Effectiveness of "catch-up" HPV vaccination on incident cervical neoplasia in a U.S. healthcare setting

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HPV vaccination

- Routine HPV vaccination recommended for boys and girls, ages 11 or 12. Vaccination can be initiated as early as 9 years and with "catch-up" vaccination up to 26 for girls and 21 for boys¹
- 2-dose schedule (0, 6–12 months) now recommended when series initiated at ages 9-14, and a 3-dose schedule (0, 1–2, 6 months) when initiated after age 15¹
- Limited HPV vaccine effectiveness studies evaluating clinical outcomes such as cervical neoplasia

1 MMWR. December 16, 2016 / 65(49);1405–1408





Objective

To evaluate population effectiveness of the HPV vaccine during "catch-up" ages to reduce incident cervical intraepithelial neoplasia 2, 3, adenocarcinoma *in situ* or cancer (CIN2+). We aimed to evaluate HPV vaccine effectiveness overall, by age at first vaccine dose, and number of doses.

This analysis is part of the CERVICCS study, a cost-effectiveness analysis designed to evaluate whether HPV vaccinated women should be screened differently than average-risk women (NCI R01CA169093, PI Sawaya).





Study setting and design

- Setting: Kaiser Permanente (KP) Northern California
- Design: nested case-control study with incidence-density sampling
 - <u>Eligibility</u>: Adult women, aged ≤26 years at some point during 2006-2014
 - <u>Cases</u>: incident CIN 2, 3 or cancer (CIN 2+)
 - <u>Controls</u>: 5:1 matched controls individually matched by age, diagnosis date, years in health plan, and date of first health plan Pap test (all +/- 1 year)
- Data: clinical variables from electronic health record





HPV vaccine history

1. Any vaccine history (≥1 dose) vs. none (ref)

2. By age at first dose 14-17 years; 18-20 years; 21-30 years None (ref)

3. By # of doses
≥3 doses; 2 doses; 1 dose
None (ref)

4. By age at first dose and # of doses 14-17 years and ≥3 doses 18-20 years and ≥3 doses 21-30 years and ≥3 doses 14-17 years and <3 doses 18-20 years and <3 doses 21-30 years and <3 doses None (ref)





Cervical neoplasia

Category	n (%)			
CIN 2	874 (20)		_	
CIN 2/3	1,634 (38)			
CIN 3	1,744 (40)	٦		CIN2+
Adenocarcinoma in situ	82 (2)			► N=4,357
Adenocarcinoma	9 (0)		CIN3+	
Squamous cell carcinoma	13 (0)		N=1,849	
Other cancer	1 (0)			





Data analysis

Confounders

Factor	CIN risk	CIN detection
Smoking	\checkmark	
Parity	\checkmark	
Sexually transmitted infections ¹	\checkmark	\checkmark
Immunosuppressed ²	\checkmark	\checkmark
Hormone replacement therapy / oral contraceptives	\checkmark	\checkmark
# outpatient visits		\checkmark
Race/ethnicity		\checkmark
¹ Recent (<18 months) herpes, gonorrhea, syphilis, chlamydia ² HIV-infected, solid organ transplant, or recent immunosuppressive	therapy	

Statistical analysis: Conditional logistic regression to estimate odds ratios, which represent unbiased estimates of rate ratios with incidence density sampling of controls





Baseline characteristics

Characteristic	Cases	Controls
Ν	4,357	21,781
Mean age, years	26	26
Healthplan membership, years	7.4	7.5
Continuous healthplan membership since 2006, %	57	57
Outpatient visits, mean/year	7.5	6.9
Race/ethnicity, % White Black/African-American Hispanic Other Unknown	49 11 22 15 3	44 10 23 19 4
Recent (<18 months) smoking	24	17
Recent (<18 months) hormonal therapy / oral contraceptive use	66	58
Recent (<18 months) sexually transmitted infection	7	4
3 or more live births, %	5	6
Immunosuppressed, %	12	12







Vaccine history, CIN2+ cases and controls

Vaccine history	Cases	Controls
Any vaccine history, n (%)	429 (9.9)	2,408 (11.1)
By age at first vaccine dose, n (%)		
No vaccine history	3,928 (90.1)	19,373 (89.0)
14-17 years	77 (1.8)	516 (2.4)
18-20 years	113 (2.6)	686 (3.1)
21-30 years	239 (5.5)	1,206 (5.5)
By # of doses, n (%)		
No vaccine history	3,928 (90.1)	19,373 (89.0)
1 dose	118 (2.7)	638 (2.9)
2 doses	97 (2.2)	457 (2.1)
≥3 doses	214 (4.9)	1,313 (6.0)





Rate ratios of <u>CIN2+</u> by vaccine history

	Unadjusted ¹		Adjusted ¹	
	RR (95% CI)	Р	RR (95% CI)	Р
Any vaccine history	0.86 (0.76, 0.96)	0.010	0.82 (0.73, 0.93)	0.001
By age at first vaccine dose				
14-17 years	0.62 (0.47, 0.83)	0.001	0.61 (0.45, 0.81)	<0.001
18-20 years	0.76 (0.61, 0.94)	0.012	0.72 (0.58, 0.90)	0.003
21-30 years	0.98 (0.84, 1.13)	0.75	0.94 (0.81, 1.09)	0.40
By # of doses				
≥3 doses	0.78 (0.66, 0.91)	0.002	0.75 (0.64, 0.89)	<0.001
2 doses	1.02 (0.82, 1.28)	0.85	0.98 (0.78, 1.23)	0.88
1 dose	0.89 (0.73, 1.09)	0.26	0.84 (0.68, 1.03)	0.088
By age at first dose and # of doses				
14-17 years and ≥3 doses	0.52 (0.36,0.74)	<0.001	0.51 (0.36, 0.74)	<0.001
18-20 years and ≥3 doses	0.68 (0.50,0.91)	0.009	0.65 (0.49, 0.88)	0.005
21-30 years and ≥3 doses	0.95 (0.78,1.17)	0.64	0.92 (0.75, 1.13)	0.44
14-17 years and <3 doses	0.80 (0.54,1.19)	0.27	0.77 (0.52, 1.14)	0.19
18-20 years and <3 doses	0.86 (0.64,1.15)	0.31	0.80 (0.59, 1.08)	0.15
21-30 years and <3 doses	1.00 (0.82,1.22)	0.99	0.95 (0.78, 1.16)	0.63

¹Rate ratios (RR) from conditional logistic regression; no vaccine history reference group for all RRs.





Rate ratios of <u>CIN3+</u> by vaccine history

	Unadjusted ¹		Adjusted ¹		
	RR (95% CI)	Р	RR (95% CI)	Ρ	
Any vaccine history	0.82 (0.68, 1.00)	0.049	0.77 (0.63, 0.94)	0.011	
By age at first vaccine dose					
14-17 years	0.45 (0.27, 0.76)	0.003	0.44 (0.26, 0.74)	0.002	
18-20 years	0.84 (0.59, 1.21)	0.35	0.75 (0.52, 1.08)	0.12	
21-30 years	0.92 (0.73, 1.17)	0.50	0.88 (0.69, 1.12)	0.29	
By # of doses					
≥3 doses	0.68 (0.52, 0.90)	0.006	0.64 (0.48, 0.84)	0.001	
2 doses	1.02 (0.71, 1.48)	0.90	0.97 (0.67, 1.41)	0.87	
1 dose	0.94 (0.68, 1.30)	0.71	0.89 (0.64, 1.24)	0.49	
By age at first dose and # of doses					
14-17 years and ≥3 doses	0.29 (0.14,0.60)	<0.001	0.27 (0.13, 0.56)	<0.001	
18-20 years and ≥3 doses	0.67 (0.41,1.10)	0.11	0.58 (0.36, 0.96)	0.034	
21-30 years and ≥3 doses	0.88 (0.62,1.25)	0.48	0.85 (0.60, 1.20)	0.36	
14-17 years and <3 doses	0.77 (0.40,1.49)	0.43	0.79 (0.40, 1.55)	0.49	
18-20 years and <3 doses	1.08 (0.66,1.75)	0.76	0.97 (0.60, 1.59)	0.92	
21-30 years and <3 doses	0.95 (0.70,1.30)	0.76	0.90 (0.65, 1.23)	0.50	

¹Rate ratios (RR) from conditional logistic regression; no vaccine history reference group for all RRs.





Summary

- Overall 18% reduction in CIN2+ and 23% reduction in CIN3+ for vaccinated women in a large integrated healthcare system
- Best protection observed for women initiating 14-17 years of age and with ≥3 doses, with a 49% reduction in CIN2+ and 73% reduction in CIN3+
- Limited CIN protection for <3 doses
- Limited CIN protection for women initiating vaccination at age ≥21 years





Strengths and limitations

Strengths

- Uniform access to comprehensive care, including cervical cancer screening
- Generalizable to the broader insured population

Limitations

- Imperfect measurement of risk factors
- Potential HPV vaccination misclassification; however a pre-planned sensitivity analysis restricting to women who were members since 2006 did not change inferences:

<u>Original</u>: RR=0.82, 95% CI=0.73-0.93 <u>Restricted</u>: RR=0.69, 95% CI=0.59-0.81





Conclusions

Our results lend support to "catch-up" HPV vaccination of females aged 14-20 years, but not ≥21 years, to prevent CIN2+ or CIN3+. No evidence found for effectiveness of <3 doses.





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