

GRADING OF RECOMMENDATIONS, ASSESSMENT, DEVELOPMENT, AND EVALUATION (GRADE) FOR HPV VACCINE FOR MALES

CDC. Recommendations on the Use of Quadrivalent Human Papillomavirus Vaccine in Males — Advisory Committee on Immunization Practices (ACIP). MMWR 2011;60:1705-8.

METHODS FOR GRADE: HPV VACCINE FOR MALES

Evidence of benefits, harms, values and preferences, and cost-effectiveness were reviewed in accordance with GRADE methods. The primary policy question was, “Should HPV4 be recommended for routine use in 11-12 year old boys”. The benefits considered included prevention of genital warts, anal intraepithelial neoplasia (AIN), and anal cancer. The harms considered included serious adverse events (SAE), venous thromboembolism (VTE), syncope, and anaphylaxis. Data on efficacy were from a randomized clinical trial of HPV4 in males; data on adverse effects were from randomized clinical trials of HPV4 in males and females, and post-licensure studies of HPV4 in females. Evidence type for each study included a review of study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations.

Recommendation Category A: Recommendation that applies to all persons in an age or risk-based group. Recommendation Category B: Recommendation for individual clinical decision making. Evidence Type 1: Randomized controlled trials, or overwhelming evidence from observational studies. Evidence Type 2: Randomized controlled trials with important limitations, or exceptionally strong evidence from observational studies. Evidence Type 3: Observational studies. Evidence Type 4: Clinical experience and observations, observational studies, or randomized controlled trials with notable limitations. Source: Ahmed F, Temte JL, Campos-Outcalt D, Schünemann HJ; for the ACIP Evidence Based Recommendations Work Group (EBRWG). Methods for developing evidence-based recommendations by the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention (CDC). *Vaccine* 29(49):9171-6, 2011.



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TABLES FOR GRADE: HPV VACCINE FOR MALES

Table 1. Quadrivalent HPV Vaccine for Males: Benefits *

Outcome HPV 6-, 11-, 16-, 18- related	No. subjects (# studies)	Incidence in controls	Incidence in vaccinated	Vaccine efficacy (95% CI)	Risk difference per 1000 (95% CI)	Number needed to vaccinate ^d
Population: Males^a						
Genital warts	2798 (1 RCT)	1.99%	0.22%	89.3% (65.3, 97.9)	-18 (-13, -20)	56
Population: MSM^b						
Genital warts ^c	402 (1 RCT)	4.33%	0.51%	88.1 (13.9, 99.7)	-38 (-6, -43)	26
AIN 1/2/3	402 (1 RCT)	11.5%	2.6%	77.5% (39.6, 93.3)	-89 (-46, -107)	11
AIN 2/3	402 (1 RCT)	6.3%	1.5%	74.9% (8.8, 95.5)	-48 (-6, -59)	21

AIN=anal intraepithelial neoplasia; MSM=men who have sex with men; CI=confidence interval; RCT=randomized controlled trial

^aFollow-up 2.3 years; ^bFollow-up 2.6 years; ^cPersonal Communication, Carlos Sattler MD, August 2011; ^dFrequently reported as number needed to treat or NNT
Reference: from Package insert for Gardasil (quadrivalent human papillomavirus types 6, 11, 16 and 18 HPV); Vaccine efficacy, risk difference, and number
needed to vaccinate calculated with GRADEpro software *Among those who received all 3 vaccine doses and were seronegative at day 1 and DNA-negative day
1 through month 7 to the respective HPV type (per protocol population)

Table 2. Quadrivalent HPV vaccine for Males: Evidence Type of Benefits

Outcome	Design (# studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Evidence Type
Population: Males							
Genital warts	RCT (1)	No serious	No serious	No serious	No serious	None	1
Population: MSM							
Genital warts	RCT (1)	No serious	No serious	No serious	No serious	None	1
AIN 1/2/3	RCT (1)	No serious	No serious	No serious ^b	No serious	None	1
AIN2/3	RCT (1)	No serious	No serious	Yes ^{a,b}	No serious	None	2

MSM=men who have sex with men; AIN=anal intraepithelial neoplasia; CI=confidence interval; AIN=anal intraepithelial neoplasia;
RCT=randomized controlled trial

^aAIN2/3 considered anal precancer lesion (surrogate for anal cancer) downgraded by one level for indirectness; ^bEvidence in MSM available from
clinical trial, no reason to suspect vaccine efficacy for boys aged 11-12 years would differ from that observed in MSM, not downgraded for
indirectness

Table 3. Quadrivalent HPV Vaccine for Males: Summary Harms from Prelicensure RCTs in Males and Females

Outcome	No. subjects (# studies)	Incidence in vaccinated %	Incidence in controls %	Summary risk ratio (95% CI)
Males^a				
SAE	4723(2 RCTs)	0.4	0.5	0.88 (0.38, 2.06)
Syncope	4723(2 RCTs)	0.04	0.1	0.50 (0.05, 5.52)
VTE	4723(2 RCTs)	0	0	NE
Anaphylaxis	4722(2 RCTs)	0	0	NE
Females^b				
SAE	18,893(4 RCTs)	1.1	1.1	0.97 (0.74, 1.27)
Syncope	18,893(4 RCTs)	0.2	0.2	0.84 (0.45, 1.55)
VTE	18,893(4 RCTs)	0.03	0.02	1.33 (0.30, 5.96)
Anaphylaxis	18,893(4 RCTs)	0	0.01	0.33 (0.01, 8.20)

NE= non estimable; VTE=venous thromboembolism; RCT=randomized controlled trial; CI=confidence interval; SAE=serious adverse events: FDA definition including death, hospitalization, life-threatening event, disability, congenital anomaly or birth defect, requiring intervention, or other serious event <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm>

VTE = deep vein thrombosis, embolism, thrombophlebitis, thrombosis, or thrombophlebitis, superficial;

^aFrom Merck protocols 018 (follow-up 2.5 years), 020 (follow-up 3 years) ^bFrom Merck protocols 007 (follow-up 3 years), 013 (follow-up 3.7 years), 015 (follow-up 3.7 years), 018 (follow-up 2.5 years). Summary risk ratio calculated using RevMan software, fixed effects

Table 4. Quadrivalent HPV Vaccine for Males: Harms from Postlicensure Vaccine Safety Datalink Observational Study in Females

Outcome, age group (yrs)	No. of doses administered	Incidence in vaccinated	Incidence in comparison	Relative risk (95% CI) ^c
		group (per 10,000 vaccinations) ^a	group (per 10,000 vaccinations)	
Syncope^b				
9-18	351,630	17.35	21.72	0.86 (0.72, 1.02)
19-26	150,544	11.29	19.31	0.54 (0.42, 0.75)
VTE^b				
9-18	292,302	0.274	0.137	1.98 ^d (0.86,3.94)
19-26	176,194	0.624	0.851	0.73 (0.37, 1.31)
Anaphylaxis^e				
9-26	600,558	0.017	0.015	N/A

VTE=venous thromboembolism; CI=confidence interval; N/A=not available

^aFor syncope, observed rates presented and risk window was day 0. For VTE, rates were adjusted by site and age. Risk window included days 1-42; ^bComparison group for syncope was concurrent vaccinated group; for VTE was historical comparison group; ^cRelative Risk adjusted by site and age; Simulated confidence intervals at the time upper limit was reached; ^dConfirmed cases of VTE among 9-17 yr olds all had risk factors for VTE (smoking, obesity, oral contraceptive pill use, hypercoaguable disorders); ^eComparison group from Bolke K, *et al.* Risk of anaphylaxis after vaccination of children and adolescents. Pediatrics 2003. Reference: from Gee J, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine 2011

Table 5. Quadrivalent HPV Vaccine for Males: Harms from Postlicensure Manufacturer Observational Study in Females

Outcome	No. of Persons	Incidence in vaccinated group (per 1000 person years)	Incidence in comparison group (per 1000 person years)	Relative risk (95% CI)^a
Syncope	189,629	24.21	4.04	6.00 (3.91,9.21) ^b
VTE	189,629	6.32	4.97	1.27 (0.57,2.86)
Allergic reaction or Anaphylactic Shock	189,629	0.16	0.21	0.75 (0.32,1.78) ^c

VTE=venous thromboembolism; CI=confidence interval; Outcome is defined as presence of diagnosis code in emergency room or hospital setting in vaccination risk period (day of vaccination for syncope & allergic reaction/anaphylactic shock, & 1-60 days after vaccination for VTE) or in post-vaccination self-comparison (i.e., “control”) period. These codes could represent a new event, a pre-existing condition, a prior history of the condition, a “rule out” diagnosis, miscoding, or a misdiagnosis. A diagnosis code also does not assume that the diagnosis is confirmed. No validation of these codes was performed by medical record review.

^aRelative risk is approximated by odds ratio, obtained from conditional logistic regression; ^bFor syncope, the relative risk elevation with lower bound CI greater than 1 suggests that syncope diagnosis codes are more likely to occur on day of vaccination than in self-comparison period; ^cFor allergic reaction/anaphylactic shock, external Safety Review Committee reviewed medical records of females with day 0 diagnosis codes & found no association between diagnosis & vaccination with quadrivalent HPV vaccine.

VTE includes the following ICD-9 codes: 452 Portal vein thrombosis; 453.0 Budd-Chiari syndrome; 453.1 Thrombophlebitis migrans; 453.2 Embolism & thrombosis of inferior vena cava; 453.3 Embolism & thrombosis of renal vein; 453.4-453.9: Acute and chronic venous embolism & thrombosis of deep or superficial vessels or veins at various sites or unspecified site; V12.51 Personal history of venous thrombosis & embolism. Reference: ACIP Presentation October 2011 by C. Velicer

Table 6. Quadrivalent HPV Vaccine for Males: Evidence Type of Harms

Outcome	Design (# studies, Sex)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Evidence type
SAE	RCT (2,M; 4,F)	No serious	No serious	No serious ^a	Yes ^b	None	2
VTE	RCT (2,M; 4,F)	No serious	No serious	No serious ^a	Yes ^b	None	2
	O (2 F)	Yes ^d	No serious	Yes ^c	No serious	None	4
Syncope	RCT (2,M; 4,F)	No serious	No serious	No serious ^a	Yes ^b	None	2
	O (2 F)	Yes ^d	No serious	Yes ^c	No serious	None	4
Anaphylaxis	RCT (2,M; 4,F)	No serious	No serious	No serious ^a	Yes ^b	None	2
	O (2 F)	Yes ^d	No serious	Yes ^c	No serious	None	4

VTE=venous thromboembolism; SAE=serious adverse events; RCT=randomized controlled trial; O=observational study

^aFemale data indirect, however male data available, not downgraded; ^bRCTs with relatively small sample size, downgraded one level for imprecision; ^cStudies conducted in females, downgraded one level for indirectness; ^dPossible uncontrolled confounding, downgraded one level for risk of bias

Summary for Harm: No evidence of increased risk for anaphylaxis, VTE, or SAE from 5 RCTs in males and females (1 RCT in both males and females), and 2 observational studies in females. One of 7 studies found persons who were vaccinated with HPV4 were more likely to faint on the day they were vaccinated than another period in which vaccine was not administered, likely a result of injection-related syncope. Injection-related syncope is an anticipated finding that is described in the package insert. In the recommendation for HPV vaccine it is stated that syncope can occur after vaccination and to avoid serious injury related to a syncopal episode, vaccine providers should consider observing patients for 15 minutes after they are vaccinated. Evidence type is 2 for RCTs and 4 for observational studies.

Table 7. Summary Evidence Type for Benefits, Harms: Quadrivalent HPV Vaccine for Males

Comparison Group		Outcome	Study design (# studies, sex)	Findings	Evidence type	Overall Evidence type ^b
HPV vaccination vs. no HPV vaccination	Benefits	Genital warts	RCT (1,M)	Decreased risk among vaccinated	1	2
		AIN1/2/3	RCT (1,M)	Decreased risk among vaccinated	1	
		AIN2/3	RCT (1,M)	Decreased risk among vaccinated	2	
	Harms	SAE	RCT (2, M; 4,F)	No difference	2	
		Syncope	RCT (2, M; 4,F)	No difference	2	
		Syncope	O (2, F)	Increased risk among vaccinated ^a	4	
		VTE	RCT (2, M; 4,F)	No difference	2	
		VTE	O (2, F)	No difference	4	
		Anaphylaxis	RCT (2, M; 4,F)	No difference	2	
		Anaphylaxis	O (2, F)	No difference	4	

RCT=randomized controlled trial; O=observational study; F=female; M=male; VTE=venous thromboembolism; SAE=serious adverse events

^aOne observational study found persons who were vaccinated with HPV4 were more likely to faint on the day they were vaccinated than another period in which vaccine was not administered ^bOverall evidence type 2 based on evidence from the strongest study design for critical harms and benefits

Table 8. Considerations for Formulating Recommendations: Quadrivalent HPV Vaccine for Males

Key factors	Comments
Balance between benefits and harms	Benefits are greater than potential harms
Evidence type for benefits and harms	Evidence Type 2 Benefit Evidence Type 2 Harm RCT Evidence Type 4 Harm O
Value	High value placed by ACIP HPV Work Group on prevention of cancer in males
Cost-effectiveness	HPV4 is most cost-effective if all HPV associated outcomes prevented, vaccine cost lower than current price, female coverage low (such as 30% 3-dose coverage at age 12 years)

RCT=randomized controlled trial; O=observational study

Summary for Benefits and Harms: Benefits are greater than potential harms and overall evidence type is 2. There is high value placed on prevention of cancer in males. Quadrivalent HPV vaccine is most cost-effective if all HPV associated outcomes are prevented, vaccine cost is lower than current price, or female coverage is low. Recommendation for routine vaccination of males aged 11 or 12 years with HPV4 administered as a 3-dose series (*recommendation category A; evidence type 2*)

References:

1. C Velicer. ACIP Presentation. Post-licensure Safety Study of Quadrivalent Human Papillomavirus Vaccine among 189,629 Females Presented at October 2011 ACIP Meeting.
2. Ahmed F, Temte JL, Campos-Outcalt D, Schönemann HJ, for the ACIP Evidence Based Recommendations Work Group (EBRWG). Methods for developing evidence-based recommendations by the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention (CDC). *Vaccine* 2011;29:9171-76.
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7. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. *N Engl J Med* 2011;364:401-11.
8. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med* 2011;365:1576-85.