)
[b]Supportive HPV9 Protocols 002 (Obs), 003 (Obs)
[b]Downgrade by 1 for indirectness due to use of cervical precancer as surrogate marker for cervical cancer

Population, Intervention, Comparison, Outcome (PICO)

- Population: Females aged 11–12 years
- Intervention: HPV9
- Comparison: HPV4
- Outcome:
  - HPV 6/11/16/18
  - HPV 31/33/45/52/58

Supportive studies for HPV9 in females aged 11–12 years

- **Protocol 002 (Obs): Immunobridging HPV9 older to younger females**
  - Non-inferior seroconversion and higher GMTs in younger females
  - Supports bridging of efficacy findings to younger females
- **Protocol 009 (RCT): Immunobridging HPV4 to HPV9 in younger females**
  - Non-inferior seroconversion and GMTs for HPV9
  - Supports bridging of HPV4 to HPV9
- **Evidence type in younger females same as for older females**
  - Due to high seroconversion rates and higher GMTs in younger females and efficacy data from per protocol population

Population, Intervention, Comparison, Outcome (PICO)

- Population: Males aged 13–21 years
- Intervention: HPV9
- Comparison: HPV4
- Outcome: HPV 6/11/16/18

HPV4 phase II and III efficacy RCTs considered for HPV9 GRADE for HPV 6/11/16/18-related outcomes

Per protocol population	Protocol	n	Outcome	Efficacy
Males aged 16–26 years	020	402 2798	AIN 2/3[a] Anogenital warts[b]	74.9% 89.3%

AIN = Anal intraepithelial neoplasia

[a]Palefsky J, Giuliano AR, Goldstone S, et al. N Engl J Med 2011;365:1576–85.
[b]Gardasil package insert:
http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263.pd

GRADE for HPV9 in males aged 13–21 years

- **Protocol 020 (RCT): HPV4 vs. placebo in older males**
  - GRADE for HPV4 in males[a] presented to ACIP in 2011
    - Anal cancer evidence type = 2
    - Anogenital warts evidence type = 1
- **Protocol 003 (RCT): Immunobridging HPV9 older females to older males**
  - Non-inferior seroconversion and GMTs in older males
  - Supports immunobridging of older females to older males

[a]GRADE for HPV4 in males: http://www.cdc.gov/vaccines/acip/recs/GRADE/hpv-vac-males.html

GRADE for HPV9 in males
Evidence type for HPV 6/11/16/18-related benefits

Benefits	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type
Anal cancer	HPV4 RCT (1)[a]	No serious	No serious	Serious[c,d]	No serious	3
Supportive data	HPV9 RCT (1), Obs (1)[b]					
Anogenital warts	HPV4 RCT (1)[a]	No serious	No serious	Serious[c]	No serious	2
Supportive data	HPV9 RCT (1), Obs (1)[b]					

[a]Data from HPV4 Protocol 020 (RCT)
[b]Supportive HPV9 Protocols 001 (RCT), 003 (Obs)
[c]Downgrade by 1 for indirectness due to use of immunobridging to females of the same age group
[d]Downgrade by 1 for indirectness due to use of AIN 2/3 as surrogate marker for anal cancer

Population, Intervention, Comparison, Outcome (PICO)

- Population: Males aged 11–12 years
- Intervention: HPV9
- Comparison: HPV4
- Outcome: HPV 6/11/16/18

Supportive studies for HPV9 in males aged 11–12 years

- **Protocol 002 (Obs): Immunobridging HPV9 older females to younger males**
  - Non-inferior seroconversion and higher GMTs in younger males
  - Supports bridging of efficacy findings from older females to younger males
- **Higher GMTS in younger males (Protocol 002) compared with older males (Protocol 003)**
  - Supports immunobridging from older males to younger males
- **Evidence type in younger males same as for older males**
  - Due to high seroconversion rates and higher GMTs in younger males and efficacy data from per protocol population

GRADE for harms due to HPV9

- **Outcomes**
  - SAE (day 1–15 and any time during study period)
  - Anaphylaxis (day 1–15)
- **Older and younger age groups**

GRADE for HPV9 in older females and males

Harms data in females and males aged 16–26 years

Protocol (Design)	Harms	Incidence in HPV9 % (n / N)	Incidence in HPV4 % (n / N)
001 (RCT)	SAE day 1–15	0.03 (2[a]/7071)	0.01 (1/7078)
	SAE any time	0.03 (2/7071)	0.03 (2/7078)
	Anaphylaxis day 1–15	0.01 (1[b]/7071)	0 (0/7078)
002, 003 (Obs)	SAE day 1–15	0.06 (1/1540)	--
	SAE any time	0.06 (1/1540)	--
	Anaphylaxis day 1–15	0 (0/1540)	--

SAE = serious adverse events

[a]Determined to be vaccine-related; study medication withdrawn for one case
[b]Determined to be due to non-study medication

GRADE for HPV9 in older females and males

Evidence type for harms

Harms	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type
SAE	RCT (1), Obs (2)[a]	No serious	No serious	No serious	Serious[b]	2
Anaphylaxis	RCT (1), Obs (2)[a]	No serious	No serious	No serious	Serious[b]	2

[a]Data from HPV9 Protocols 001 (RCT), 002 (Obs), 003 (Obs)
[b]Downgrade by 1 for imprecision due to small sample size

GRADE for HPV9 in younger females and males

Harms data in females and males aged 9–15 years

Protocol (Design)	Harms	Incidence in HPV9 % (n / N)	Incidence in HPV4 % (n / N)
009 (RCT)	SAE day 1–15	0 (0/299)	0 (0/300)
	SAE any time	0 (0/299)	0 (0/300)
	Anaphylaxis day 1–15	0 (0/299)	0 (0/300)
002, 005, 007 (Obs)	SAE day 1–15	0.02 (1/4880)	--
	SAE any time	0.02 (1/4880)	--
	Anaphylaxis day 1–15	0 (0/4880)	--

SAE = Serious adverse events

GRADE for HPV9 in females and males aged 11–12 years
Evidence type for harms

Harms	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type
SAE	RCT (1), Obs[a] (3)	No serious	No serious	No serious	Serious[b]	2
Anaphylaxis	RCT (1), Obs[a] (3)	No serious	No serious	No serious	Serious[b]	2

[a]Data from HPV9 Protocols 002 (Obs), 005 (Obs), 007 (Obs), 009 (RCT)
[b]Downgrade by 1 for imprecision due to small sample size

Overall quality of evidence for HPV9 in older females

Comparison		Outcome	Design (# studies)	Findings	Evidence type	Overall
HPV9 vs. HPV4	Benefits	**HPV 6/11/16/18** **Cervical precancer** **Cervical cancer** **Anogenital warts**	HPV4 RCT (3)[a] HPV9 RCT (1), Obs (2)[b]	High efficacy for HPV4; non-inferior immunogenicity for HPV 6/11/16/18 and comparable risk for outcomes	2–3	2
		HPV 31/33/45/52/58 **Cervical precancer** **Cervical cancer**	HPV9 RCT (1)[c] HPV9 Obs (2)[d]	Decreased risk for HPV 31/33/45/52/58-related outcomes	1–2	
	Harms	**SAE**	HPV9 RCT (1), Obs (2)[e]	Few cases	2	
		Anaphylaxis		No vaccine-related cases		

[a]Data from HPV4 Protocols 007 (RCT), 013 (RCT), 015 (RCT)
[b]Supportive HPV9 Protocols 001 (RCT), 002 (Obs), 003 (Obs)
[c]Data from HPV9 Protocol 001 (RCT)
[d]Supportive HPV9 Protocols 002 (Obs), 003 (Obs)
[e]Data from HPV9 Protocols 001 (RCT), 002 (Obs), 003 (Obs)

Overall quality of evidence for HPV9 in younger females

Comparison		Outcome	Design (# studies)	Findings	Evidence type	Overall
HPV9 vs. HPV4	Benefits	**HPV 6/11/16/18** **Cervical cancer** **Cervical precancer** **Anogenital warts**	HPV4 RCT (3)[a] HPV9 RCT (2), Obs (4)[b]	Non-inferior immunogenicity	2–3	2
		HPV 31/33/45/52/58 **Cervical cancer** **Cervical precancer**	HPV9 RCT (1)[c] HPV9 RCT (1), Obs (4)[d]	Non-inferior immunogenicity	1–2	
	Harms	**SAE**	HPV9 RCT (1), Obs (2)[e]	No cases	2	
		Anaphylaxis		No cases		

[a]Data from HPV4 Protocols 007 (RCT), 013 (RCT), 015 (RCT)
[b]Supportive HPV9 Protocols 001 (RCT), 002 (Obs), 003 (Obs), 005 (Obs), 007 (Obs) 009 (RCT)
[c]Data from HPV9 Protocol 001 (RCT)
[d]Supportive HPV9 Protocols 002 (Obs), 003 (Obs), 005 (Obs), 007 (Obs), 009 (RCT)
[e]Data from HPV9 Protocols 002 (Obs), 005 (Obs), 007 (Obs), 009 (RCT)

Overall quality of evidence for HPV9 in older males

Comparison		HPV 6/11/16/18 Outcome	Design (# studies)	Findings	Evidence type	Overall
HPV9 vs. HPV4	Benefits	**Anal cancer** **Anogenital warts**	HPV4 RCT (1)[a] HPV9 RCT (1), Obs (1)[b]	High efficacy for HPV4; non-inferior immunogenicity	2–3	3
	Harms	**SAE**	HPV9 RCT (1), Obs (2)[c]	Few cases	2	
		Anaphylaxis		No vaccine-related cases		

[a]Data from HPV4 Protocol 020 (RCT)
[b]Supportive HPV9 Protocols 001 (RCT), 003 (Obs)
[c]Data from HPV9 Protocols 001 (RCT), 002 (Obs), 003 (Obs)

Overall quality of evidence for HPV9 in younger males

Comparison		HPV 6/11/16/18 Outcome	Design (# studies)	Findings	Evidence type	Overall
HPV9 vs. HPV4	Benefits	Anal cancer Anogenital warts	RCT (1)[a] RCT (1), Obs (1)[b]	Non-inferior immunogenicity	2–3	3
	Harms	SAE	RCT (1), Obs (4)[c]	No cases	2	
		Anaphylaxis		No cases		

[a]Data from HPV4 Protocol 020 (RCT)
[b]Supportive HPV9 Protocols 001 (RCT), 002 (Obs)
[c]Data from Protocols 002 (Obs), 005 (Obs), 007 (Obs), 009 (RCT)

Overall GRADE summary table for HPV9

		Outcomes	Age group	Evidence type	Interpretation
Benefits and Harms	**Females**	Cervical cancer Cervical precancer Anogenital warts SAE Anaphylaxis	Older	2	Moderate confidence
			Younger	2	Moderate confidence
	Males	Anal cancer Anogenital warts SAE Anaphylaxis	Older	3	Low confidence
			Younger	3	Low confidence

Acknowledgments

DSTDP/NCHHSTP/CDC

Lauri Markowitz

Susan Hariri

Eileen Dunne

Faruque Ahmed

ACIP HPV Vaccine Work Group

Thank you

For more information please contact Centers for Disease Control and Prevention

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Visit: www.cdc.gov | Contact CDC at: 1-800-CDC-INFO or www.cdc.gov/info