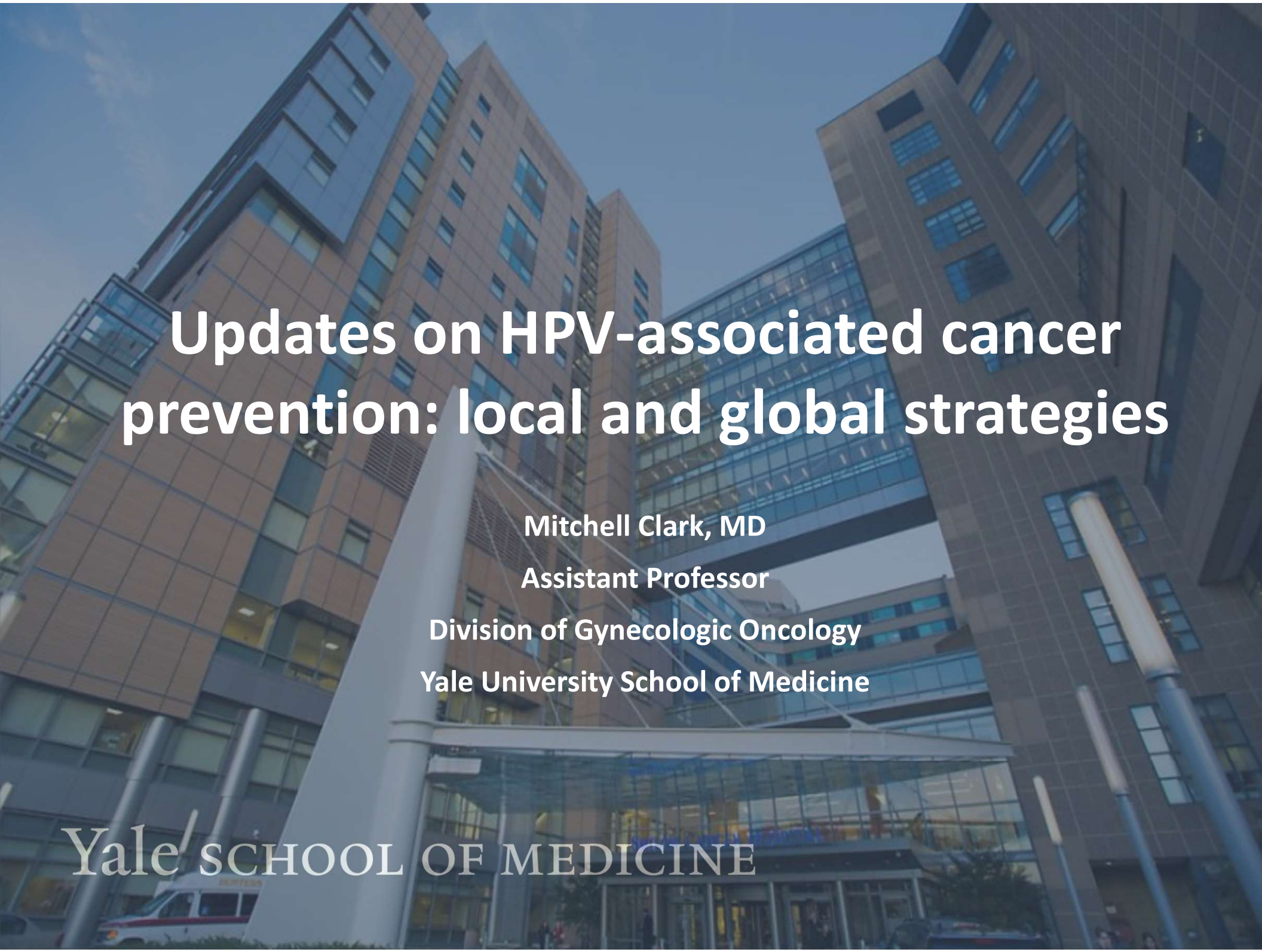
Updates on HPV-associated cancer prevention: local and global strategies
Mitchell Clark, MD
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Yale SCHOOL OF MEDICINE

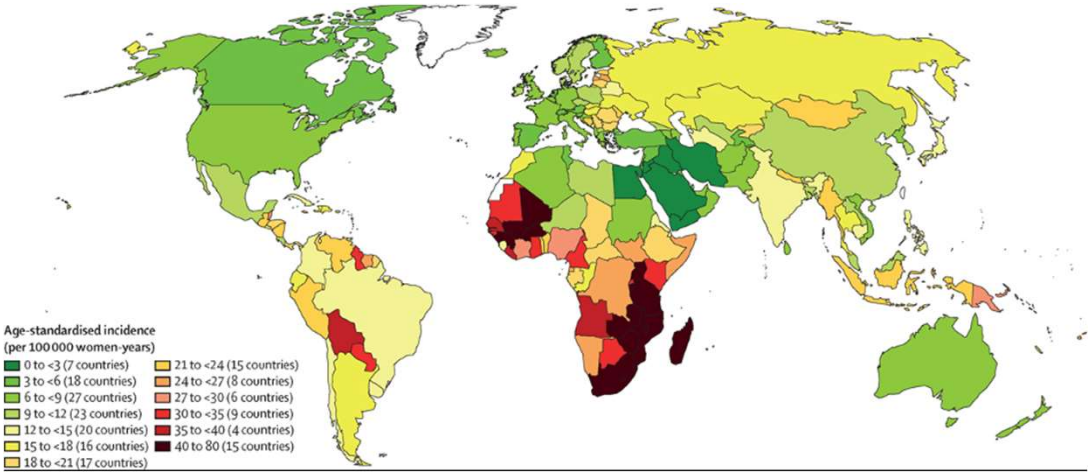
Disclosures

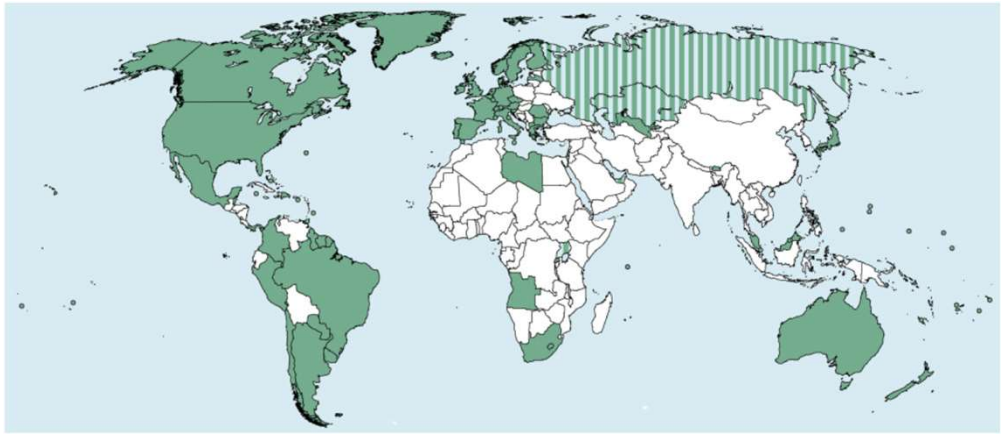
I have no financial disclosures relevant to the content of this presentation.

I will be discussing off-label use of some treatments or medications.

Worldwide Burden of Cervical Cancer

- 4th most common cause of cancer in women
- In 2018 570,000 women diagnosed; 311,000 died
- 99% of cervical cancers are related to HPV
- Despite increase in vaccination programs, few include low, low-middle income countries



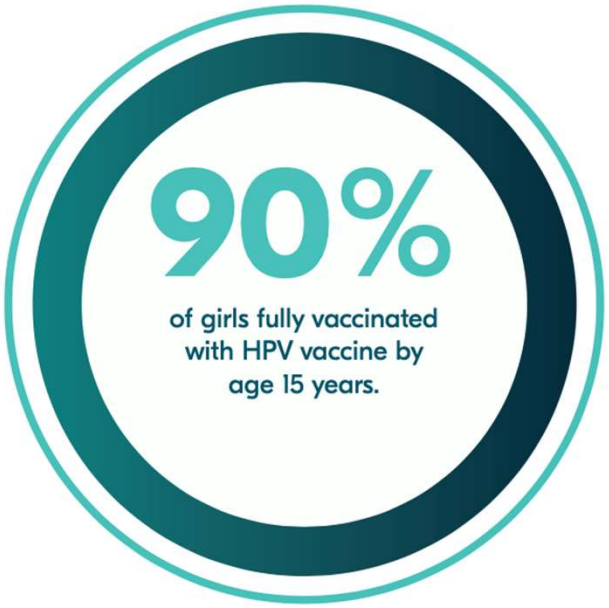


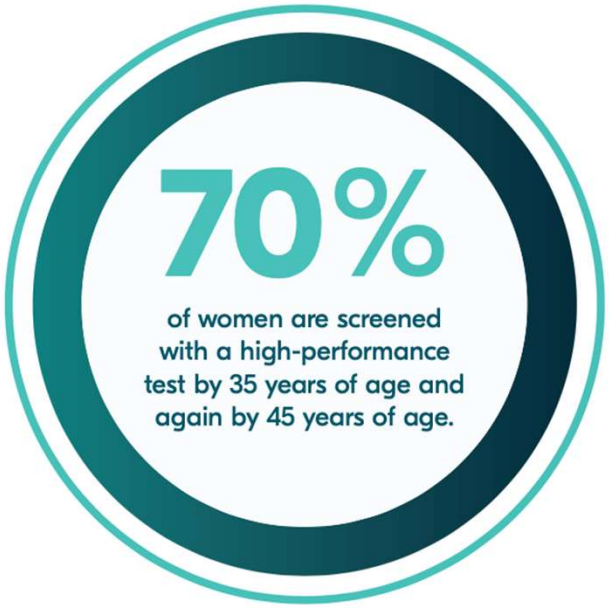
Countries that have introduced a publicly funded national human papillomavirus vaccination programme since 2006, by year

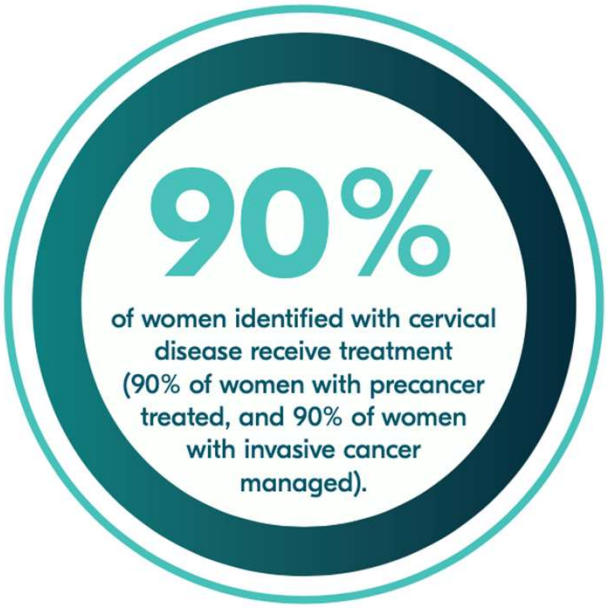
Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, Bray F. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Health. 2020 Feb;8(2):e191-e203.

https://www.who.int/health-topics/cervical-cancer#tab=tab_1

World Health Organization

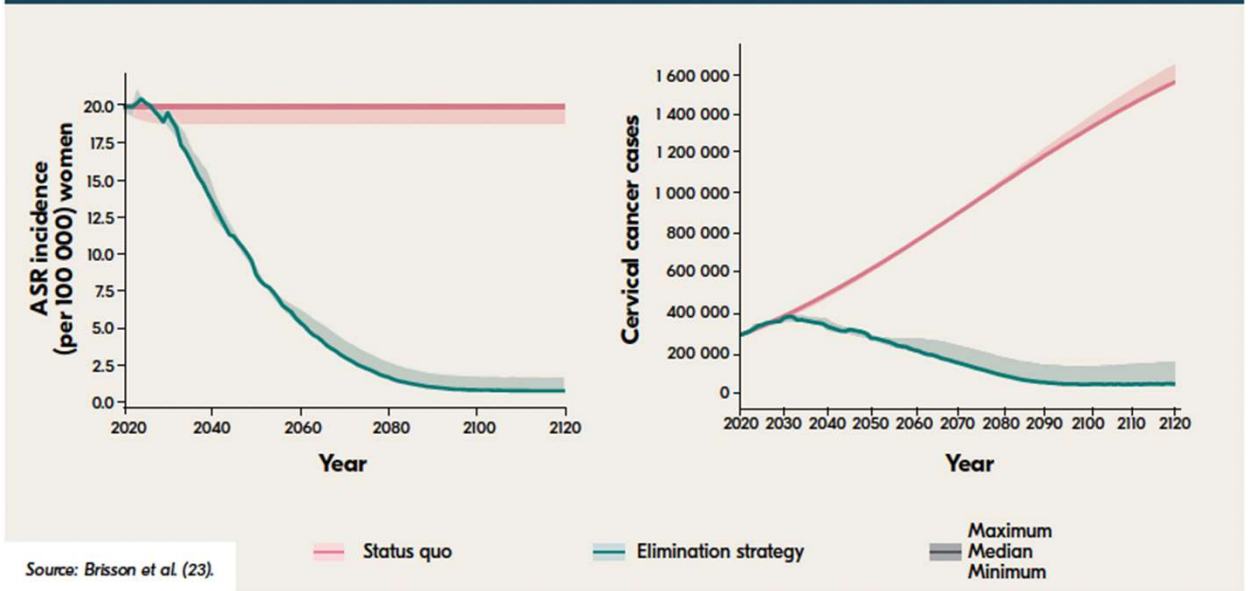






https://www.who.int/publications/i/item/9789240014107

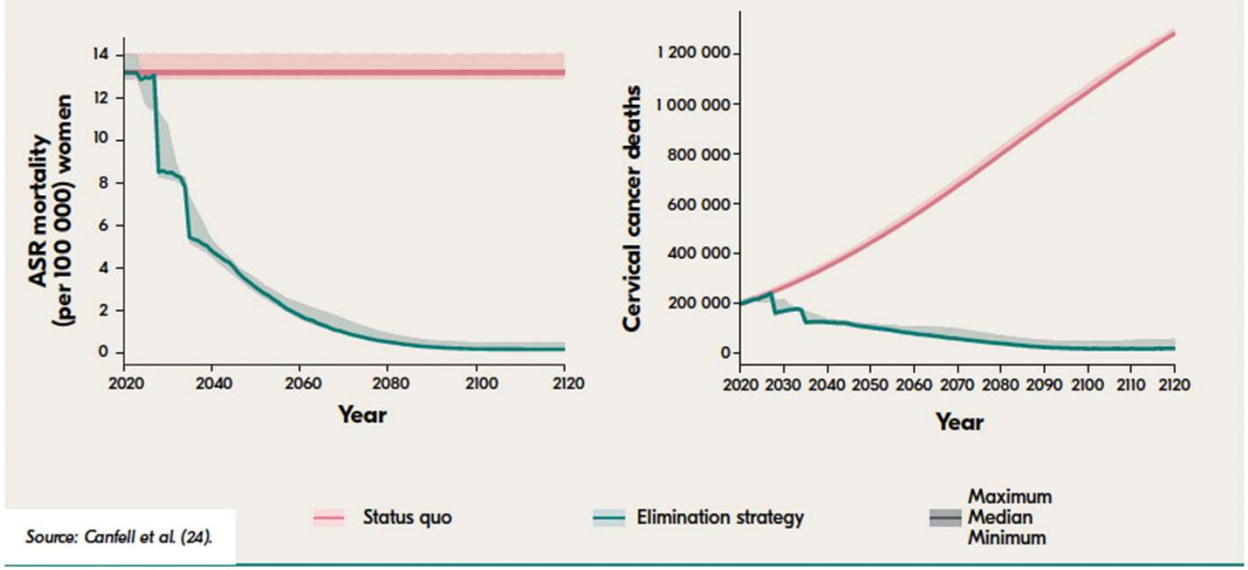
Fig. 7. Cervical cancer incidence rate and cervical cancer case projections in 78 low- and lower-middle-income countries, 2020–2120, by elimination strategy and with status quo



Source: Brisson et al. (23).

Achieving the 90-70-90 targets by 2030 would mean that median reduction in cervical cancer incidence rate would be 2%, 42% and 97% by 2030, 2045 and 2120, respectively, resulting in 74 million cases averted (Fig. 7).

Fig. 8. Cervical cancer mortality (age-standardized) rate and cervical cancer death projections in 78 low- and lower-middle-income countries, 2020–2120, by elimination strategy and with status quo

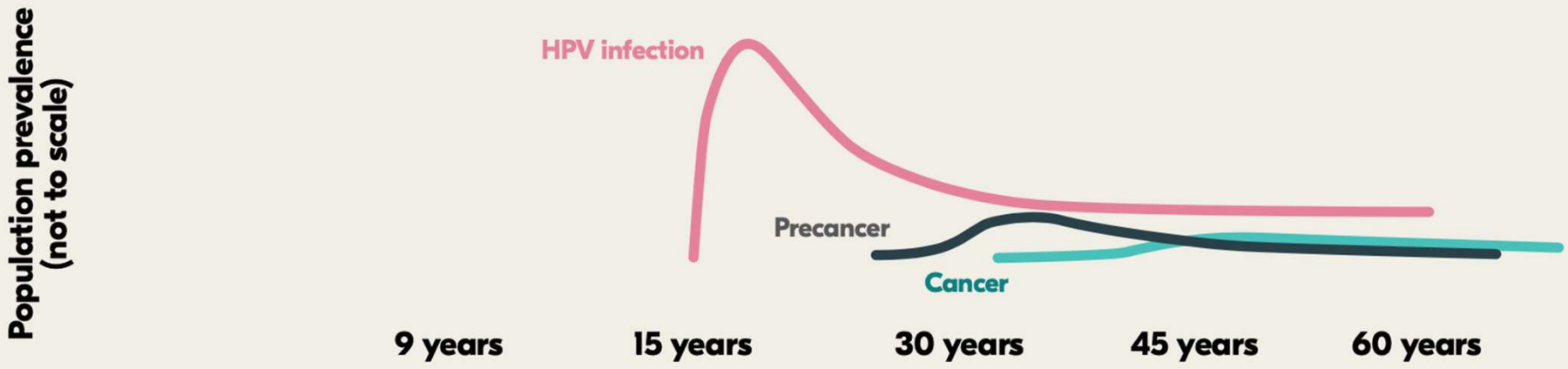


Source: Canfell et al. (24).

Correspondingly, the cumulative number of cervical cancer deaths averted would be about 2 million, 5 million and over 62 million by 2040, 2050 and 2120, respectively (Fig. 8)

World Health Organization

Fig. 9. Life-course approach to cervical cancer interventions



Primary Prevention

Girls 9–14 years

- HPV vaccination

Girls and boys, as appropriate

- Health information and warnings about tobacco use
- Sexuality education tailored to age and culture
- Condom promotion/provision for those engaged in sexual activity
- Male circumcision

Secondary Prevention

Women > 30 years of age

- Screening with a high-performance test equivalent to or better than HPV test
- Followed by immediate treatment or as quickly as possible, of precancerous lesions.

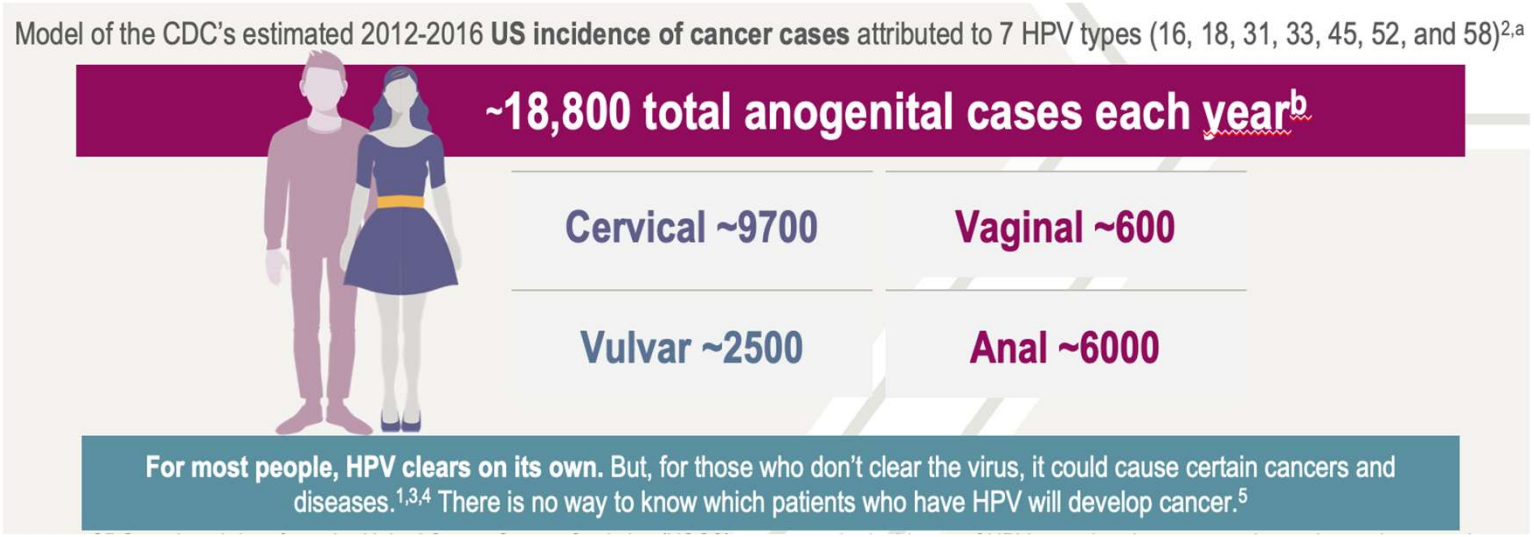
Tertiary Prevention

All women, as needed

Treatment of invasive cancer at any age

- Surgery
- Radiotherapy
- Chemotherapy
- Palliative care

Not just an international problem…



Efficacy of the HPV vaccine on anogenital processes

5 AAHS-CONTROLLED CLINICAL STUDIES

16–26 years old

20,541 FEMALES | 4055 MALES

Vulvar cancer
HPV 16- or 18-related VIN 2/3
100% n=7772

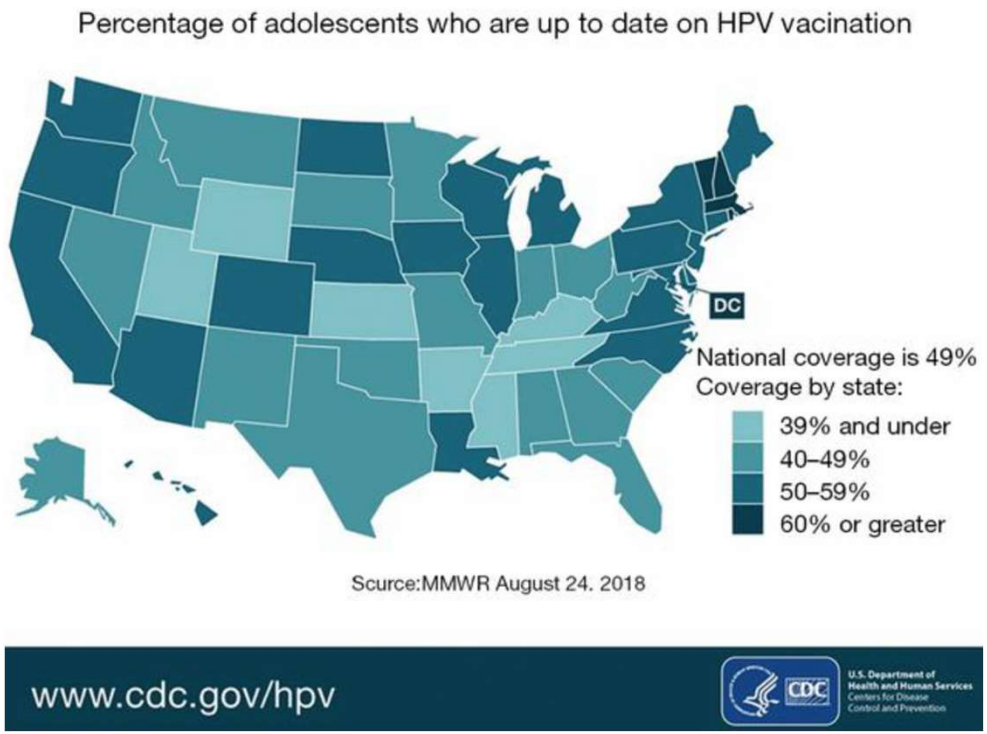
Vaginal cancer
HPV 16- or 18-related VaIN 2/3
100% n=7772

Cervical cancer
HPV 16- or 18-related CIN 2/3 or AIS
98% n=8493

Genital warts
HPV 6-, 11-, 16-, or 18-related genital warts
99% IN FEMALES n=7900
89% IN MALES n=1394

Anal cancer in males
HPV 6-, 11-, 16-, or 18-related AIN 2/3
75% n=194

State-wide vaccination rates



CT Vaccination Rates as of 2018

	Time Period	Current Actual Value	Current Target Value	Current Trend	Baseline % Change
Estimated HPV vaccination coverage for female adolescents 13 to 17 years of age in Connecticut. (HCT2020)	2018	54.7	52.3	↘ 1	135% ↗
Estimated HPV vaccination coverage for male adolescents 13 to 17 years of age in Connecticut. (HCT2020)	2018	51.6	10.2	↘ 1	507% ↗

FDA HPV Vaccination Indications

- Indicated in **girls and women 9 through 45 years of age** for the prevention of the following diseases:
  - Cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers caused by Human Papillomavirus (HPV)
  - Genital warts (condyloma acuminata) caused by HPV types 6 and 11.
  - CIN, VIN, VAIN, AIN

- Indicated in **boys and men 9 through 45 years of age** for the prevention of the following diseases:
  - Anal, oropharyngeal and other head and neck cancers
  - Genital warts (condyloma acuminata) caused by HPV types 6 and 11.
  - Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

FUTURE III:

British Journal of Cancer (2011) 105, 28 – 37

www.bjcancer.com

BJC OPEN

End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24–45 years of age

X Castellsagué*,[1], N Muñoz[2], P Pitisuttithum[3], D Ferris[4], J Monsonego[5], K Ault[6], J Luna[2], E Myers[7], S Mallary[8], OM Bautista[8], J Bryan[8], S Vuocolo[8], RM Haupt[8] and A Saah[8]

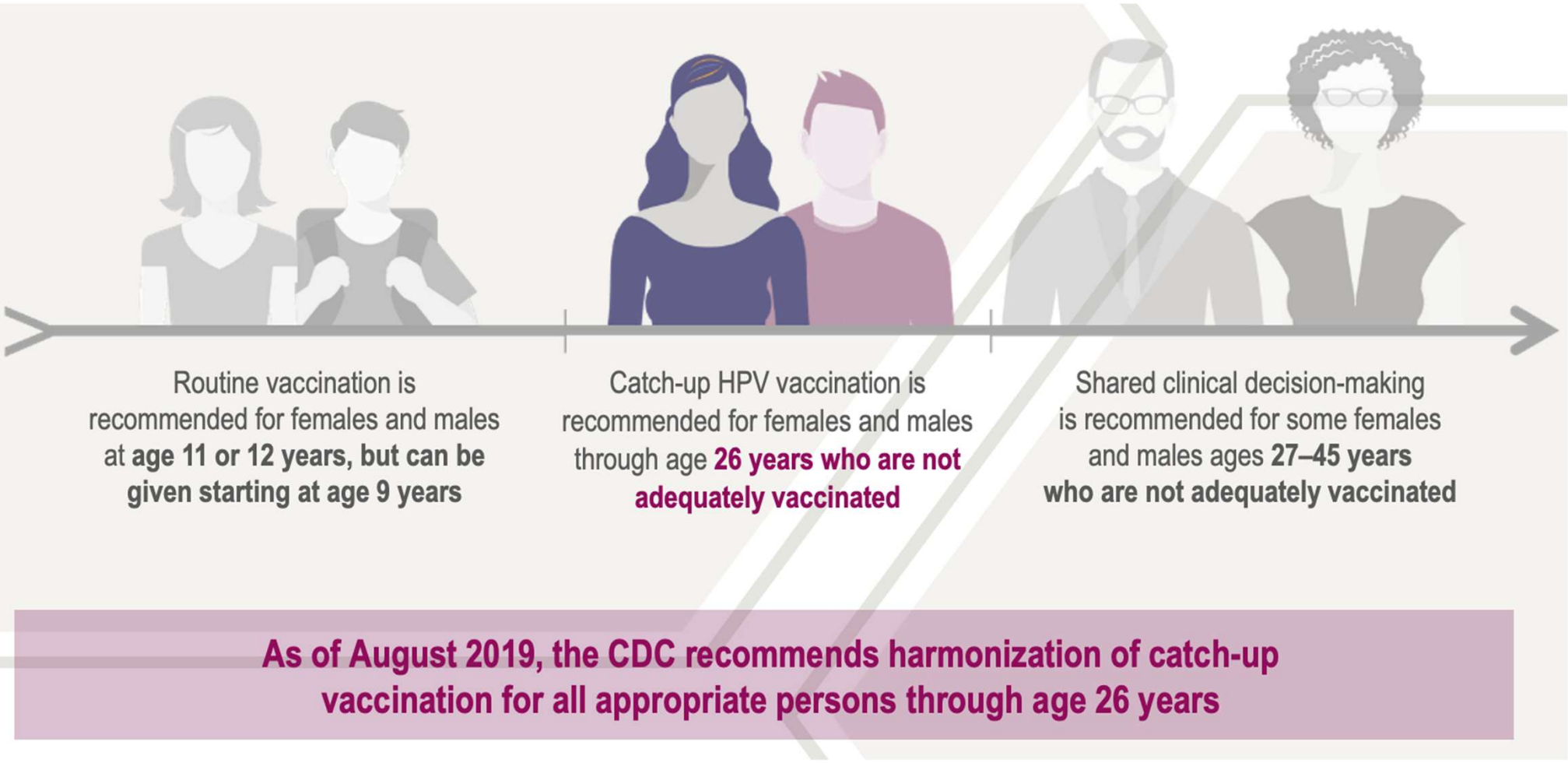
- Women aged 24-45 with no recent (5 years) history of anogenital warts of cervical dysplasia
- Randomized to 4-valent vaccine or placebo
- Outcomes of Interest:
  - 1) the combined incidence of HPV 6-, 11-, 16-, or 18-related persistent infection (includes CIN, VIN, VaIN, AIS, cervical, vulvar, or vaginal cancer, and genital warts) and
  - 2) the combined incidence of HPV 16- or 18-related persistent infection, cervical, and external genital disease.

FUTURE-III Trial

	HPV 6/11/16/18-related outcomes				HPV 16/18-related outcomes			
	n(*m*)				*n*(*m*)			
Analysis population end point	**qHPV**	**Placebo**	**Observed efficacy**	**95% CI**	**qHPV**	**Placebo**	**Observed efficacy**	**95% CI**
Per-protocol efficacy population (PPE)								
Overall persistent infection, CIN, or EGL	10 (4)	86 (41)	88.7	(78.1, 94.8)	8 (4)	51 (23)	84.7	(67.5, 93.7)
24–34-year-olds	5 (2)	56 (24)	91.3	(78.4, 97.3)	5 (2)	35 (13)	86.0	(64.0, 95.7)
35–45-year-olds	5 (2)	30 (17)	83.8	(57.9, 95.1)	3 (2)	16 (10)	81.8	(36.3, 96.6)
By end point								
Persistent infection	9 (2)	85 (39)	89.6	(79.3, 95.4)	7 (2)	50 (21)	86.2	(69.4, 94.7)
CIN (any grade)	1 (1)	17 (9)	94.1	(62.5, 99.9)	1 (1)	13 (7)	92.4	(49.1, 99.8)
CIN 2/3 or worse	1 (1)	6 (4)	83.3	(−37.6, 99.6)	1 (1)	6 (4)	83.4	(−36.7, 99.6)
EGL	0 (0)	7 (4)	100	(30.8, 100)	0 (0)	0 (0)	NA	NA
Condyloma	0 (0)	7 (4)	100	(30.8, 100)	0 (0)	0 (0)	NA	NA
VIN 2/3 or VaIN 2/3	0 (0)	0 (0)	NA	NA	0 (0)	0 (0)	NA	NA

Abbreviations: CI = confidence interval; CIN = cervical intraepithelial neoplasia; EGL = external genital lesion; NA = not applicable; qHPV = quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine; VaIN; = vaginal intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia. *n* = number of cases at the end of study (mean follow-up time per subject of 3.8 years); *m* = number of cases in original report (mean follow-up time per subject of 2.2 years). Subjects are counted once in each applicable end point category. A subject may appear in more than one category.

Current CDC Recommendations



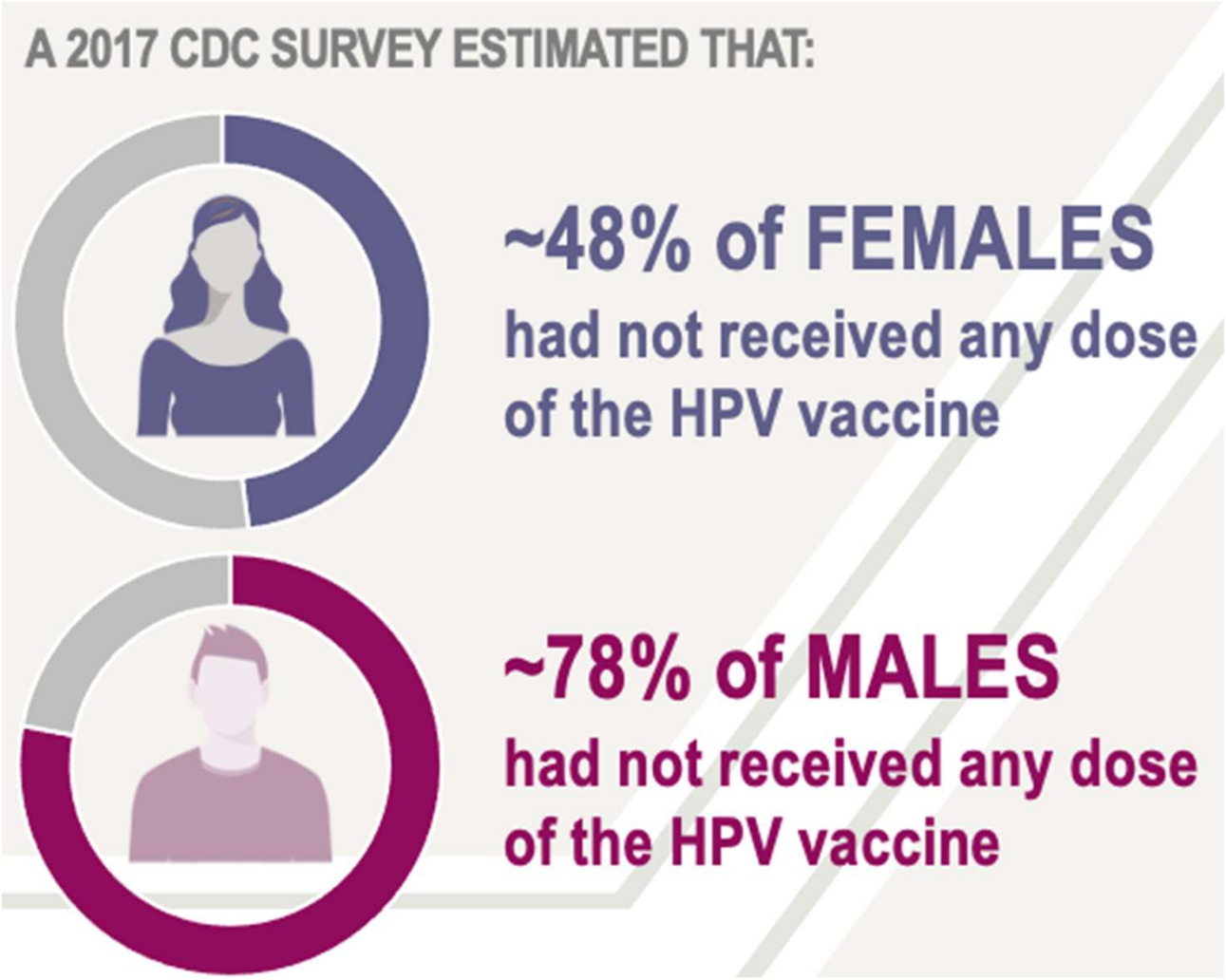
Routine vaccination is recommended for females and males at **age 11 or 12 years, but can be given starting at age 9 years**

Catch-up HPV vaccination is recommended for females and males through age **26 years who are not adequately vaccinated**

Shared clinical decision-making is recommended for some females and males ages **27–45 years who are not adequately vaccinated**

As of August 2019, the CDC recommends harmonization of catch-up vaccination for all appropriate persons through age 26 years

Current state of vaccination among 19-26: "The Catch Up Cohort"



Safety

Population (n)	Injection Site, % (1 to 5 days postvaccination)			Systemic, %	
	Pain	Swelling	Erythema	Headache (1 to 15 days postvaccination)	Oral Temperature ≥100.0°F[b] (1 to 5 days postvaccination)
Females ages 9–15 y (n=299)	89.3	47.8	34.1	11.4	6.7
Females ages 16–26 y (n=7071)	89.9	40.0	34.0	14.6	6.0
Males ages 9–15 y (n=639)	71.5	26.9	24.9	9.4	10.4
Males ages 16–26 y (n=1394)	63.4	20.2	20.7	7.3	4.4

Safety of GARDASIL 9 in individuals ages 27–45 years is inferred from the safety data of GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] in individuals ages 9 through 45 years and GARDASIL 9 in individuals ages 9 through 26 years.

How can we increase vaccination rates ?

- **ASSESS** immunization status of all patients at every clinical encounter
- Strongly **RECOMMEND** vaccines that patients need
- **ADMINISTER** or **REFER** your patients to a vaccination provider
- **DOCUMENT** vaccines received by your patients

How can we increase vaccination rates in CT?

ACOG endorses implementing these strategies to enhance immunization programs for OB-GYN patients

Advocate

Routinely discuss recommended vaccines with each patient, including the HPV vaccine

Create an Immunization Culture

Educate and involve all staff in immunization processes, and designate an immunization champion or team

Assess

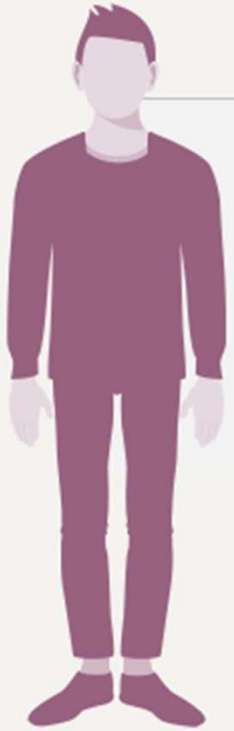
Develop a standard process for assessing and documenting vaccination status

Adolescent GYN Patient Population

According to the AAP, the ideal transition age from child- to adult-oriented health care **should occur between the ages of 18 and 21 years**, and this may involve choosing a new physician[1]

Give your patients a **vaccine questionnaire** to complete at check-in to assess which vaccines they may need[2]

Recommend the HPV Vaccine When Giving Other Vaccines



As per current immunization recommendations, adults ages 19–26 years may be **receiving various immunizations** recommended for their age group[1]

Consider identifying age-appropriate patients who may be **eligible for HPV vaccination** when they are receiving other routine vaccinations[2]

College Matriculation Can Prompt HPV Vaccination Recommendations

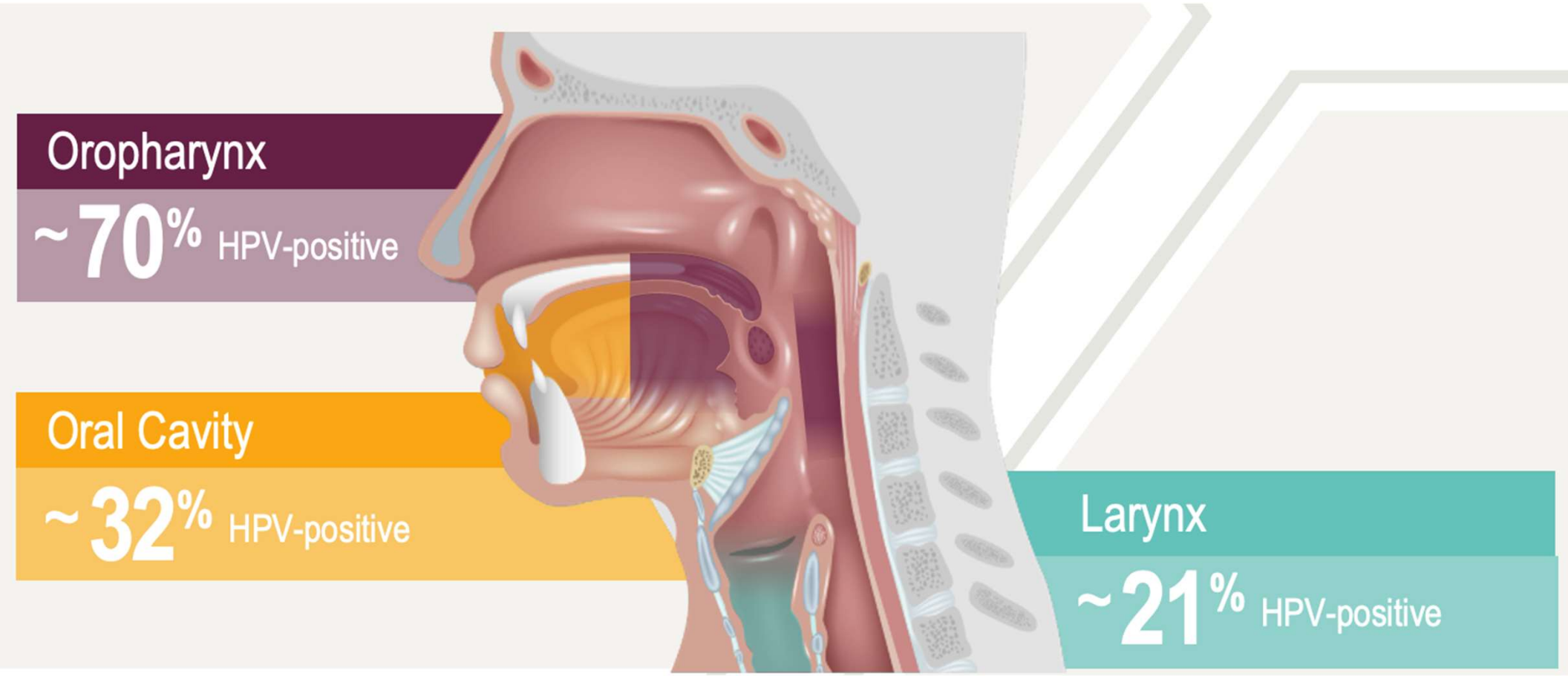
The American College Health Association Vaccine-Preventable Diseases Advisory Committee strongly supports the use of vaccines to protect the health of individual students and campus communities, and suggests that **college matriculation may provide the opportunity** to ensure students receive the appropriate vaccines recommended for young adults, such as HPV vaccination[1]

When it's time to recommend, consider stating:
"You might be at risk for certain HPV-related cancers later in life. Let's start your vaccination today."[2]

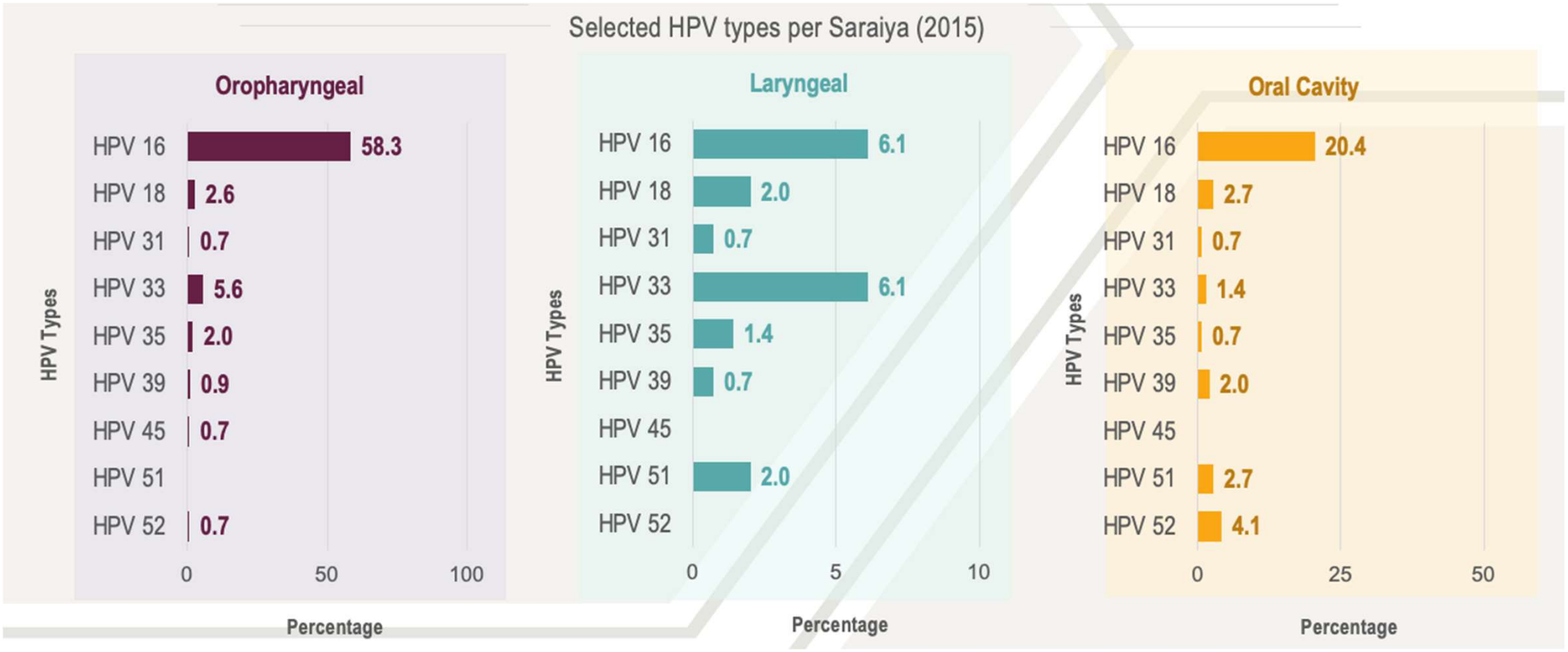
HCP Recommendation Can Make a Difference

According to the NVAC Standards for Adult Immunization Practices, **a recommendation from their HCP is the strongest predictor** of whether adult patients get vaccinated[2]

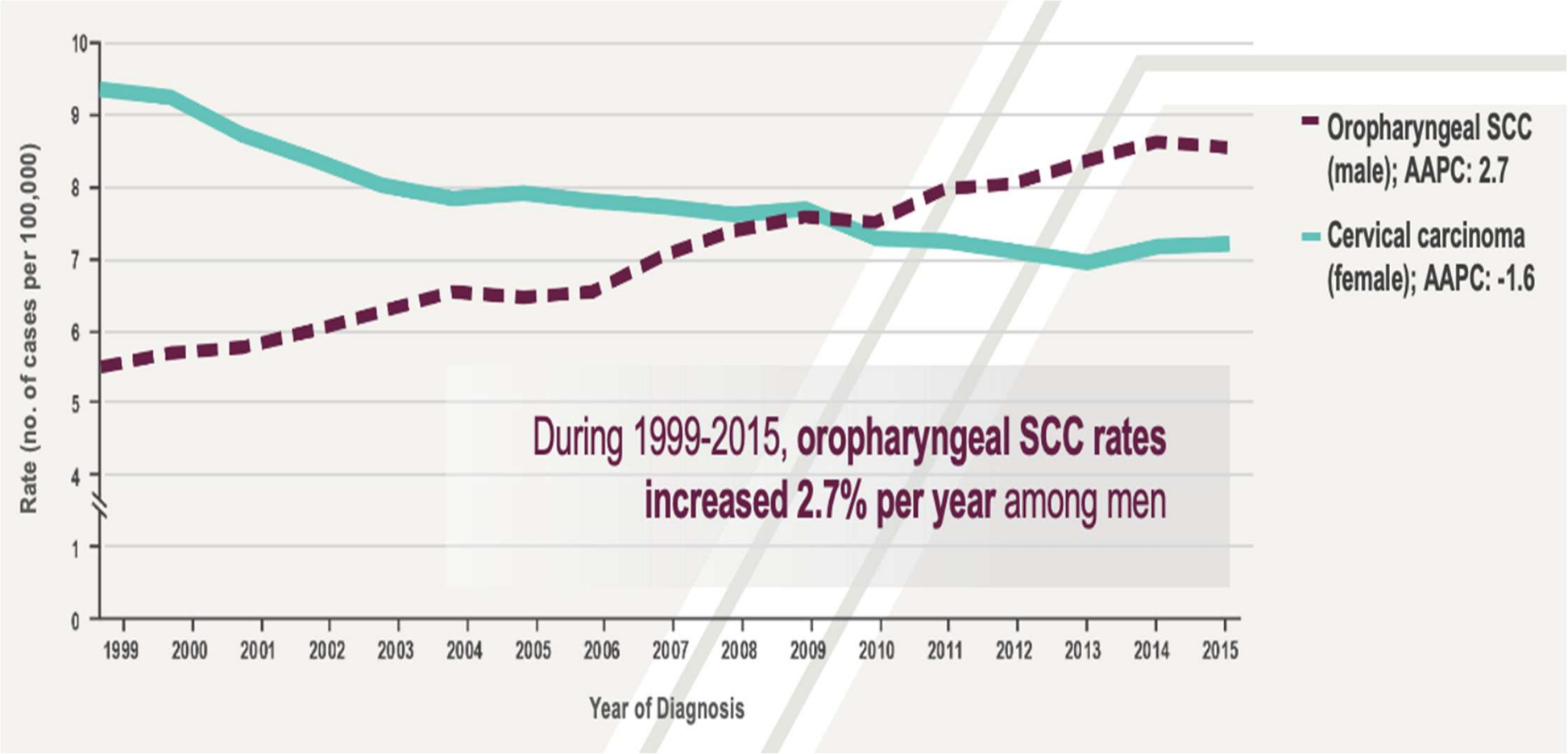
HPV and Cancers of the Head and Neck



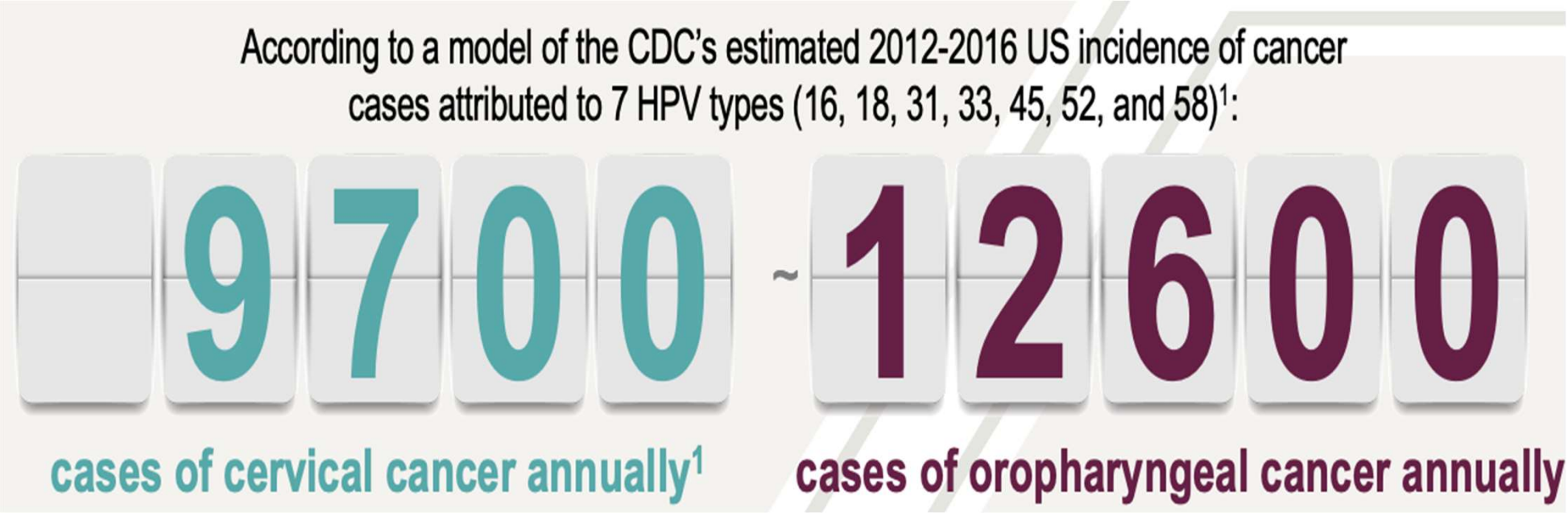
HPV Type Detection Differed Depending on Anatomical Location



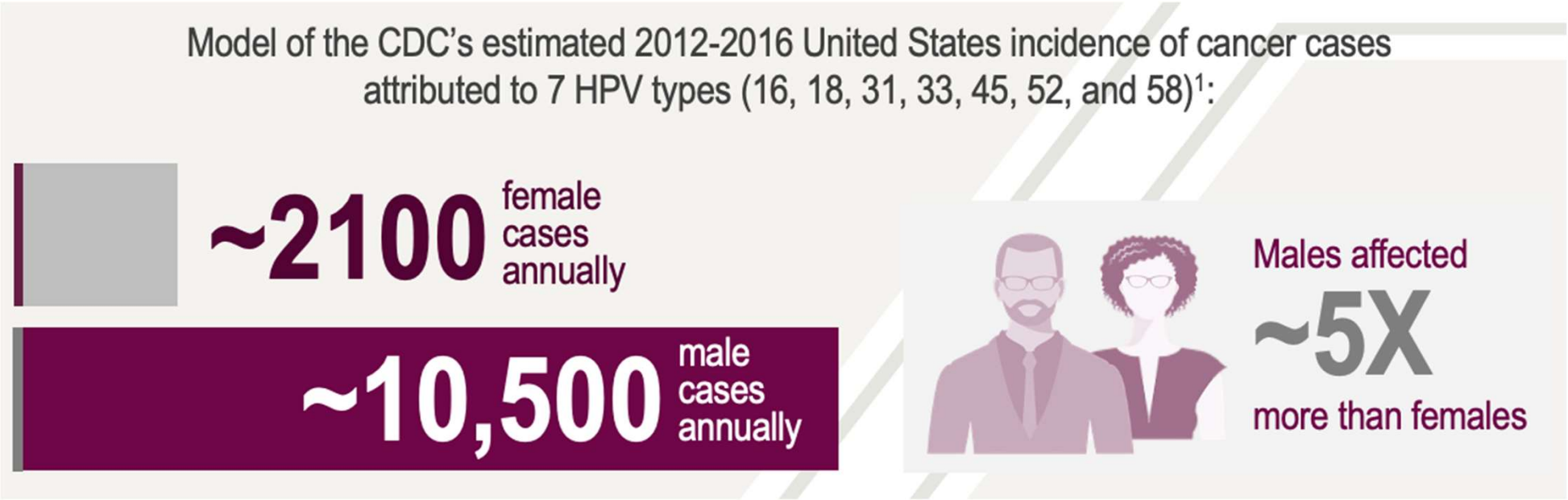
HPV-Associated Oropharyngeal Cancer Rates in Males Surpassed Cervical Cancer Rates in Females



Oropharyngeal Cancer Is the Most Prevalent Type of HPV-Attributed Cancer in the United States (2012-2016)



The Majority of HPV-Attributed Oropharyngeal Cancer Occurs in Males (2012-2016)

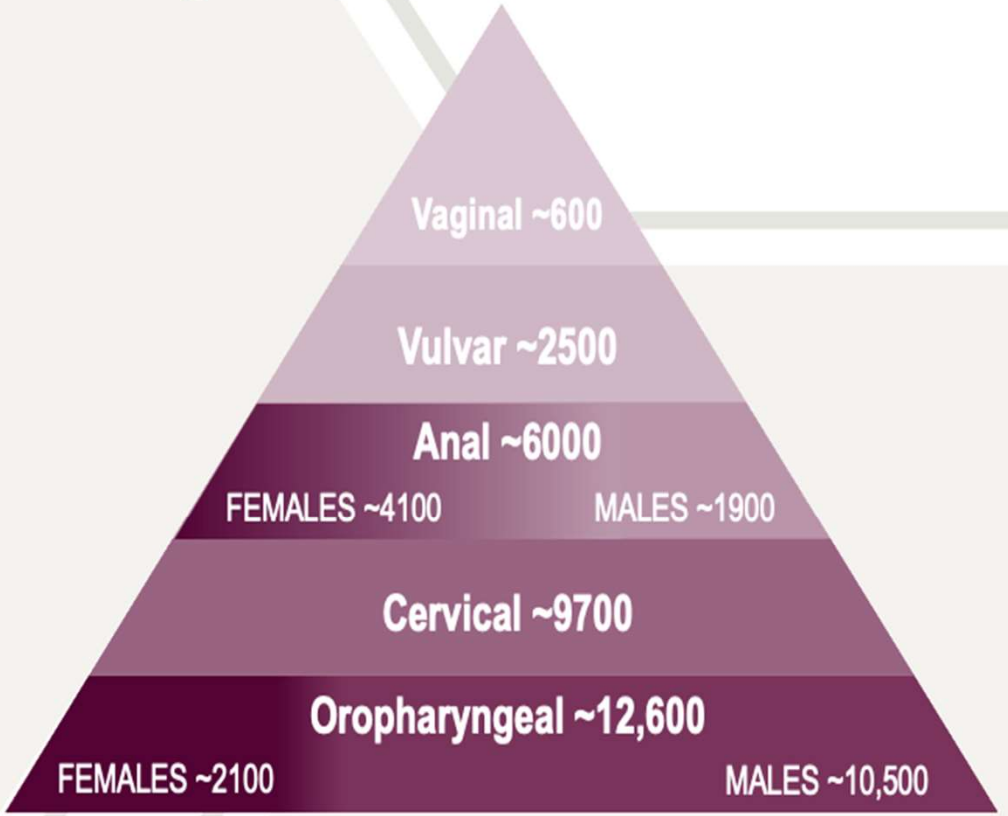


- Take clinical encounters with the mother of a child or young adult aged 11-26 to educate them on the benefits related to the MALE burden of HPV related cancers
- Move the conversation away from HPV as an infection towards HPV as the cause of cancer in women ***AND*** men

Focus on Cancer Prevention When Discussing the HPV Vaccine With Patients

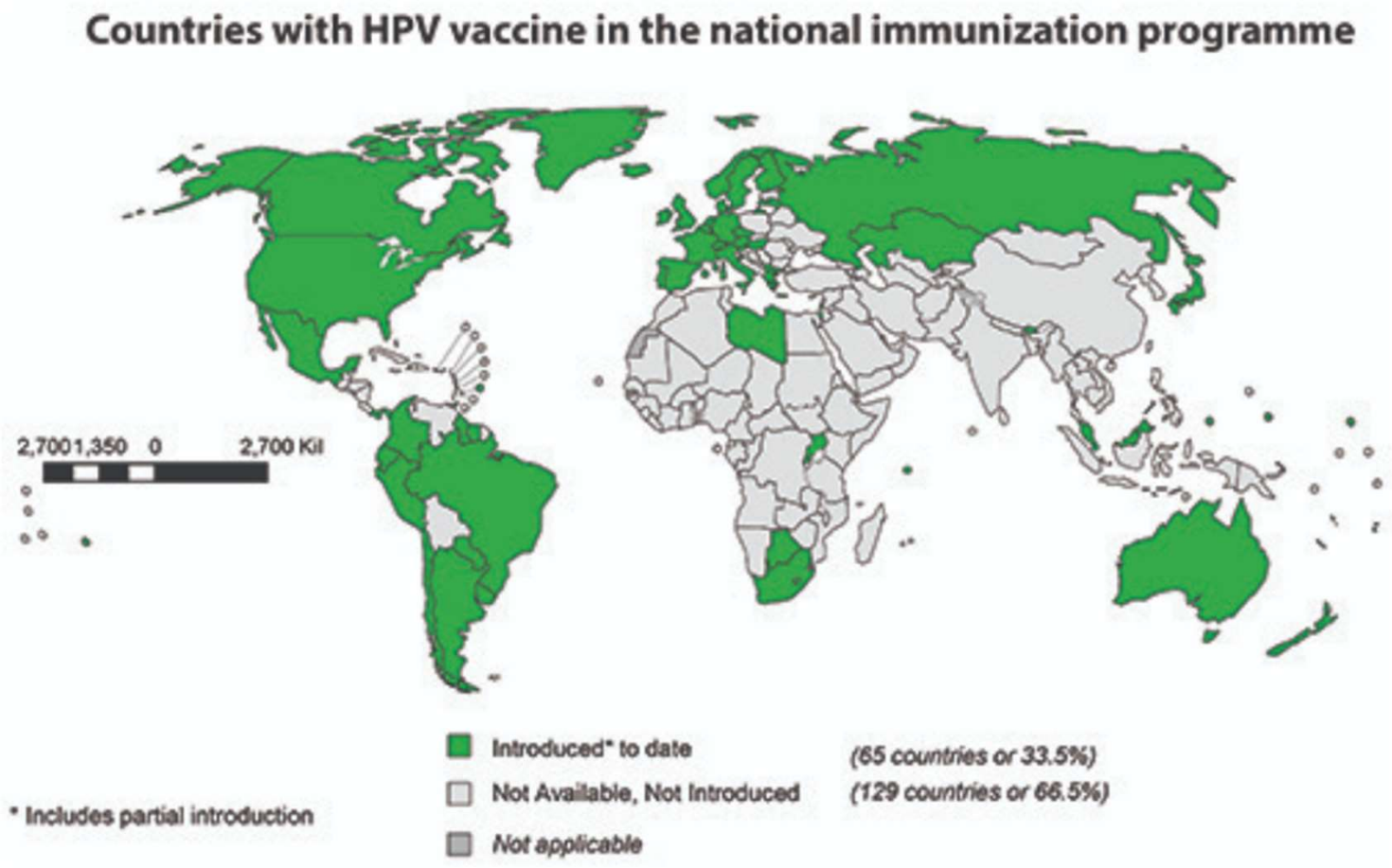
Model of the CDC's estimated 2012-2016 **United States incidence of cancer cases** attributed to 7 HPV types (16, 18, 31, 33, 45, 52, and 58)[1]

~31,400 total cases each year



- Consider re-phrasing how you counsel patients on the importance of HPV vaccination as a CANCER PREVENTION strategy as opposed to just a vaccine against HPV
- Emphasize impact on men and women
- Remove the sexualized stigma associated with HPV vaccination

Effectives of HPV vaccination: A real world example



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Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

The impact of a universal human papilloma virus (HPV) vaccination program on lower genital tract dysplasia and genital warts

M. Clark [a,*,1], N. Jembere [b], R. Kupets [a,b,c]

- Malignancy is not the only sequelae of HPV infection.
- Healthcare costs associated with the diagnosis and treatment of HPV related disease (benign + malignant) exceed $6B USD each year.
- Colposcopy services are centralized in Ontario and often inundated with referrals.
- School-based vaccination programs for HPV have been in place since 2007- - but are they working?

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- Retrospective population-level cohort study.
- Women born in 1995 would have been the first cohort of eligible girls to undergo vaccination.
- They were compared to a historical control born in 1985 prior to availability of the HPV vaccine in Canada.
- Participation rates ~60% at initial roll out

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- Cytobase:
  - Central repository of cervical cytology in Ontario
  - >90% of all Pap smears collected

- Ontario Health Insurance Plan (OHIP)
  - Unique identifier to all citizens and refugees

- Women were followed longitudinally for 5 years after entering the Pap smear screening program to assess for :
  - Cervical Dysplasia
  - Rates of referral to colposcopy
  - LEEP and conization procedures
  - Treatment of anogenital warts
  - Cryo-ablation of cervical dysplasia

- Results were stratified for socio-economic status and geographic region

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	High-grade dysplasia		Low-grade dysplasia		Overall rate of abnormal
Vaccinated (100,020)	206	0.21%	5,011	5.01%	5.2%
Unvaccinated (121,019)	932	0.77%	10,241	8.46%	9.2%

Table 1. Rate of cytologic abnormalities on cervical cancer screening among the vaccinated and unvaccinated cohorts.

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	TCA	Laser of vulvar lesion	Cervical Conization	LEEP	Cryotherapy	Colposcopy	Overall rate of treatment
Vaccinated (100,020)	98 (0.10%)	77 (0.08%)	53 (0.05%)	94 (0.09%)	18 (0.02%)	3734 (3.73%)	2.7%
Unvaccinated (121,019)	488 (0.40%)	715 (0.59%)	356 (0.29%)	840 (0.69%)	129 (0.11%)	8777 (7.25%)	5.2%

Table 2. Rates of treatment of various pre-invasive and benign HPV related conditions as well as referral for colposcopic services. TCA: trichloracetic acid treatment; LEEP: Loop electrosurgical procedure.

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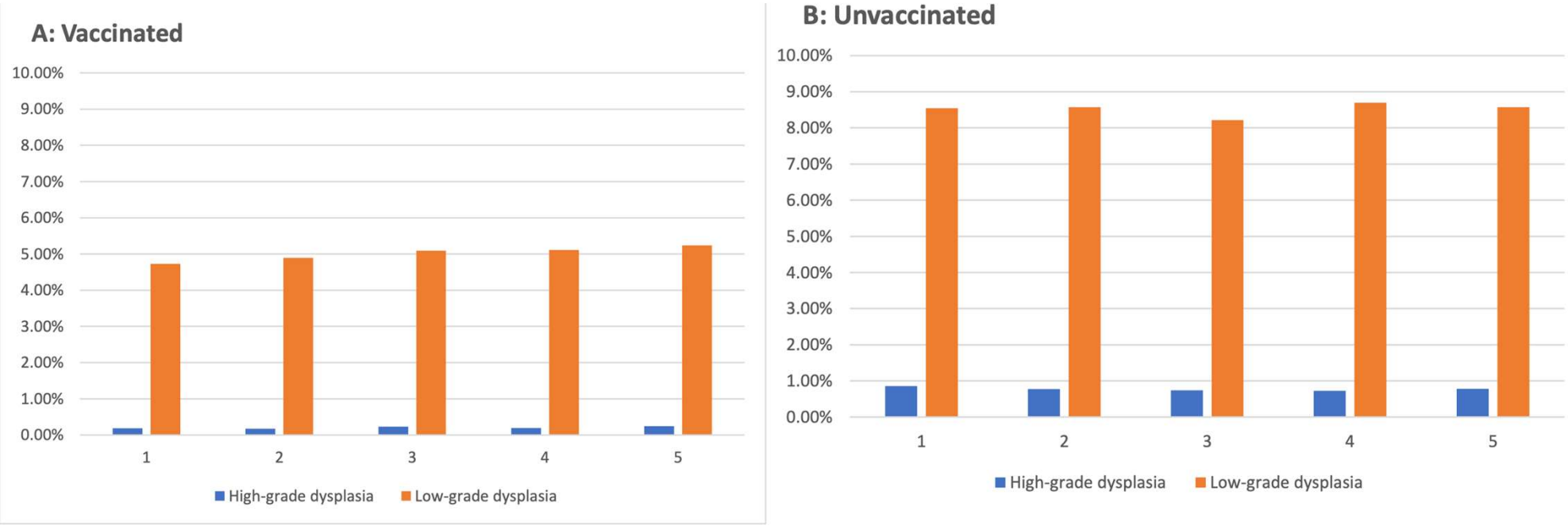

Figure 1. A. Rates of cervical dysplasia among *vaccinated* cohort by income quintile and B. Rates of cervical dysplasia among *unvaccinated* cohort by income quintile. Income quintile is represented on the x-axis.

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Geographic Region	# of females of vaccinated	# of females of unvaccinated	Abnormal high grade	Abnormal low grade	Total abnormal	Colposcopy	Treatment
Urban	76,438	63,726	9.1	3.1	3.4	2.5	7.9
Rural	8,711	8,619	9.7	2.8	3.1	2.5	8.3

Table 3. Relative risk of high and low-grade cytology as well as use of colposcopic services and treatment of pre-malignant of benign conditions for unvaccinated cohort based on geographic region.

The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study

Milena Falcaro, Alejandra Castañon, Busani Ndlela, Marta Checchi, Kate Soldan, Jamie Lopez-Bernal, Lucy Elliss-Brookes, Peter Sasieni

	Cervical cancer			CIN3		
	20·0 to <24·5 years	24·5 to <26·0 years	26·0 to <30·0 years	20·0 to <24·5 years	24·5 to <26·0 years	26·0 to <30·0 years
Unvaccinated cohorts						
Cohort 1: invited from age 20·0 years and no vaccine	4·2 (70)	11·7 (246)	16·1 (1532)	233·8 (3893)	498·3 (10 522)	446·9 (42 443)
Cohort 2: invited from age 20·0 years or 25·0 years and no vaccine	2·5 (38)	27·0 (176)	20·4 (352)	100·6 (1504)	847·3 (5520)	489·0 (8443)
Cohort 3: invited from age 25·0 years and no vaccine	2·0 (109)	28·2 (557)	18·8 (987)	52·9 (2868)	1027·6 (20 298)	476·4 (25 020)
Cohort 4: invited from age 24·5 years and no vaccine	1·8 (37)	27·8 (211)	18·0 (315)	29·9 (629)	1141·7 (8680)	452·9 (7948)
Vaccinated cohorts						
Cohort 5: invited from age 24·5 years and offered vaccine in school years 12–13	1·0 (47)	20·0 (340)	11·5 (174)	15·9 (755)	673·2 (11 452)	312·8 (4752)
Cohort 6: invited from age 24·5 years and offered vaccine in school years 10–11	0·7 (21)	14·5 (49)	..	6·3 (188)	434·9 (1466)	..
Cohort 7: not invited before age 24·5 years and offered vaccine in school year 8	0·3 (7)	..	..	2·0 (49)	..	..

Data are incidence (number of cases). CIN=cervical intraepithelial neoplasia.

Table 2: **Crude incidence rates per 100 000 women-years by cohort and age group (for simplicity, restricted to age <30·0 years) for cervical cancer and CIN3**

Falcaro M, Castañon A, Ndlela B, Checchi M, Soldan K, Lopez-Bernal J, Elliss-Brookes L, Sasieni P. The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study. Lancet. 2021 Nov 3:S0140-6736(21)02178-4. doi: 10.1016/S0140-6736(21)02178-4.

The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study

Milena Falcaro, Alejandra Castañon, Busani Ndlela, Marta Checchi, Kate Soldan, Jamie Lopez-Bernal, Lucy Elliss-Brookes, Peter Sasieni

	Cervical cancer			CIN3		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Unvaccinated cohorts						
Cohort 1: invited from age 20·0 years and no vaccine	0·99 (0·89–1·10)	1·00 (0·90–1·11)	0·99 (0·89–1·10)	0·97 (0·93–1·00)	0·98 (0·94–1·01)	0·97 (0·94–1·01)
Cohort 2: invited from age 20·0 years or 25 years and no vaccine	1·08 (0·95–1·22)	1·09 (0·97–1·23)	1·08 (0·96–1·22)	1·02 (0·98–1·06)	1·03 (0·99–1·07)	1·03 (0·99–1·06)
Cohort 3: invited from age 25·0 years and no vaccine	1·03 (0·93–1·15)	1·04 (0·94–1·16)	1·04 (0·93–1·15)	1·01 (0·97–1·04)	1·02 (0·98–1·05)	1·01 (0·98–1·05)
Cohort 4: invited from age 24·5 years and no vaccine (reference category)	1·00	1·00	1·00	1·00	1·00	1·00
Vaccinated cohorts						
Cohort 5: invited from age 24·5 years and offered vaccine in school years 12–13	0·67 (0·59–0·75)	0·66 (0·58–0·74)	0·66 (0·59–0·75)	0·61 (0·59–0·64)	0·61 (0·58–0·64)	0·61 (0·59–0·64)
Cohort 6: invited from age 24·5 years and offered vaccine in school years 10–11	0·39 (0·31–0·50)	0·37 (0·29–0·47)	0·38 (0·29–0·48)	0·26 (0·24–0·29)	0·24 (0·22–0·27)	0·25 (0·23–0·28)
Cohort 7: not invited before age 24·5 years and offered vaccine in school year 8	0·13 (0·06–0·27)	0·12 (0·06–0·26)	0·13 (0·06–0·28)	0·03 (0·02–0·04)	0·03 (0·02–0·04)	0·03 (0·02–0·04)

Data are IRR (95% CI). Model 1 adjusts for all main effects for age and cohort, age-by-cohort interactions, linear trend (drift), and dummy variables for the Jade Goody and seasonal effects. Model 2 contains all effects in model 1 plus adjustment for under-registration. Model 3 includes all effects in model 1 plus adjustment for the screening awareness campaign. The estimates are adjusted for the covariates included in the models, details in the methods. IRRs=incidence rate ratios. CIN=cervical intraepithelial neoplasia.

Table 3: **Estimated IRRs and 95% CIs of either cervical cancer or CIN3 among the vaccinated and unvaccinated birth cohorts.**

Looking to the future: Using the HPV vaccination in creative ways: Post-LEEP

1. Post Hoc Analsysis of PATRICIA trial, 2016

Bivalent vaccine BEFORE LEEP

2. Kang, 2013

4v vaccine AFTER LEEP

3. Speranza Trial

4v vaccine AFTER LEEP

Looking to the future: Using the HPV vaccination in creative ways: Post-LEEP

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SPERANZA project: HPV vaccination after treatment for CIN2+

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- PROSPECTIVE CASE CONTROL
- TO EVALUATE THE CLINICAL EFFECTIVENESS OF HPV VACCINATION AFTER SURGICAL TREATMENT (LEEP) IN WOMEN WITH HSIL AND MICROINVASIVE CERVICAL CANCER.

Speranza Project: Post-LEEP Vaccination

HPV vaccination clinic

Enrolling all patinets with CIN2+ to Figo IA1 post LEEP

Jan 2013-Mar 2017

First visit: 30 days post LEEP

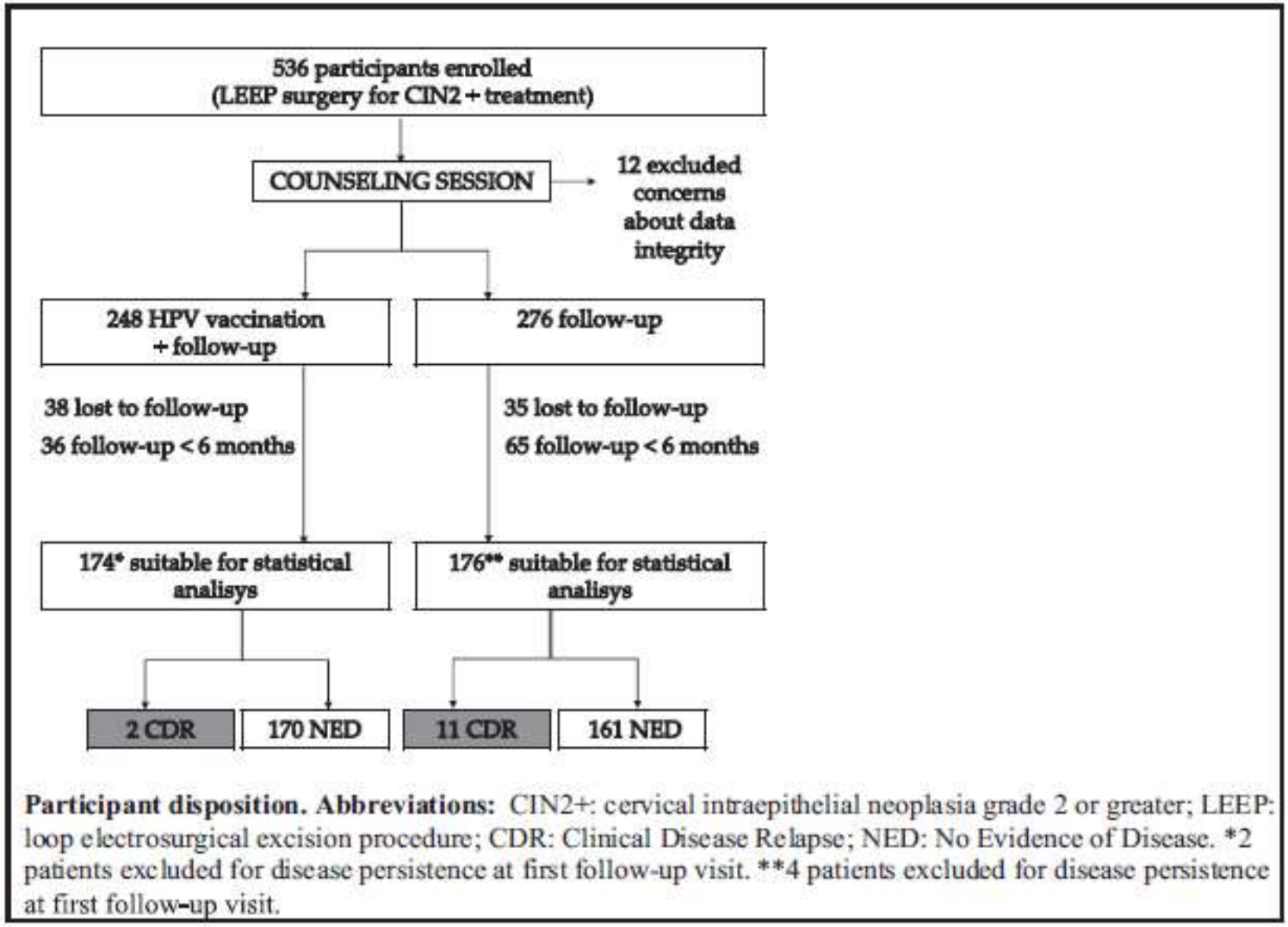
Patient counselling session 90 mins

Voluntary participation

1st dose at this 30 day visit

FU: HPV test, colpo, pap q6 mos x 2 years then annual

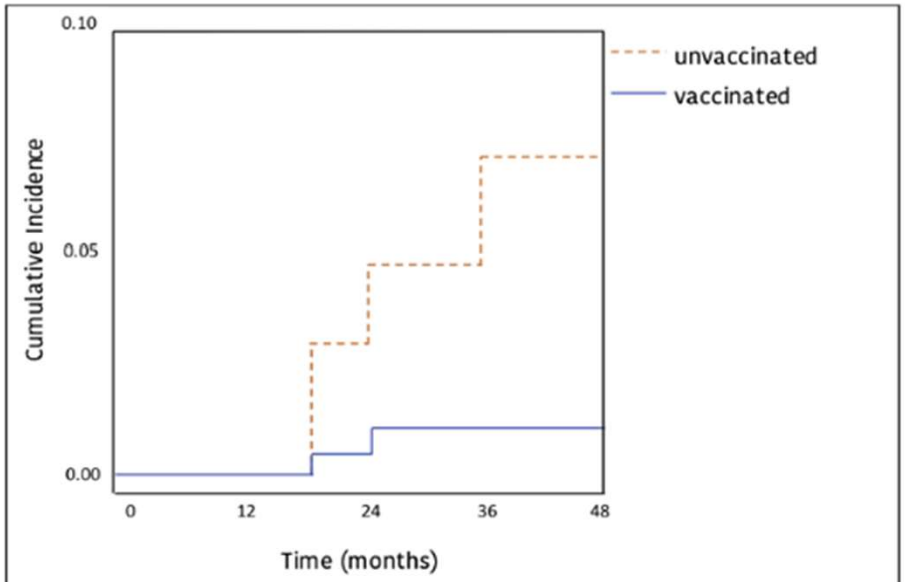
Speranza Project: Post-LEEP Vaccination



Participant disposition. Abbreviations: CIN2+: cervical intraepithelial neoplasia grade 2 or greater; LEEP: loop electrosurgical excision procedure; CDR: Clinical Disease Relapse; NED: No Evidence of Disease. *2 patients excluded for disease persistence at first follow-up visit. **4 patients excluded for disease persistence at first follow-up visit.

Speranza Project: Post-LEEP Vaccination

IMPACT OF VACCINATION ON DISEASE RELAPSE AFTER CERVICAL CONIZATION



CDR irrespective of causal HPV type (CIN2+)			
	V-group	NV-group	% risk reduction in rate with vaccine
No. of evaluable women	172	172	81,2% [95% CI: 34,3-95,7]
No. of women with CDR recurrence rate (%)	2 1.2	11 6.4	

Legend: CDR: clinical disease relapse; V-group: vaccinated patients; NV-group: unvaccinated patients. Impact of quadrivalent HPV vaccine on incidence of subsequent disease relapse among women who had undergone cervical conization; 95% CI: confidence interval of the estimates.

	Recurrence	4 yr probability recurrence
Vaccine group	2 cases	1.2% (95%CI 0,3-4,6)
Control	11 cases	6.4% (95%CI 3,9-12,4)
		P= 0,0112

- **Vaccination : significant risk reduction of subsequent HPV-related HSIL post LEEP by 81,2% (95%CI 34,3-95,7)**

Sperenza Project: Post-LEEP Vaccination

HPV vaccination **IMMEDIATELY** after the surgical treatment ↑ local AB within cervical BM

Post op tissue repair

-excision of infected tissue stim immune resp (TNF-a, cytokines)+ Generation of new mucosa

Med time: **36 months** between cleared cervical lesion and disease relapse is clinically reasonable.

" when the cells with integrated HPV in the primary lesion are removed by surgery, the antibodies evoked by the HPV-vaccine, after the surgical treatment, can prevent the HPV reactivation/re-infection or the de novo HPV infection".

Summary:

- Consider education and counseling at each clinical encounter
- Stress the importance with a strong recommendation for eligible participants or mothers, sisters, aunts of eligible boys, girls and young adults
- Emphasize the important of HPV vaccination as a CANCER PREVENTION strategy for multiple cancers in men and women
- Identify a vaccination champion in your practice to evaluate your current performance and identify areas for improvement
- Routinely re-assess your vaccination strategies to assess effectiveness

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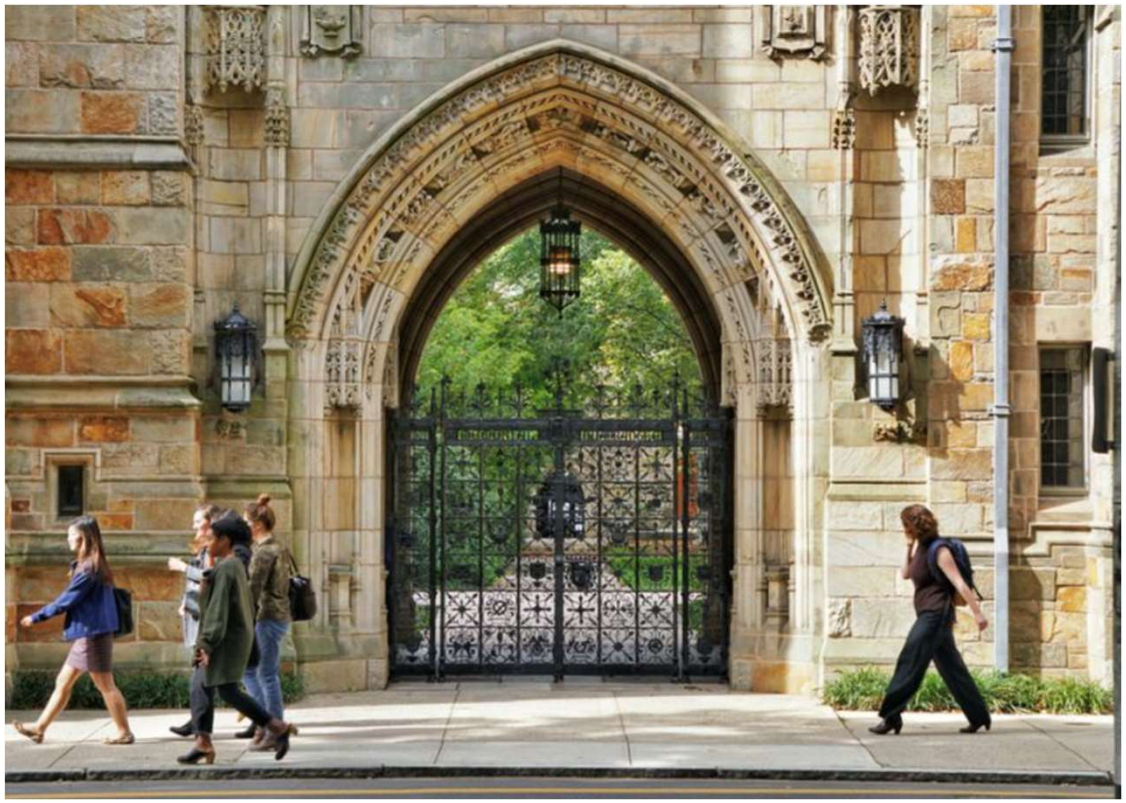
  - Cancer Care Ontario



Questions & Discussion