

HPV Vaccine Considerations for Males

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Advisory Committee on Immunization Practices

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Outline

- GRADE Review for Male HPV Vaccine
 - Review study question, benefits, harms
 - Overview of value and preferences
 - Summary of considerations for routine recommendations
- Draft recommendations
- Vote

- Summary of considerations for vaccination of 13-26 year olds
- Vote
- Summary of considerations for special populations

Quadrivalent HPV vaccine for males

Study Question: Should quadrivalent HPV vaccine be recommended for routine use in 11-12 year old boys?

Quadrivalent HPV vaccine for males

- Does HPV4 prevent:
 - Condyloma?
 - Anal intraepithelial neoplasia (AIN 1/2/3)?
 - Anal cancer?
 - Oropharyngeal cancer?
 - Penile cancer?
- Does HPV4 in males prevent cervical cancer in females?

Quadrivalent HPV vaccine for males

- Does HPV4 prevent
 - Condyloma?
 - Anal intraepithelial neoplasia (AIN 1/2/3)?
 - Anal cancer?
 - Oropharyngeal cancer?*
 - Penile cancer?*
- Does HPV4 in males prevent cervical cancer in females?*

* no clinical trial available

Studies submitted in support of licensure Quadrivalent HPV Vaccine for males

- V501-020: RCT, 4065 males 16-26 years
 - Sub Study: Men who have sex with men (MSM)
- V501-016: RCT, outcomes of immunogenicity and safety, 508 males 10-15 years
- V501-018: RCT, outcomes of immunogenicity and safety, 842 males 9-15 years

Background on clinical trials

Protocol 20

- Randomized double-blind, placebo-controlled trial
- Multiple continents/countries
- Vaccine/placebo administered at Day 1, Months 2 and 6
- Subjects:
 - 3463 Heterosexual Men (HM) 16-23 years
 - 602 Men who have sex with men (MSM) 16-26 years
- Exclusion criteria: history of genital warts, genital lesions possibly HPV related, >5 or <1 lifetime sexual partner
- Outcomes:
 - All men: Condyloma
 - MSM: Condyloma, AIN
- Per protocol analysis: Males who were naïve to the respective vaccine-type infection (by DNA and by serologic assessment)

Benefits: HPV vaccine for males per protocol efficacy All Males

Outcome HPV 6, 11,16,18 related	No. of subjects (# studies)	Incidence in controls % (n/N)	Incidence in vaccinated % (n/N)	Vaccine efficacy % (95% CI)	Absolute risk difference per 1000 (95% CI)	Number Needed to Vaccinate
Condyloma	2798 (1 RCT)	1.99% (28/1404)	0.22% (3/1394)	89.3% (65.3, 97.9)	-18 (-13, -20)	56

Reference: Package Insert, page 504 Table 12: Analysis of Efficacy of GARDASIL in the PPE. Population of 16- through 26 year old Boys and Men for Vaccine. Incidence over the follow-up period of 2.3 years.

Benefits: HPV vaccine for males per protocol efficacy Men who have sex with men (MSM)

Outcome HPV 6, 11,16,18 related	No. of subjects (# studies)	Incidence in controls % (n/N)	Incidence in vaccinated % (n/N)	Vaccine efficacy % (95% CI)	Absolute risk difference per 1000 (95% CI)	Number Needed to Vaccinate
Condyloma*	403 (1 RCT)	4.33% (9/208)	0.51% (1/195)	88.1 (13.9, 99.7)	-38 (-6, -43)	26
AIN 1/2/3	402 (1 RCT)	11.5% (24/208)	2.6% (5/194)	77.5% (39.6, 93.3)	-89 (-46, -107)	11
AIN 2/3	402 (1 RCT)	6.3% (13/208)	1.5% (3/194)	74.9% (8.8, 95.5)	-48 (-6, -59)	21

Reference: Package Insert, page 504 Table 13: Analysis of Efficacy of GARDASIL for Anal Disease in the PPE Population of 16- through 26- year old boys and men in the MSM Sub-Study for Vaccine HPV types, Follow-up period was 2.6 years.

*unpublished data from manufacturer. Follow-up period was 2.6 years.

Benefits: HPV vaccine general population males

Outcome	Lifetime incidence in non-vaccinated cohort, per 1000	Lifetime incidence in vaccinated cohort, per 1000	Absolute risk difference per 1000	Number Needed to Vaccinate
Condyloma	78	21	-57	18
Anal cancer	1	0.37	-0.63	1,581

Estimates calculated using HPV model of a single birth cohort of males vaccinated at age 12 years, assuming 90% vaccine efficacy for prevention of condyloma and 75% efficacy for prevention of anal cancer. The number needed to vaccinate reflects the number of 12-year-old males needed to vaccinate to prevent a single case of the given outcome (genital warts, anal cancer) over the lifetime of the birth cohort of males. This application of the model does not include indirect effects (herd immunity). If including indirect effects, the number needed to vaccinate could be notably higher if female coverage is high. See Chesson et al (*Vaccine* 2011) for model details.

Type of evidence

Randomized controlled trials (RCTs), or overwhelming evidence from observational studies	1
RCTs with important limitations, or exceptionally strong evidence from observational studies	2
RCTs with notable limitations, or observational studies	3
RCTs with several major limitations, observational studies with important limitations, or clinical experience and observations	4

Evidence type: studies in all males

Outcome HPV 6, 11,16,18 related	Design (# studies)	Risk of bias	Inconsis- tency	Indirect- Ness	Impreci- sion	Other considera- tions	Evidence type
Condyloma	RCT (1)	No serious	No serious	No serious	No serious	None	1

Evidence type: studies in MSM

Outcome HPV 6, 11,16,18 related	Design (# studies)	Risk of bias	Inconsis- tency	Indirect- Ness	Impreci- sion	Other considera- tions	Evidence type
Condyloma	RCT (1)	No serious	No serious	No serious	No serious	None	1
AIN 1/2/3	RCT (1)	No serious	No serious	No serious ²	No serious	None	1
Anal cancer	RCT (1)	No serious	No serious	Yes ^{1,2}	No serious	None	2

MSM= Men who have sex with men

¹AIN2/3 a surrogate marker for anal cancer

²RCT conducted exclusively in men who have sex with men, not downgraded as primary efficacy trials conducted in MSM

Harm outcomes

- Serious Adverse Events (SAE)
- Syncope
- Venous Thromboembolic Events (VTE)
- Anaphylaxis

Methods for evaluation of harm

- Review of RCTs with comparison group:
 - 2 RCTs in males, 4,723 males
 - 4 RCTs in females, 18,893 females
- Review of observational studies: females (VSD, post licensure data from manufacturer)

Harm: summary data RCTs males, females

Outcome	No. of Studies	Incidence in vaccinated % (n/N)	Incidence in controls % (n/N)	Summary Risk Ratio (95% CI)
<u>Males*</u>				
SAEs	2	0.4% (11/2504)	0.5% (11/2219)	0.88 (0.4, 2.1)
Syncope	2	0.03% (1/2634)	0.1% (3/2349)	0.30 (0.03,2.9)
VTE	2	(0/2585)	(0/2303)	NE
Anaphylaxis	2	(0/2585)	(1/2303)	NE
<u>Females**</u>				
SAEs	4	1.1% (101/9584)	1.1% (103/9309)	0.97 (0.7, 1.3)
Syncope	4	0.2% (18/9641)	0.2% (20/9366)	0.9 (0.5, 1.7)
VTE*	4	0.05% (5/9690)	0.13% (12/9412)	0.4 (0.2,1.2)
Anaphylaxis	4	(0/9690)	(0/9412)	NE

NE= non estimable, 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 = venous thromboembolic events (deep vein thrombosis, embolism, thrombophlebitis, thrombosis, or thrombophlebitis, superficial);

**From 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);

* From Merck protocols 018 (follow-up 2.5 years), 020 (follow-up 3 years)

VSD rapid cycle analysis quadrivalent HPV vaccine, females

Outcome	No. of Doses administered	Observed Incidence in vaccinated group (per 10,000 vaccinations) *	Incidence in comparison group (per 10,000 vaccinations)	Relative Risk (95% CI)†
Syncope**	9-18 yrs: 351,630	17.35	21.72	0.86 (0.72, 1.02)
	19-26 yrs: 150,544	11.29	19.31	0.54 (0.42, 0.75)
VTE**	9-18 yrs: 292,302	0.274	0.137	1.98‡ (0.86,3.94)
	19-26 yrs: 176,194	0.624	0.851	0.73 (0.37, 1.31)
Anaphylaxis¥	9-26 yrs: 600,558	0.017	0.015	N/A

*For 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. ** Comparison group for syncope was concurrent vaccinated group; for VTE was historical comparison group

† RR adjusted by site and age; Simulated confidence intervals at the time UL was reached

‡ Confirmed cases of VTE among 9-17 yr olds all had risk factors for VTE (smoking, obesity, OCP use, hypercoaguable disorders) ¥ Comparison group from Bolkhe et al. Risk of Anaphylaxis after vaccination of children and adolescents. Pediatrics 2003

Gee J, et al. Vaccine. 2011 (in press) VSD=Vaccine Safety Datalink

Manufacturer post licensure study, females

Outcome*	No. of Females vaccinated	Incidence in vaccinated group (per 1000 person yrs)	Incidence in comparison group (per 1000 person yrs)	Relative Risk (95% CI)†
Syncope	189,629	24.21	4.04	6.00 (3.91,9.21)**
Allergic reaction or anaphylactic shock	189,629	6.32	4.97	1.27 (0.57-2.86)‡
VTE	189,629	0.16	0.21	0.75 (0.32,1.78)

* “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.

† Relative risk is approximated by odds ratio, obtained from conditional logistic regression. CI=confidence interval.

** For syncope, the RR 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.

‡ For 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 GARDASIL.

§ VTE = Venous thromboembolism, 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.

Evidence Type: Harm

HPV vaccine for males- syncope

Outcome	Design (#studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Evidence type
Syncope	RCT: (2 M, 4 F)	None	None	None [†]	Yes [¥]	None	2
	O: (2 F)	Yes [*]	None ^{**}	Yes [‡]	None	None	4

† RCT Evidence type, female data is indirect but male data available, not downgraded

¥ Imprecision, downgraded -1

‡O Evidence type 3 downgraded -1 for indirectness

*Possible confounding due to risk factors ,downgraded -1 for risk of bias

**Differences in findings found from the two observational studies due to differences in comparison groups: self-controls (manufacturer data) vs. vaccinated controls (VSD RCA), not downgraded

RCT=randomized controlled clinical trial, O=observational

Summary of Evidence: HPV vaccine for males, benefits and harms

Comparison		Outcome	Study Design (Numbers) Sex	Findings	Evidence Type	Overall Type
HPV vaccine vs no HPV vaccine	Benefits in Males	Condyloma	RCT (1) M	Decreased risk among vaccinated	1	2
		AIN 1/2/3	RCT (1) M	Decreased risk among vaccinated	1	
		Anal Cancer	RCT (1) M	Decreased risk among vaccinated	2	
	Harms in Males, Females	SAE	RCT(2) M, RCT (4) F	No difference	2	
		Syncope	RCT (2) M, RCT (4) F	No difference	2	
		Syncope	O (2) F	Increased in one observational study	4	
		VTE	RCT (2) M, RCT (4) F	No difference	2	
		VTE	O (2) F	No difference	4	
		Anaphylaxis	RCT (2) M, RCT (4) F	No difference	2	
		Anaphylaxis	O (2) F	No difference	4	

Factors Determining Recommendation Category

Balance between benefits and harms	The larger the difference between the benefits and harms, the more likely a category A recommendation is warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely a category B recommendation is warranted.
Evidence type	The higher the evidence quality, the more likely a category A recommendation is warranted.
Values and preferences	The higher the importance and consistency in “values and preferences”, the more likely a category A recommendation is warranted.
Economic analysis	The higher the cost-effectiveness of vaccination, the more likely a category A recommendation is warranted.

Values

- Values represent the relative importance of a decision (outcomes related to benefits, harms, and costs) and play a role in every recommendation
- The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely is a category B recommendation warranted

Assessment of HPV vaccine: values and preferences

- Survey to ACIP HPV Work Group, 9 point scale to assess importance of specific outcomes:
 - Prevention of genital warts and cancer in males
 - Prevention of cervical cancer and cancers in females
 - Adverse events including injection site reactions, serious adverse events
- Willingness to Pay: evaluation of study on willingness to pay for HPV vaccine for various outcomes

Assessment of value: survey results

- All cancer outcomes considered of critical importance
 - Little variability in Work Group member responses
 - From perspective of parents/patients
 - From perspective of Work Group members “clinicians”
- Genital warts considered of moderate importance
 - Substantial variability in Work Group member responses
 - Work Group member “clinicians” (n=18) placed higher value on genital warts than other Work Group members

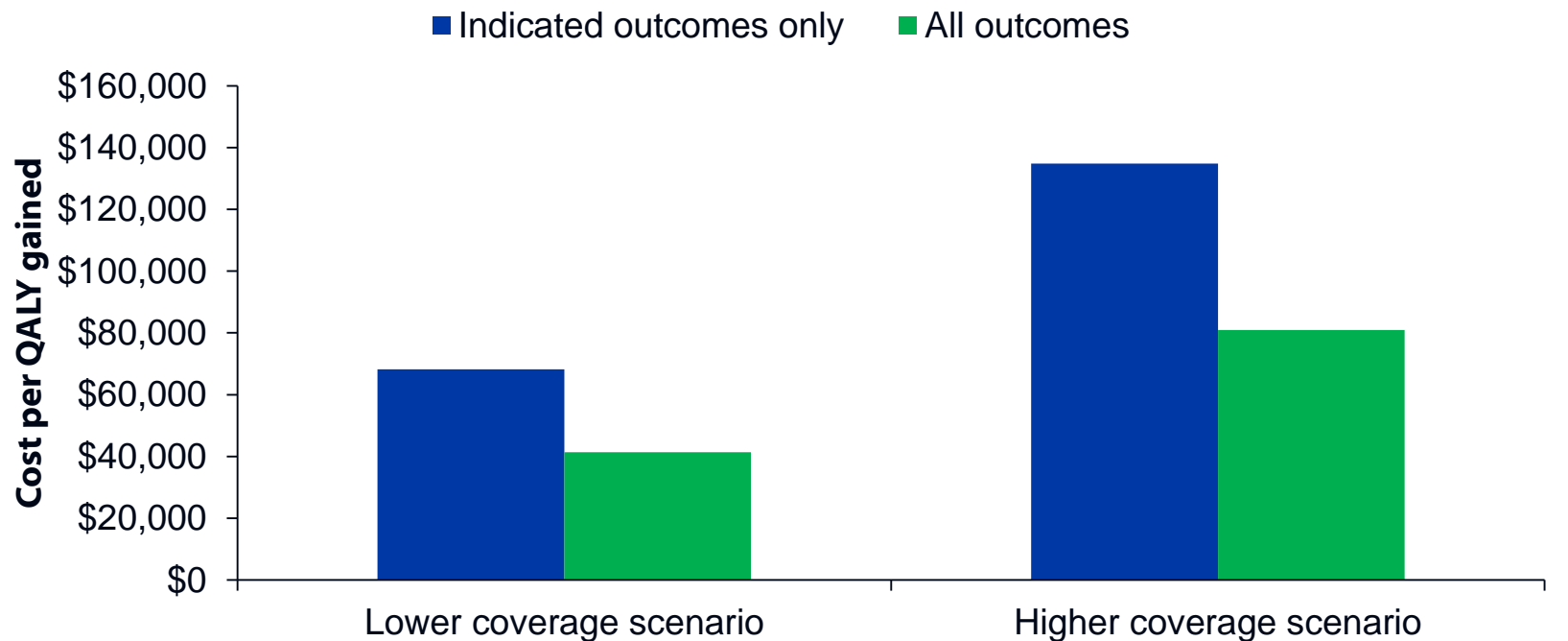
Other evaluations of value/preferences willingness to pay (WTP)

- WTP for cervical cancer protection ~2 times higher than for a genital warts protection

Brown et al, Vaccine 2010

Cost-effectiveness of male vaccination*

Cost per QALY gained by vaccinating 12 year-old boys



*Includes transmission effects to females

“Indicated” outcomes include cervical outcomes, vaginal, vulvar, anal cancers, and genital warts. All outcomes include indicated outcomes plus oropharyngeal cancer, penile cancer, and recurrent respiratory papillomatosis. Lower coverage scenario: 30% 3-dose coverage at age 12 and 50% 3-dose coverage by age 26. Higher coverage scenario: 50% 3-dose coverage at age 12 and 70% 3-dose coverage by age 26.

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 WG on prevention of cancers 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)*

Summary: GRADE HPV vaccine for males

- Routine use of quadrivalent HPV vaccine in 11-12 year old boys should be considered by ACIP
 - Category A recommendation:
 - Benefits are greater than potential harms
 - High level of evidence
 - High value placed on prevention of cancers in males

Options for policy considerations quadrivalent HPV vaccine for males

- Retain existing guidance “HPV4 may be given to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts”
- Routine recommendation for boys aged 11-12 years

Draft Language Recommendations for Vaccination

ACIP recommends routine vaccination of males aged 11-12 years with 3-doses of HPV4. The vaccination series can be started beginning at age 9 years.

Vote

Males 11-12 years

CONSIDERATIONS FOR MALES AGED 13-26 YEARS

Considerations for vaccinating males 13-26 years

- Vaccine Efficacy
- Benefits and cost-effectiveness
- Programmatic issues
- ACIP HPV work group opinions
- Draft language

Vaccine efficacy

- Intent to treat may provide best information on efficacy of vaccine for boys and young men aged 13-26 years
 - Males aged 16-26 years in clinical trial
 - All regardless of baseline HPV DNA or serology
 - Same exclusion criteria (history of genital warts, history of genital lesions possibly HPV related, >5 or <1 lifetime sexual partner)

HPV vaccine for males intent to treat population

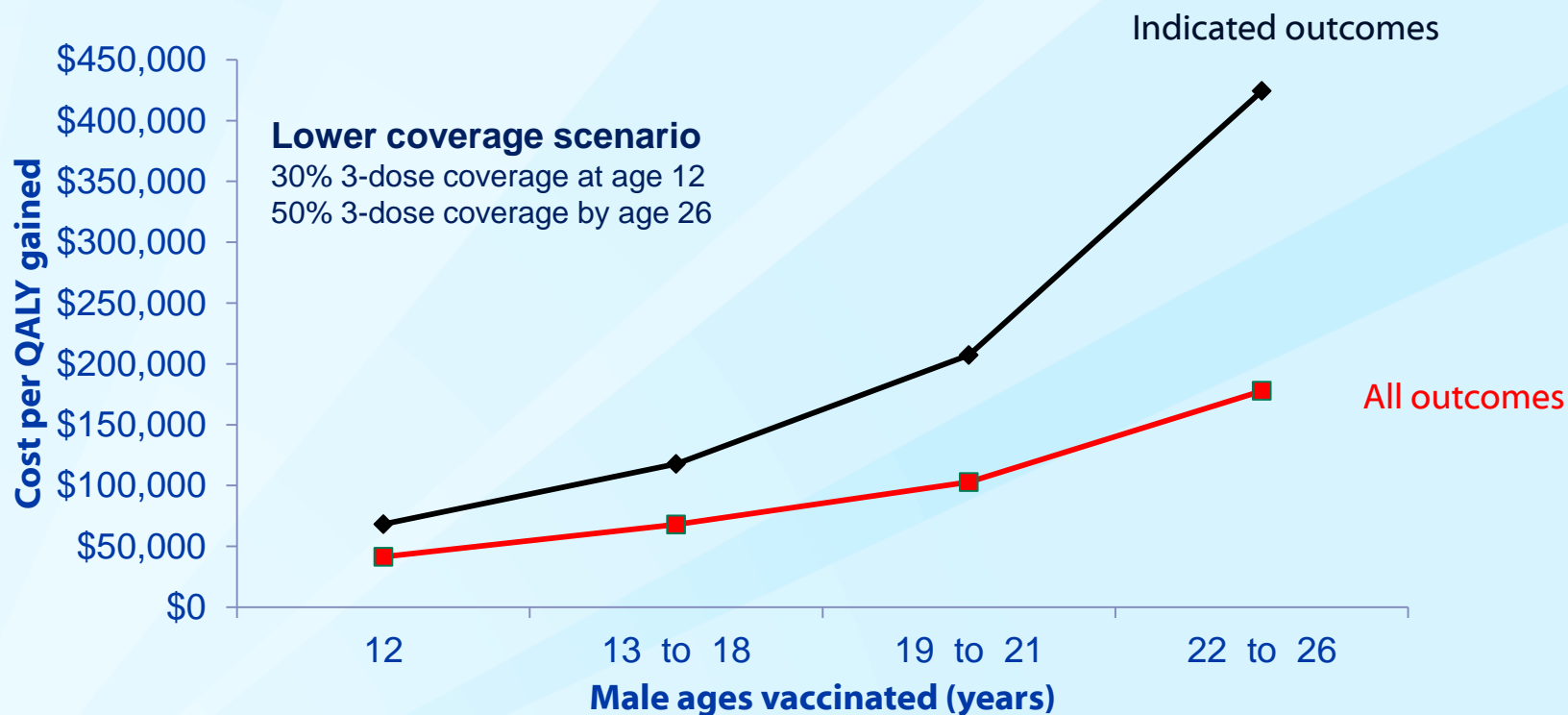
Outcome HPV 6, 11,16,18 related	No. of subjects (# studies)	Incidence in controls % (n/N)	Incidence in vaccinated % (n/N)	Vaccine efficacy % (95% CI)
Condyloma	3880 (1 RCT)	3.82% (74/1937)	1.23% (24/1943)	68.1% (48.8, 80.7)
AIN 1/2/3*	551 (1 RCT)	27.89% (77/276)	13.81% (38/275)	50.3% (25.7, 67.2)
AIN 2/3*	551 (1 RCT)	14.13% (39/276)	6.54% (18/275)	54.2% (18.0, 75.3)

*Clinical trial conducted in men who have sex with men

Reference: Package insert, Table 16 for outcomes of Condyloma, AIN1/2/3, and AIN2/3

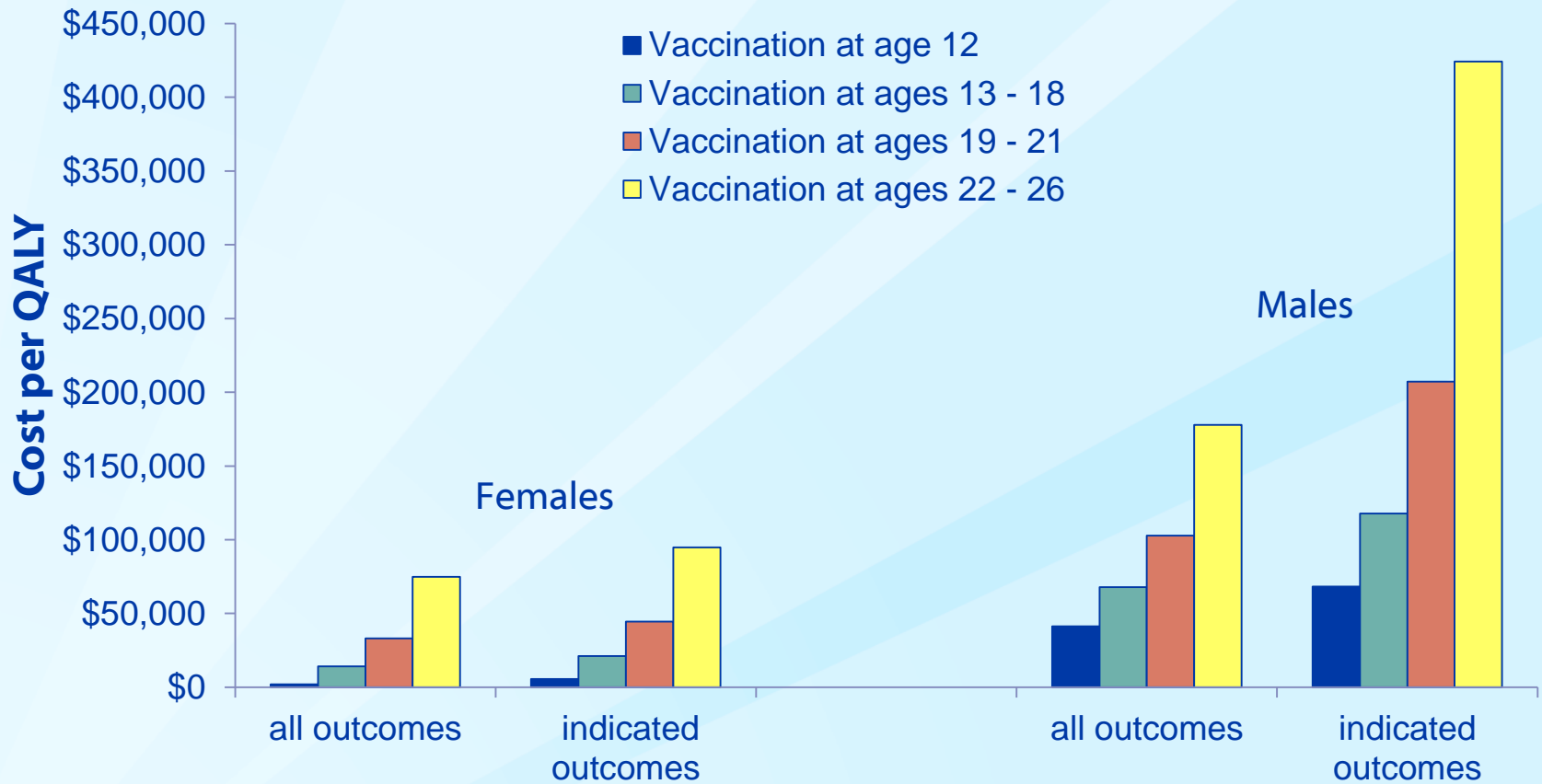
Cost-effectiveness of male catch-up vaccination

Incremental cost per QALY gained by adding males to female-only vaccination



“Indicated” outcomes include cervical outcomes, vaginal, vulvar, and anal cancers, and genital warts. All outcomes include indicated outcomes plus oropharyngeal cancer, penile cancer, and recurrent respiratory papillomatosis. For females aged 12 to 26 the same coverage assumptions listed above for males were used.

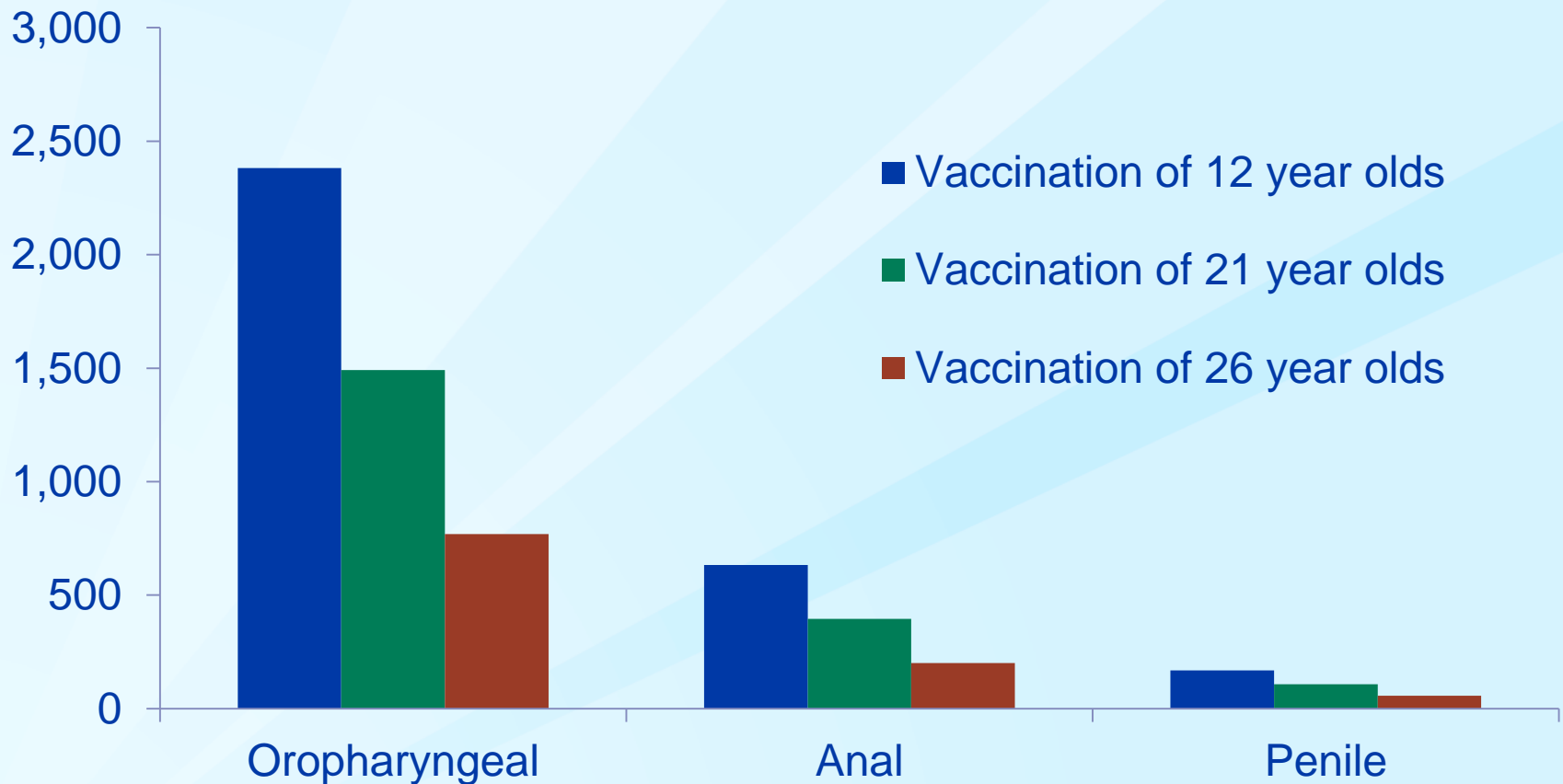
Cost per QALY gained by age at vaccination*



*Lower coverage scenario: 3-dose coverage 30% at age 12, 50% by age 26 (after ~ 20 yrs)

Vaccination of older age groups is incremental to vaccination of younger age groups. Results for male vaccination show the incremental cost-effectiveness of expanding male vaccination to include additional age groups, in the context of an existing vaccine program for females aged 12-26 years. Coverage assumptions apply to males and females. "Indicated" outcomes include cervical outcomes, vaginal, vulvar, and anal cancers, and genital warts. All outcomes include indicated outcomes plus oropharyngeal cancer, penile cancer, and recurrent respiratory papillomatosis. QALY: quality-adjusted life year.

Number of lifetime cancer cases averted by vaccinating 1 million males in a birth cohort



Excludes indirect effects (herd immunity). Outcomes are not discounted. Results obtained from Chesson et al model, Vaccine 2011. Vaccine efficacy was assumed to be 90% against HPV 6/11 genital warts and 75% against HPV 16/18 cancers in males.

Considerations for vaccinating males 13-26 years: Implementation issues

- Most implementation through age 18 years
- Implementation in >18 years:
 - NHANES (2007-2008):
 - 10.5% females aged 19-26 years
 - NHIS (2008, 2010): estimate of ~3% vaccine initiation in females aged 22-26 years
 - Although low vaccine initiation in ages 22-26 years, over \$100 million first year cost
 - Costs would decrease with increasing vaccination in younger age groups over time

Why prioritize youngest age group (<22 years) for HPV Vaccine?

- Cost/Qaly increases with increasing age of vaccination
 - Interest in best use of public health resources
- Inclusive of boys, young adults through college age

ACIP HPV WG member opinions

- Two primary options have been discussed—vaccination through age 26 years and vaccination through age 21 years (permissive 22-26 years)
- Work Group favors an approach that may support vaccination through age 26 years but emphasizes the youngest age group (<22 years) for vaccination
 - opportunities to provide greatest public health benefit, and use resources most effectively
- Harmonization of female and male recommendations
 - Benefits include communication, and “gender neutral” approach
 - Concern about change of female program, especially with recent vaccine implementation challenges

Quadrivalent HPV vaccine for males

vaccination through age 26 years or through age 21 years

Age 26

- Pro
 - Harmonization with current recommendations for females
 - Includes males <27 years, including MSM seeking care
- Con
 - Cost-effectiveness models show higher cost/QALY above age 21

Age 21

- Pro
 - Focus program on younger age group; greatest benefit and most cost-effective
 - Still inclusive of young adult men, including college students
- Con
 - Harmonization would require changing female recommendations through age 21
 - Uncertainty about insurance coverage for those who want vaccine

Draft Language

Recommendations for Vaccination Males 13-26 years

Option 1: Vaccination is recommended for males aged 13 through 26 years who have not been vaccinated previously or who have not completed the 3-dose series. Priority should be given to males aged <22 years as vaccination of young men and boys would provide the greatest benefit.

OR

Option 2: Vaccination is recommended for males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series. Males aged 22 through 26 years may be vaccinated. Priority should be given to males aged <22 years as vaccination of young men and boys would provide the greatest benefit.

Males	Female Recommendation Options
<p>Option 1 Through age 26</p>	<p>-No change</p> <p><i>or</i></p> <p>-Change: minor modification, addition of priority statement</p>
<p>Option 2 Through age 21</p>	<p>-No change</p> <p><i>or</i></p> <p>-Change: modification, "through age 21 years", may vaccinate age 22-26 years</p>

Current and Draft

Recommendations for Vaccination Females 13-26 years

Current

Vaccination is recommended for females aged 13 through 26 years who have not been vaccinated previously or who have not completed the 3-dose series.

Harmonized with Option 1

Vaccination is recommended for females aged 13 through 26 years who have not been vaccinated previously or who have not completed the 3-dose series.

Priority should be given to females aged <22 years as vaccination of young women and girls would provide the greatest benefit.

Harmonized with Option 2

Vaccination is recommended for females aged 13 through **21 years** who have not been vaccinated previously or who have not completed the 3-dose series.

Females aged 22 through 26 years may be vaccinated. Priority should be given to females aged <22 years as vaccination of young women and girls would provide the greatest benefit.

Draft Language

Recommendations for Vaccination Males 13-26 years

Option 1: Vaccination is recommended for males aged 13 through 26 years who have not been vaccinated previously or who have not completed the 3-dose series. Priority should be given to males aged <22 years as vaccination of young men and boys would provide the greatest benefit.

OR

Option 2: Vaccination is recommended for males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series. Males aged 22 through 26 years may be vaccinated. Priority should be given to males aged <22 years as vaccination of young men and boys would provide the greatest benefit.

Vote

Males 13-26 years

SPECIAL POPULATIONS

HPV vaccine in MSM, and HIV-infected

- Burden of HPV-associated disease and cancer highest in MSM and HIV-infected persons (genital warts, anal intraepithelial neoplasia, anal cancers)
- No routine screening for anal cancers
- Non live vaccine
- Cost-effective through age 26 years (<\$50,000/QALY)
- 2 completed studies in HIV-infected (HIV infected boys/girls, HIV infected men) found vaccine to be safe and immunogenic

MJ Levin et al, JAIDS 2010, Wilkins et al, JID 2010, Kim J et al, Lancet ID 2010

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.