Effectiveness of Human Papillomavirus (HPV) Vaccine against HPV16/18-positive High-grade Cervical Lesions

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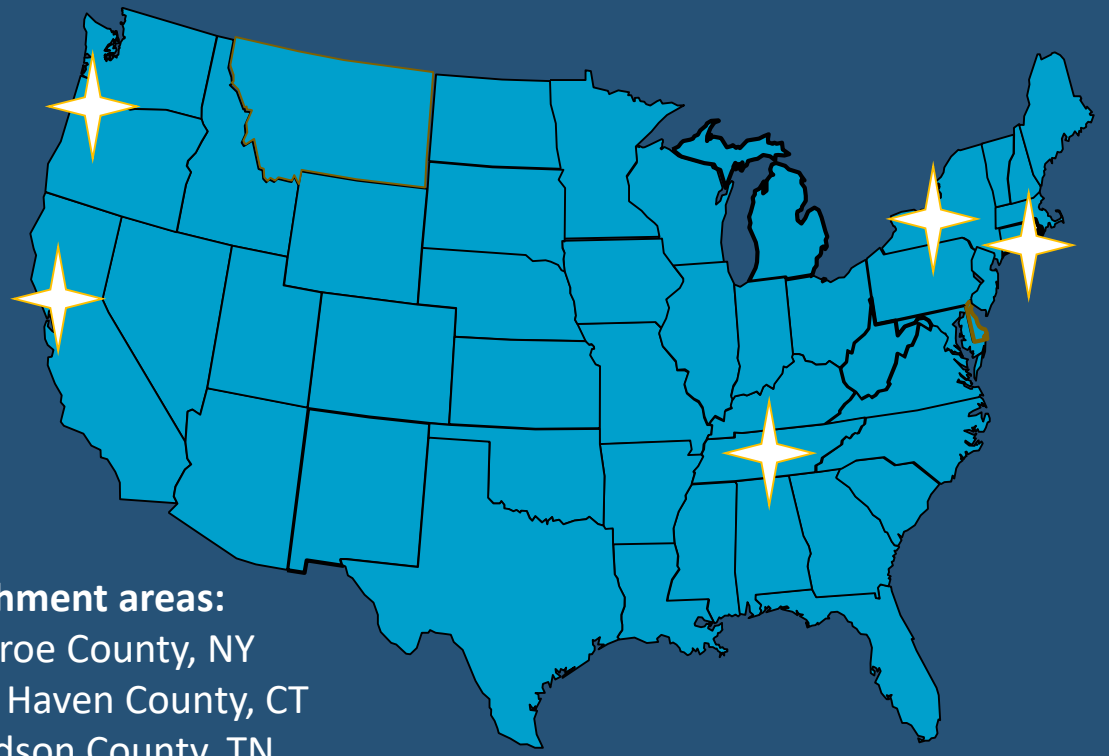
Background

- Randomized controlled trials demonstrated high efficacy of HPV vaccines against high-grade cervical lesions
- To date, real-world vaccine effectiveness (VE) has been demonstrated for HPV prevalence, anogenital warts, and high-grade cervical lesions
- Variety of study designs and populations
- Few studies have evaluated VE against HPV type-specific cervical lesions

HPV-IMPACT: Detection of cervical cancer precursors and associated HPV types



Catchment areas:
Monroe County, NY
New Haven County, CT
Davidson County, TN
8-City Area (Alameda County), CA
28-Zipcode Area (Portland metro), OR

- HPV Vaccine Impact Monitoring Program (HPV-IMPACT)
- Part of Emerging Infections Program
- Active surveillance for cervical precancers in women ≥18 years in catchment area
- Determine HPV types in lesions from subset of women 18–39 years, vaccine history
- Estimate annual cervical cancer screening

Case definition

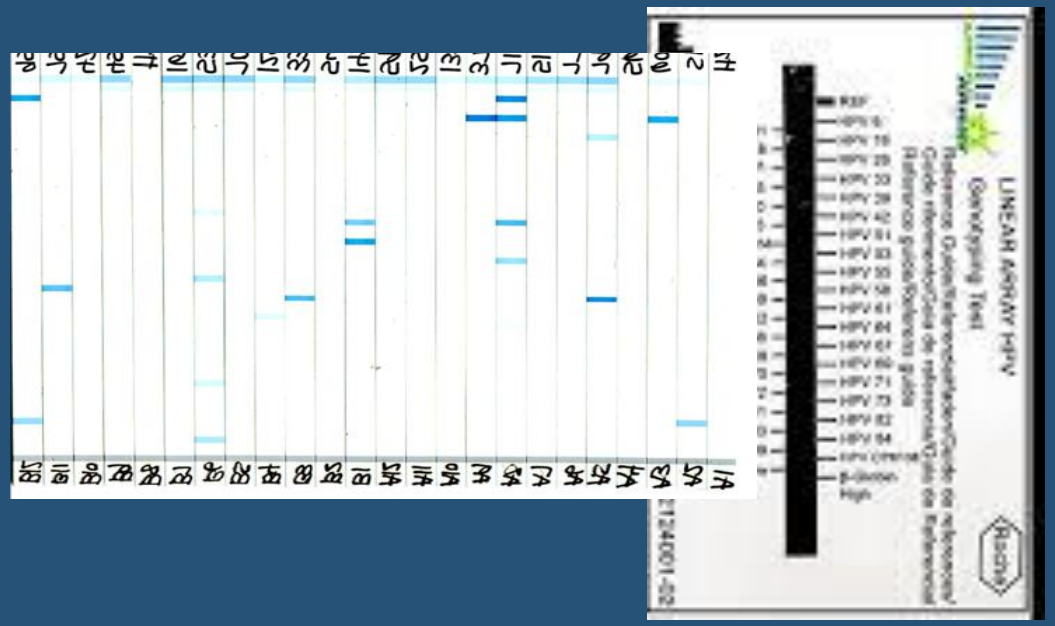
- **CIN2+**: cervical intraepithelial neoplasia (CIN) grades 2, 3, 2/3, and adenocarcinoma in situ (AIS)
- Woman aged ≥18 years
- Resident of catchment area
- Year 2008 or later

Data elements

- All cases
  - Demographics (date of birth, race, insurance)
  - Diagnosis
- Additional data elements for cases aged 18–39 years
  - Cervical cancer screening event that led to diagnosis
  - History of HPV vaccination
  - Residual tissue specimen obtained for HPV typing

HPV typing

- At each surveillance site
  - Tissue blocks cut per CDC protocol
  - Specimens sent to CDC
- At CDC HPV laboratory
  - Slides reviewed to confirm representative lesion present
  - HPV typing: 37 HPV types



Objective

- To estimate vaccine effectiveness against vaccine-type CIN2+ by timing of vaccination relative to outcome ascertainment
  - Interval between vaccination and screening test that led to CIN2+ diagnosis, or vaccination-to-trigger Pap interval

Inclusion criteria

- Diagnosed with CIN2+ in 2008–2014
- Age-eligible for vaccination
- Known date of screening test that led to CIN2+ diagnosis
- Known date of HPV vaccination
- Valid HPV typing result

Vaccination history: vaccinated, unvaccinated, unknown

- Verified through medical records and vaccine registries
- Vaccinated, ≥1 dose of HPV vaccine:
  - History of vaccination noted in medical record or registry
  - Started vaccine series at ages 9-26 years
- Unvaccinated:
  - Medical record documented lack of HPV vaccination
  - Continuously enrolled in insurance plan and no claim
- Unknown: excluded from analysis

Time between vaccination and outcome assessment

- HPV vaccine must be administered prior to infection to be effective
- It can take years after infection for CIN2+ lesions to develop
- With longer interval, higher likelihood that vaccination occurred prior to infection responsible for CIN2+ lesion
  - We evaluated intervals <1 month/unvaccinated, 1–11 months, 12–23 months, 24–35 months, 36–47 months, and ≥48 months

Vaccine effectiveness (VE) design

- Indirect cohort, aka test-negative design or Broome method
- Variation on case-control study that uses only cases of disease
  - "Cases": CIN2+ with vaccine type (HPV16/18 positive)
  - "Controls": CIN2+ without vaccine type (HPV16/18 negative)

VE analysis

- Logistic regression
  - Estimate odds ratio by vaccination-to-trigger Pap interval
  - Adjust for site, race, insurance
  - VE = 1 – aOR
- Evaluated VE stratified by birth cohort group
  - Tested statistical interaction
  - Younger cohort, born 1987–1995
  - Older cohort, born 1979–1986

Interval between vaccination and trigger Pap (N=3310)

Interval	N	%
Vaccinated <1 month before trigger or no vaccine	2374	71.7
Never vaccinated	1801	54.4
Vaccinated after trigger	544	0.9
Vaccinated <1 month before trigger	29	22.9
Vaccinated ≥1 month before trigger	936	28.3
1-11 months	170	5.1
12-23 months	195	5.9
24-35 months	146	4.4
36-47 months	133	4.0
≥48 months	292	8.8

Characteristics of CIN2+ cases by vaccination history

Characteristic	All %	Vaccinated %	Unvaccinated %	P-Value
Diagnosis years				<0.01
2008-2010	52	38	57	
2011-2014	48	62	43	
Age at diagnosis (years)				<0.01
18-20	7	8	6	
21-24	40	47	37	
25-29	43	41	43	
30-34	11	4	14	
Birth cohort group				<0.01
1987-1994	35	50	29	
1979-1986	65	50	71	

Characteristics of CIN2+ cases by vaccination history

Characteristic	All %	Vaccinated %	Unvaccinated %	P-Value
Diagnosis				<0.01
CIN2	55	60	53	
CIN2/3	14	14	15	
CIN3/AIS	31	26	32	
Race/ethnicity				0.09
Non-Hispanic White	57	62	56	
Non-Hispanic Black	17	17	16	
Hispanic	10	8	11	
Asian	3	3	2	
Other	13	12	14	
Insurance				<0.01
Private	55	62	53	
Public	25	19	27	
None/other/missing	20	19	21	

Vaccine effectiveness by vaccination-to-trigger interval

Months before screening	Cases (16/18+) N (%)	Controls (16/18-) N (%)	OR	95% CI	aOR*	95% CI	VE
<1 mo. or no vaccine	1228 (78.0)	1146 (68.8)	1.00		1.00		
1-11 months	94 (6.0)	76 (4.4)	1.15	(0.84-1.58)	1.13	(0.83-1.56)	
12-23 months	91 (5.8)	104 (6.0)	0.82	(0.61-1.09)	0.77	(0.57-1.04)	
24-35 months	55 (3.5)	91 (5.2)	0.56	(0.40-0.80)	0.56	(0.40-0.80)	44%
36-47 months	40 (2.6)	93 (5.3)	0.40	(0.28-0.59)	0.39	(0.27-0.58)	61%
48+ months	61 (3.9)	231 (13.3)	0.25	(0.18-0.33)	0.24	(0.18-0.33)	76%

*Adjusted for insurance, race, site.

Differences by birth cohort group

Descriptor	Born 1987-1994 "Younger cohort"	Born 1979-1986 "Older cohort"
Ages at diagnosis with CIN2+	18-26 years	22-34 years
Opportunity to be vaccinated	12-26 years	20-26 years
Median [IQR] age at vaccination	19 [17-25] years	23 [22-25] years
% vaccinated	20%	11%

Vaccine effectiveness by vaccination-to-trigger interval, stratified by birth cohort

	Younger Cohort (born 1987-1995)*		Older Cohort (born 1979-1986)*	
Months before screening	**aOR (95% CI)****	**Vaccine effectiveness**	**aOR (95% CI)****	**Vaccine effectiveness**
<1 mo. or no vaccine	1.00	--	1.00	--
1-11 months	0.85 (0.53-1.36)	--	1.46 (0.94-2.25)	--
12-23 months	0.69 (0.43-1.10)	--	0.84 (0.57-1.23)	--
24-35 months	0.53 (0.31-0.89)	47%	0.59 (0.37-0.94)	41%
36-47 months	0.26 (0.14-0.48)	74%	0.55 (0.33-0.90)	45%
48+ months	0.16 (0.11-0.25)	84%	0.41 (0.27-0.63)	59%

*P-value for cohort x vaccination interaction = 0.008. **Adjusted for insurance, race, site.

Summary of vaccine effectiveness findings

- Significant effectiveness against HPV16/18 positive CIN2+ when vaccine given at least 24 months before screening
  - 44% at 24-35 months
  - 61% at 36-47 months
  - 76% at ≥48 months
- Younger cohort had higher VE than older cohort
  - Younger cohort born 1987-1994: VE range 47-84% (24-48+ months)
  - Older cohort born 1979-1986: VE range 41-59% (24-48+ months)

Limitations

- Many women missing complete vaccination history
- Few women vaccinated at recommended age

Conclusion

- Vaccine effectiveness against HPV16/18 positive CIN2+ significant when vaccine administered at least 24 months before CIN2+ diagnosis
- Higher effectiveness in younger cohort and with longer intervals consistent with high efficacy seen in trials in per protocol populations
- Affirms importance of vaccination at younger ages, before exposure to HPV
- Continued monitoring needed

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