Cancer Prevention through HPV Vaccination

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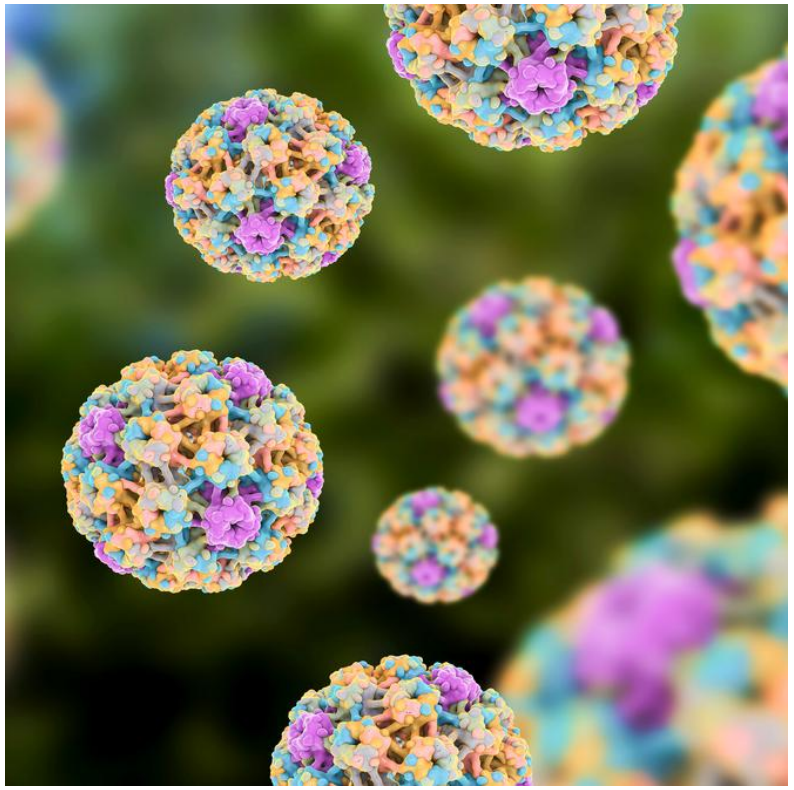
Objectives

- To describe the epidemiology of HPV infection
- To review evolving recommendations for HPV vaccination
- To describe the effects of HPV vaccination on HPV infection and precancers
- To review efforts to realize goals of HPV-associated cancer prevention

I have no conflicts of interest to disclose

Audience Participation

- Which country is on track to be the first to eliminate cervical cancer as a public health threat?
    - Canada
    - United States
    - Scotland
    - Australia
    - Denmark



HUMAN PAPILLOMAVIRUS

Google images

HPV Transmission

- Genital HPV transmission usually through sexual intercourse
  - Risk increases with number of sexual partners
  - One study described HPV infection in 14.3% of females 18-25yo with ONE lifetime partner (Manhart et al. Sex Trans Dis 2006;33:502-8)
- May be transmitted by non-penetrative intimate sexual contact
  - Implications for adolescents “not having sex”
- Mother-to-infant transmission at birth (rare)

Human Papillomavirus (HPV)

- Small, nonenveloped, double-stranded DNA viruses of *Papillomaviridae* family
- Hundreds of types
- Infect squamous epithelium
  - Asymptomatic
  - Cutaneous (benign epithelial proliferation)
    - Skin warts: common, plantar, flat, thread-like (filiform)
  - Mucosal
    - Low- v. high-risk types

Mucosal HPV Infection Manifestations

- Low-risk HPV types
  - Papillomas
    - upper respiratory tract, oral, nasal, conjunctival, anogenital (condyloma acuminata)
  - Low-grade cervical/anogenital dysplasia
- High-risk HPV types
  - Cervical/anogenital dysplasia (low- or high-grade)
  - Precancers
  - Cancers

Cervical Dysplasia

- Cytology ("Pap smear")
  - Squamous intraepithelial lesion
    - LSIL (low-grade SIL): mild dysplasia
    - HSIL (high-grade SIL): moderate-severe dysplasia
- Histology (colposcopy-directed biopsies)
  - Cervical intraepithelial neoplasia (CIN)
    - CIN 1: mild dysplasia
    - CIN 2*: moderate dysplasia
    - CIN 3*: severe dysplasia/carcinoma *in situ*

* Precancerous lesions

HPV & Cancer

- Precancerous lesions
  - Intraepithelial neoplasia grades 2 and 3
    - Cervical (CIN), anal (AIN), vulvar (VIN), vaginal (VaIN), penis (PeIN or PIN)
  - Endocervical glandular precancer (adenocarcinoma *in situ*, AIS)
- Cancers
  - Cervical
  - Anogenital: anal, vulvar, vaginal, penile
  - Oropharyngeal

EPIDEMIOLOGY

Risk of HPV Infection

- HPV is the most common sexually-transmitted infection
- Nearly EVERYONE will be infected with at least one type of HPV at some point in their lives
- Most people never know they've been infected
- Currently ~80 million Americans infected
- About 14 million Americans become infected each year

www.cdc.gov/hpv

Risk of Cancer due to HPV

- 90% of HPV infections will resolve spontaneously within 2 years
- 33,700 Americans diagnosed each year with cancer due to persistent HPV infection
- Established guidelines for routine screening for cervical cancer*
  - Beginning at age 21
  - Screen every 3 years
  - HR HPV co-testing every 5 years for 30-65yo

*for women at average risk, assuming negative results

www.cdc.gov/hpv
www.cdc.gov/cancer/cervical

Cervical Cancer

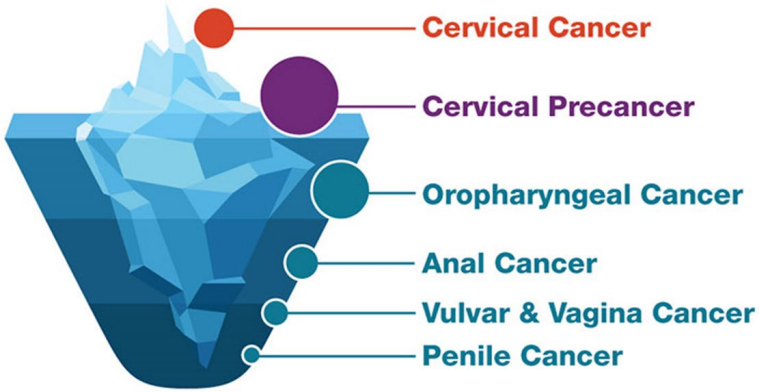
Don't rely on screening to catch it later.
Protect them now with HPV vaccination.

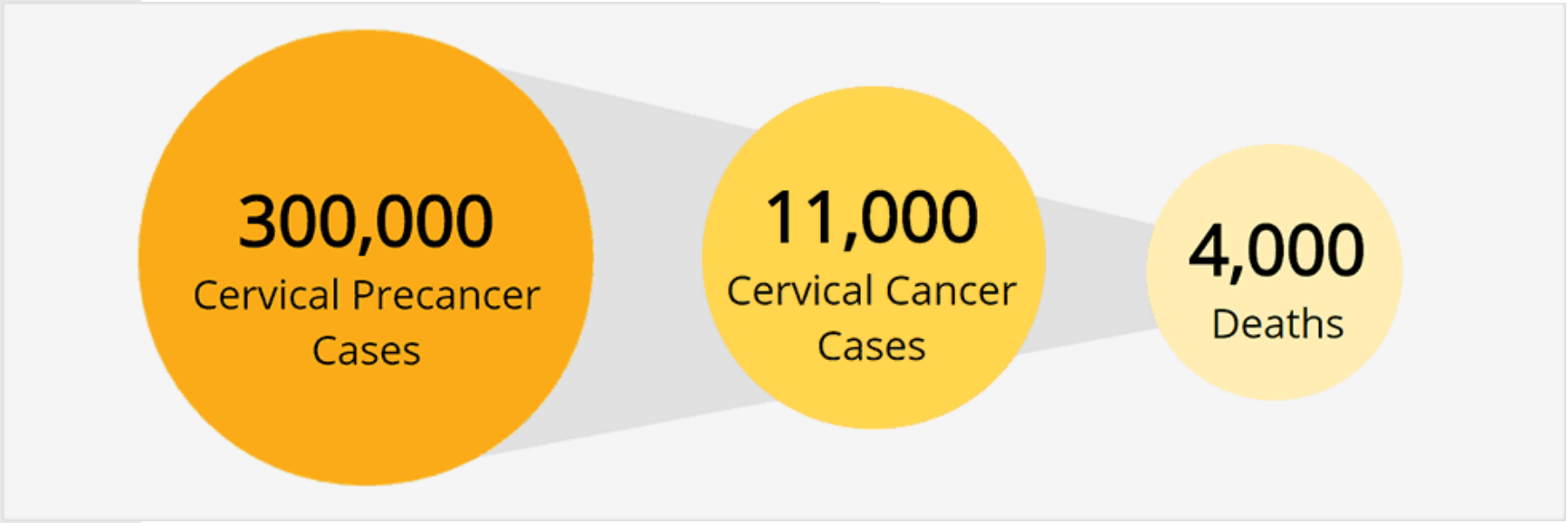
https://www.cdc.gov/hpv/hcp/more-than-screening/index.html

CDC

HPV VACCINE
IS CANCER PREVENTION

Tip of the Iceberg

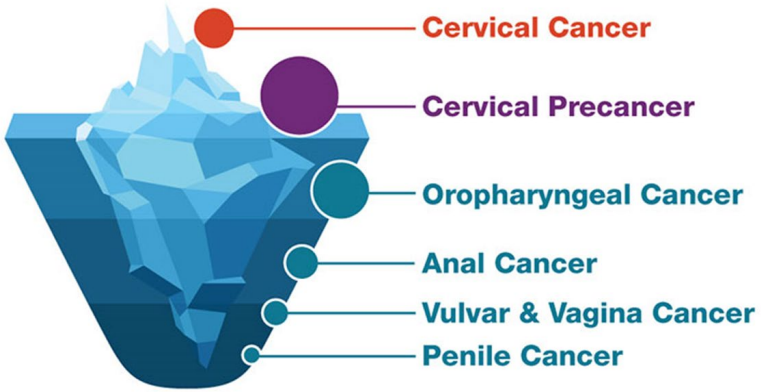


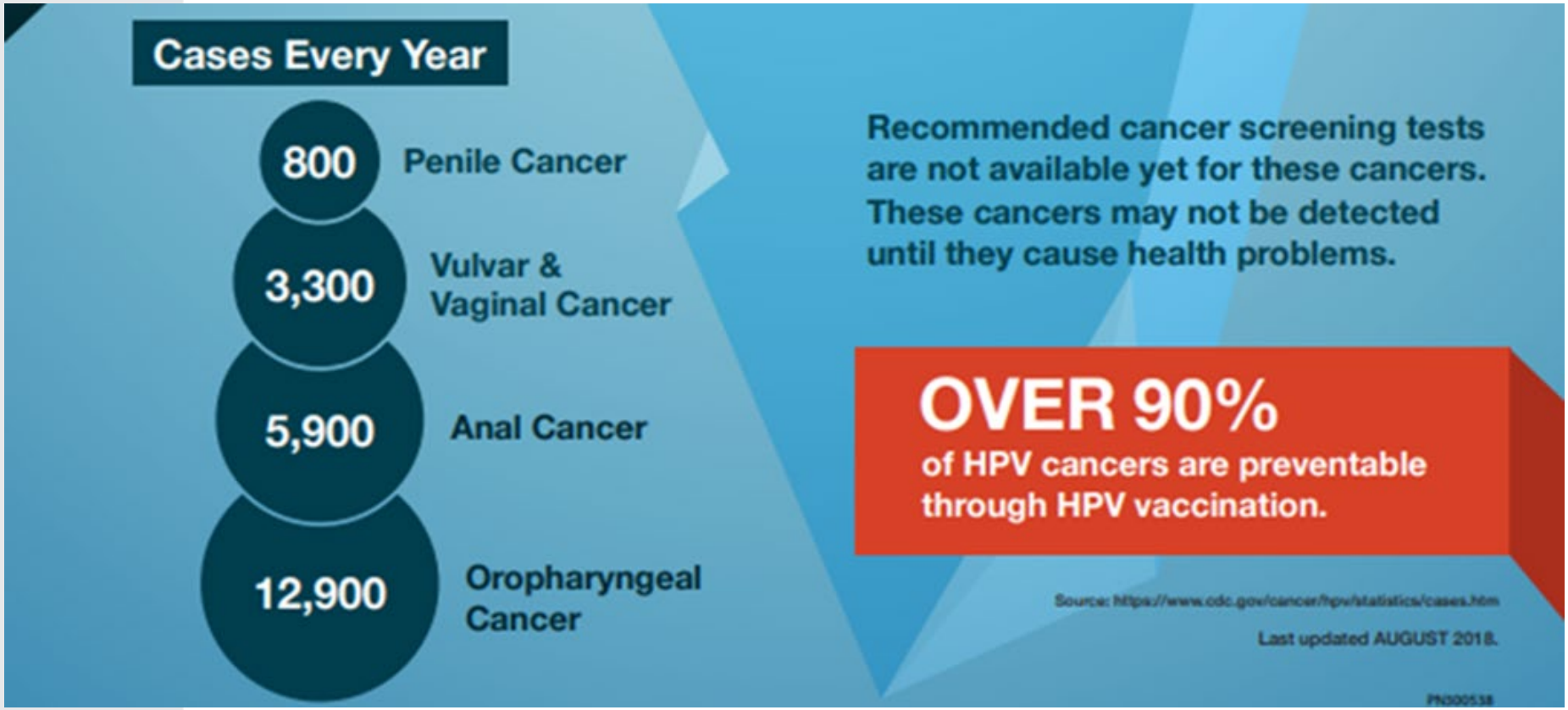


99% of cervical precancers are due to HPV
90% of cervical cancers are due to HPV

www.cdc.gov/hpv

Other HPV Cancers





www.cdc.gov/hpv

Annual Incidence of HPV Cancers

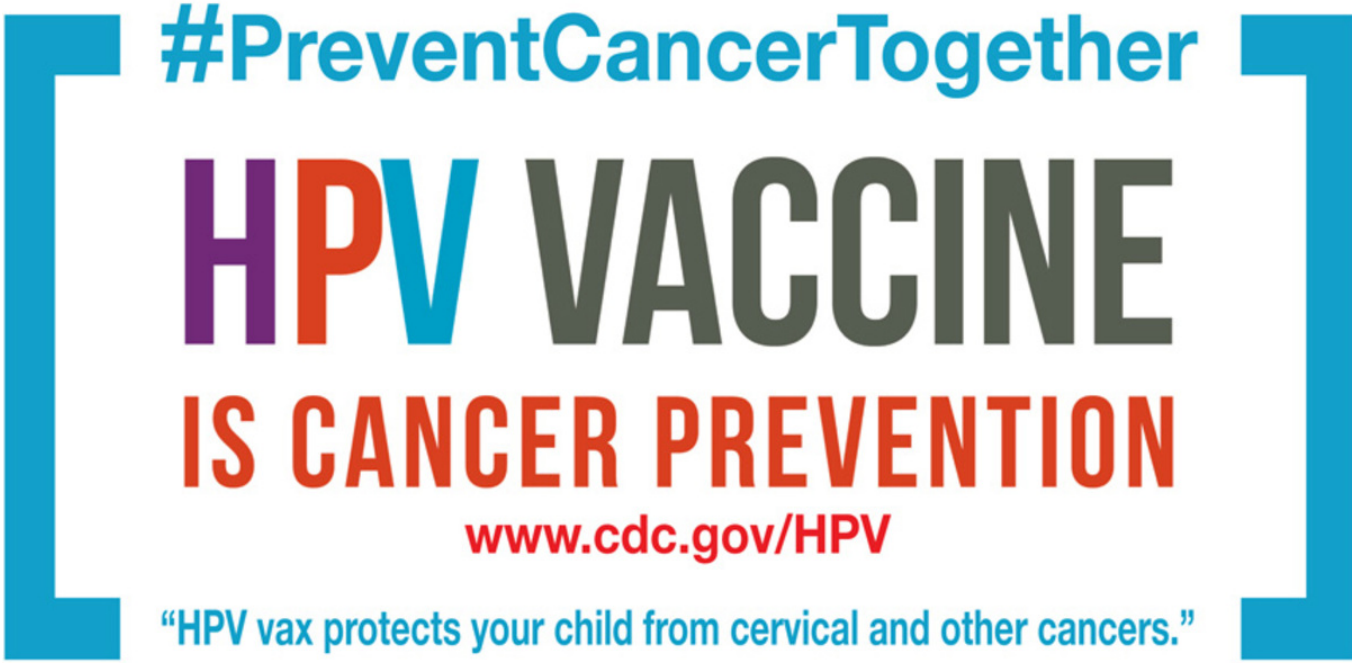
	Cases in Women	Cases in Men
Back of Throat	2,200	10,700
Cervical	10,800	0
Anal	4,000	1,900
Vulvar	2,700	0
Penile	0	800
Vaginal	600	0
Total	**20,300**	**13,400**

Source: HPV-Associated Cancers Statistics
Data as of August 2018

www.cdc.gov/hpv

Cancer site	Average number of cancers per year in sites where HPV is often found (HPV-associated cancers)	Percentage probably caused by any HPV type[a]	Number probably caused by any HPV type[a]
Cervix	11,866	91%	10,751
Vagina	846	75%	635
Vulva	3,934	69%	2,707
Penis	1,269	63%	803
Anus[b]	6,530	91%	5,957
Female	4,333	93%	4,008
Male	2,197	89%	1,949
Oropharynx	18,226	70%	12,885
Female	3,412	63%	2,160
Male	14,814	72%	10,725

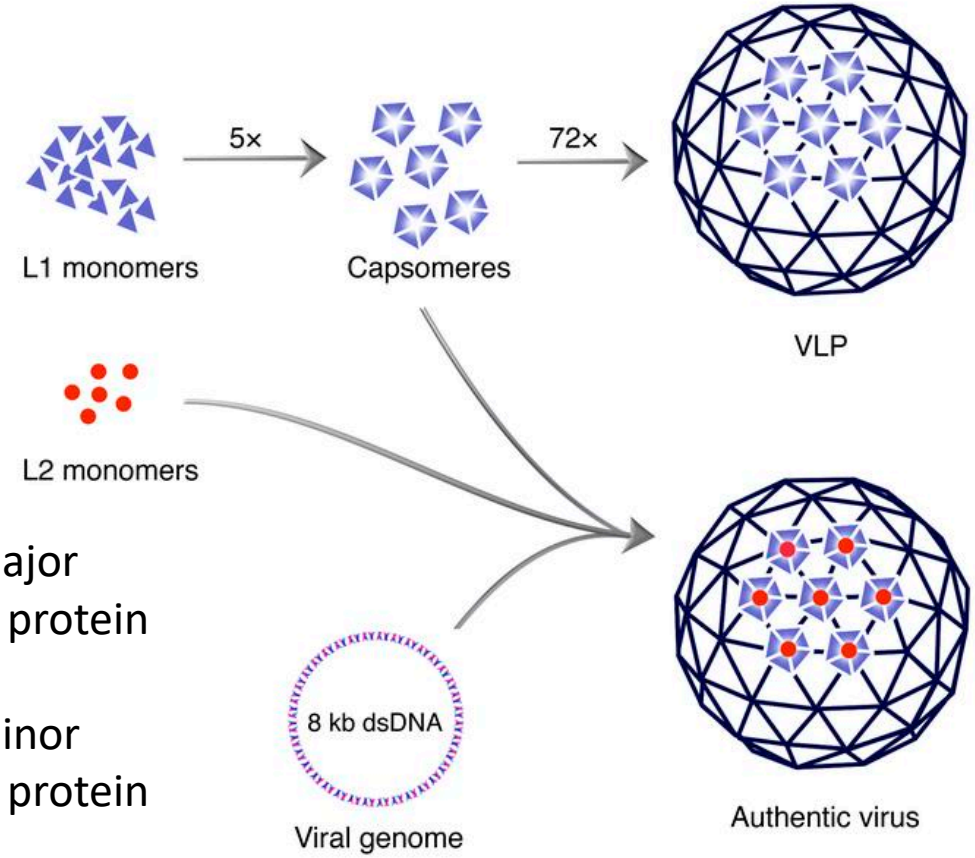
Saralya M et al. Journal of the National Cancer Institute 2015;107:djv086


#PreventCancerTogether
HPV VACCINE
IS CANCER PREVENTION
www.cdc.gov/HPV
"HPV vax protects your child from cervical and other cancers."

HPV VACCINE

HPV Vaccine Assembly

Recombinant DNA technology, L1 protein expressed in yeast *Saccharomyces cerevisiae*



L1 = major capsid protein

L2 = minor capsid protein

VLP = virus-like particle

Schiller et al. Lancet Oncol. 2015;16(5):e217-e225

HPV Vaccines

- 2006 – Gardasil® (4vHPV) Merck
  - Low-risk types 6 and 11 (90% genital warts)
  - High-risk types 16 and 18 (70% cervical cancer)
  - 3 doses at 0, 2, and 6 months
- 2009 – Cervarix® (2vHPV) GlaxoSmithKline
  - High-risk types 16 and 18
- 2014 – Gardasil®9 (9vHPV) Merck
  - Components of original Gardasil®, plus:
  - 5 additional high-risk types: 31, 33, 45, 52, 58 (20% cervical cancer)

4vHPV Pre-Licensing Efficacy Data

TABLE 3. Summary of quadrivalent human papillomavirus (HPV) vaccine efficacy studies in the per protocol populations*

Outcome and protocol	Quadrivalent vaccine No.†	Quadrivalent vaccine Cases	Placebo No.	Placebo Cases	% Efficacy	(95% CI§)
HPV 16- or 18- related CIN 2/3 or AIS¶						
Protocol 005**	755	0	750	12	100.0	(65.1–100.0)
Protocol 007	231	0	230	1	100.0	(-3734.9–100.0)
Protocol 013	2,200	0	2,222	19	100.0	(78.5–100.0)
Protocol 015	5,301	0	5,258	21	100.0††	(80.9–100.0)
Combined protocols§§	8,487	0	8,460	53	100.0††	(92.9–100.0)
HPV 6-, 11-, 16-, 18- related CIN (CIN 1, CIN 2/3) or AIS						
Protocol 007	235	0	233	3	100.0	(-137.8–100.0)
Protocol 013	2,240	0	2,258	37	100.0††	(89.5–100.0)
Protocol 015	5,383	4	5,370	43	90.7	(74.4–97.6)
Combined protocols§§	7,858	4	7,861	83	95.2	(87.2–98.7)
HPV 6-, 11-, 16-, 18- related genital warts						
Protocol 007	235	0	233	3	100.0	(-139.5–100.0)
Protocol 013	2,261	0	2,279	29	100.0	(86.4–100.0)
Protocol 015	5,401	1	5,387	59	98.3	(90.2–100.0)
Combined protocols¶¶	**7,897**	**1**	**7,899**	**91**	**98.9**	**(93.7–100.0)**

MMWR 2007 Vol.56 RR-2

Greater Immunogenicity in Younger Females

TABLE 6. Immunogenicity bridging between females aged 9–15 years in the immunogenicity studies to females aged 16–26 years in the quadrivalent human papillomavirus (HPV) vaccine efficacy studies (per-protocol immunogenicity population*)

	Females aged 9–15 years in immunogenicity studies			Females aged 16–26 years in efficacy studies		
Assay (cLIA†)	No.	GMT§ (mMU/mL)	(95% CI¶)	No.	GMT (mMU/mL)	(95% CI)
Anti-HPV 6	915	928.7	(874.0–986.8)	2,631	542.6	(526.2–559.6)
Anti-HPV 11	915	1,303.0	(1,223.1–1,388.0)	2,655	761.5	(735.3–788.6)
Anti-HPV 16	913	4,909.2	(4,547.6–5,299.5)	2,570	2,293.9	(2,185.0–2,408.2)
Anti-HPV 18	920	1,039.8	(954.9–1,120.4)	2,796	461.6	(444.0–480.0)

Source: Food and Drug Administration. Product approval information—licensing action, package insert: GARDASIL (quadrivalent human papillomavirus types 6, 11, 16, and 18), Merck & Co. Whitehouse Station, NJ: Food and Drug Administration; 2006. Available at http://www.fda.gov/cber/label/HPVmer013007LB.pdf.

* Includes all persons who were not general protocol violators, received all three vaccinations within acceptable day ranges, were seronegative at day 1 and (for all persons except those aged <16 years in the immunogenicity studies who were not tested) polymerase chain reaction–negative day 1 through month 7 for the relevant HPV type(s), and had a month 7 serum sample collected within an acceptable day range.

† Competitive luminex immunoassay.

§ Geometric mean titer; mMU: milli-Merck units.

¶ Confidence interval.

- 99% seropositivity for all age groups for all vaccine types
- At 1 month after 3rd dose, titers in younger group noninferior to older group
- At month 18, titers in younger group were 2-3x higher than in older group

MMWR 2007 Vol.56 RR-2

4vHPV

- FDA licensed in 2006 for females 9-26yo
- (Efficacy studies in males were ongoing)
- Advisory Committee on Immunization Practices (ACIP) recommended giving at 11-12yo, catch-up vaccination for 13-26yo

Rationale for 2006 Vaccine Recommendations

- Cost-effective: combine with existing well-child visits with immunizations
- Vaccinate before onset of sexual debut to be maximally effective
    - High probability of infection soon after sexual debut
    - 2002 National Survey of Family Growth: 24% of 15yo females had had sex
- Greater immunogenicity when vaccinated at younger age

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HPV Vaccine History in the US

- 2006 – 4vHPV – FDA licensed for females 9-26yo
  - Advisory Committee on Immunization Practices (ACIP) recommended at 11-12yo, catch-up for 13-26yo
- 2009 – 4vHPV – FDA licensed for males 9-26yo for prevention of genital warts
  - ACIP did not recommend routine vaccination of males (not cost-effective if female vaccination >80%)
- 2009 – Cervarix® (2vHPV) – FDA licensed for females 10-25yo
- 2010 – 4vHPV – FDA added indication for prevention of anal cancer in females & males

HPV Vaccine History in the US

- 2011 – ACIP recommended 4vHPV for males at 11-12yo, catch-up for 13-21yo
  - New indication for cancer prevention in males
  - Had not achieved high rates of vaccination in females (only 1/3 of females <17yo had received 3-dose series)
- 2014 – Gardasil®9 (9vHPV) FDA licensed, 4vHPV began being phased out
- 2016 – 2vHPV & 4vHPV no longer available in US
- 2016 – 9vHPV two-dose schedule approved, recommended by ACIP
- 2018 – FDA approved expanded indication to include females & males 27-45yo
  - No change to ACIP recommendations

WHERE ARE WE OVER A DECADE LATER?

Google images

DOSING RECOMMENDATIONS

Alternate Dosing Regimens

- Vaccine costs, logistics, make completion of 3-dose series difficult, particularly in resource-limited settings
- Evidence from 2vHPV vaccine v. control study, that 2 doses (possibly even 1 dose) may be as effective as 3*
- Subsequent studies showed noninferiority of vaccine response to 2 doses of 2vHPV or 4vHPV in girls compared to 3 doses in girls or women°
- 2-dose series already licensed in some countries when World Health Organization recommended this in 2014 for girls 9-14yo

*Kreimer et al. JNCI 2011;103:1444-1451

°Dobson et al. JAMA 2013;309(17):1793-1802

2 doses of 9vHPV

- Study of 1518 participants at 52 centers in 15 countries
- 5 cohorts:
  - Girls 9-14yo, 2 doses 6 months apart
  - Boys 9-14yo, 2 doses 6 months apart
  - Girls & boys 9-14yo, 2 doses 12 months apart
  - Girls 9-14yo, 3 doses over 6 months
  - (Control) females 16-26yo, 3 doses over 6 months
- Immunogenicity noninferior at 4 weeks after last dose

Iversen et al. JAMA 2016;316(22):2411-2421.

Current HPV Vaccine Guidelines

- Target age for initiation: 11-12 year visit (may give as early as 9yo)
- 2 doses of vaccine
  - If initiating series before 15th birthday (2nd dose may be after 15th birthday)
  - 2nd dose 6-12 months after the first
- 3 doses of vaccine
  - If initiating series after 15th birthday
  - 2nd dose at 1-2 months, 3rd dose at 6 months

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Special Populations

- Catch-up immunizations
  - Females through age 26
  - Males through age 21
- Males who have sex with males/transgender
  - Through age 26
- Immunocompromising conditions
  - 3 dose series for all through age 26
  - B lymphocyte antibody deficiencies, T lymphocyte complete or partial defects, HIV, malignancies, transplant recipients, autoimmune disease, immunosuppressive therapy
- History of sexual abuse or assault
  - Begin series at 9yo

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Interrupted Schedules

- No need to restart
- In studies of 3 doses of 4vHPV, longer intervals between the 1st and 2nd, and 2nd and 3rd, doses resulted in **higher** antibody responses after the subsequent dose

Further Study

- Persistence of antibody responses after 2 doses
    - Need for boosters?
- Effects of vaccination on clinical outcomes
- Use/outcomes in older populations
    - 9vHPV approved through 45yo (still not recommended for routine schedules)
- Additional alternate schedules
    - 1 dose?
    - 2 doses in older populations?

HPV CANCER PREVENTION

Global Momentum

- May 2018 – World Health Organization Director-General issued global call to action to eliminate cervical cancer
- June 2018 – American Cancer Society launches Mission: HPV Cancer Free
- June 2018 – all National Cancer Institute-designated cancer centers endorse goal of eliminating HPV-related cancers

Healthy People 2020

- Office for Disease Prevention and Health Promotion, establishes benchmarks and monitors progress for 10-year objectives
- Objective: Increase percentage of adolescents 13-15yo who receive recommended doses of HPV vaccine to **80%**
  - In 2016: 45.1% of females, 36.4% of males
  - From 2016 to 2017:
    - AR: 30% to 41.9% for females, 27.5% to 20% for males
    - TN: 37.6% to 43.1% for females, 30.9% to 26.6% for females

https://www.healthypeople.gov/2020/topics-objectives/topic/immunization-and-infectious-diseases/objectives

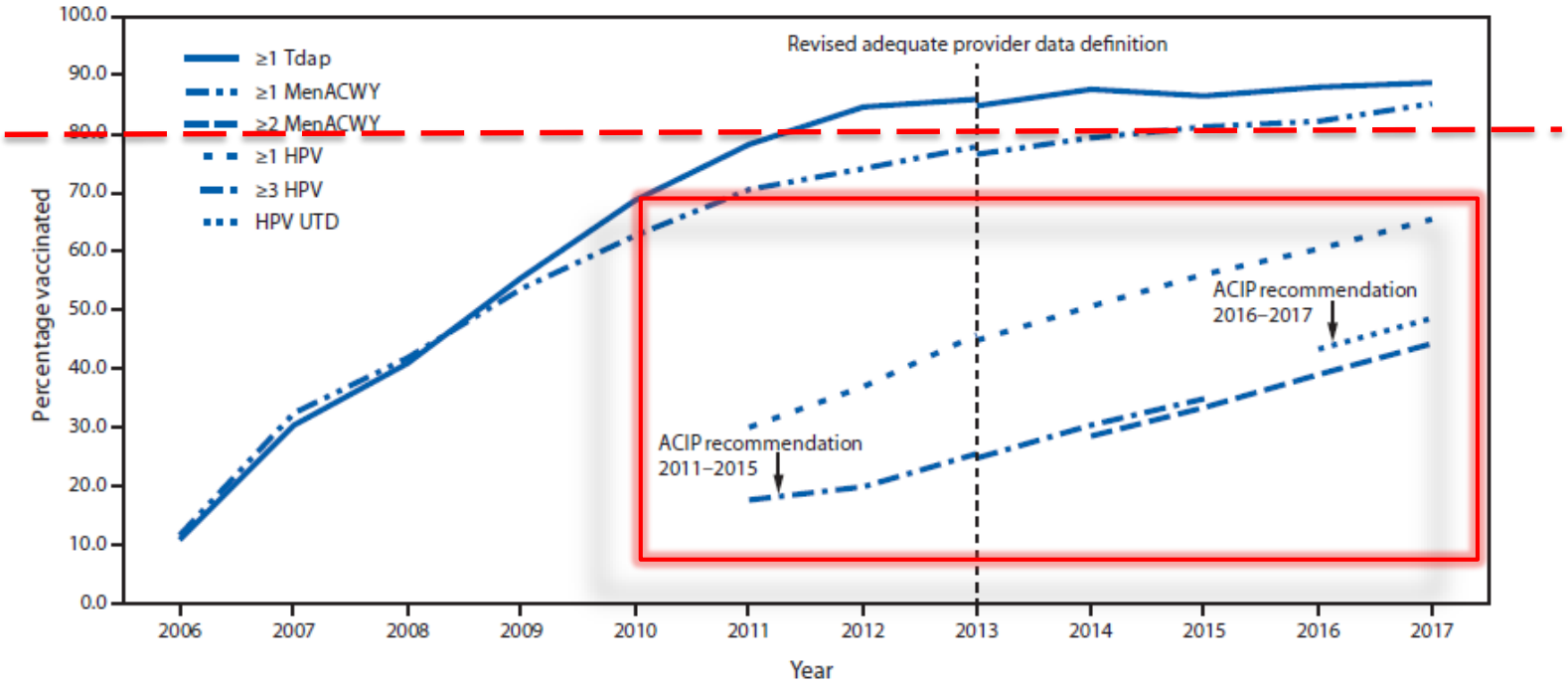
Mission: HPV Cancer Free

- Goal: 80% vaccination rate by 2026 (20 years after introduction of the first HPV vaccine)
- "If we can achieve sustained 80% HPV vaccination … combined with continued screening and treatment for cervical pre-cancers, *we could see the elimination of cervical cancer in the US* ***within 40 years***."

- Richard C. Wender, MD, American Cancer Society

HPV Vaccination Coverage

FIGURE. Estimated coverage with selected vaccines and doses* among adolescents aged 13–17 years, by survey year and ACIP recommendations† — National Immunization Survey-Teen, United States, 2006–2017§

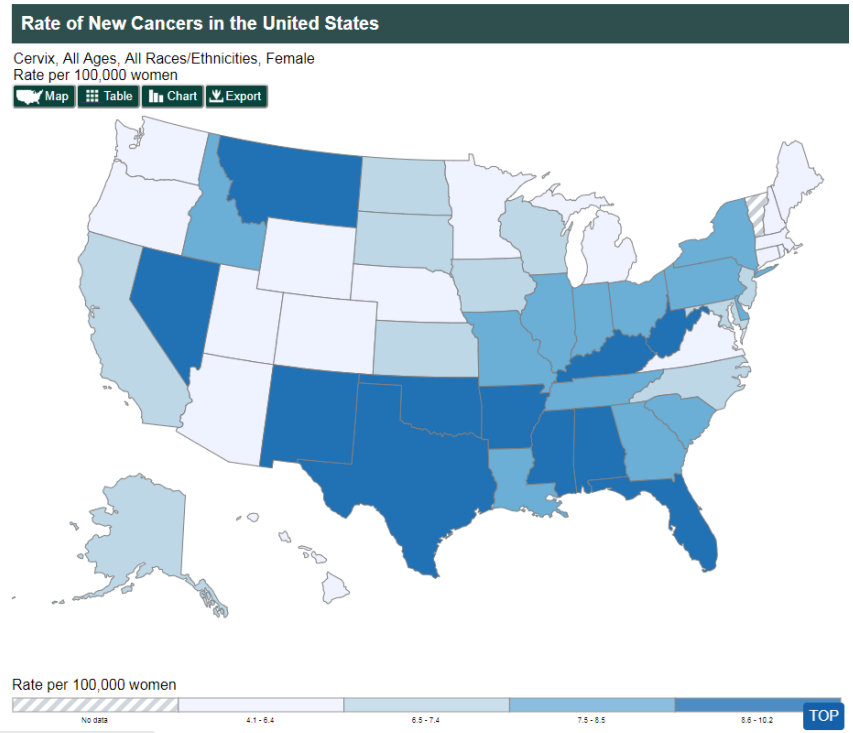


- No data on HPV vaccination for all adolescents before 2011, when ACIP recommended for boys as well as girls
- ACIP recommendation 2016 allowed for 2-dose schedule (changing definition of up-to-date)

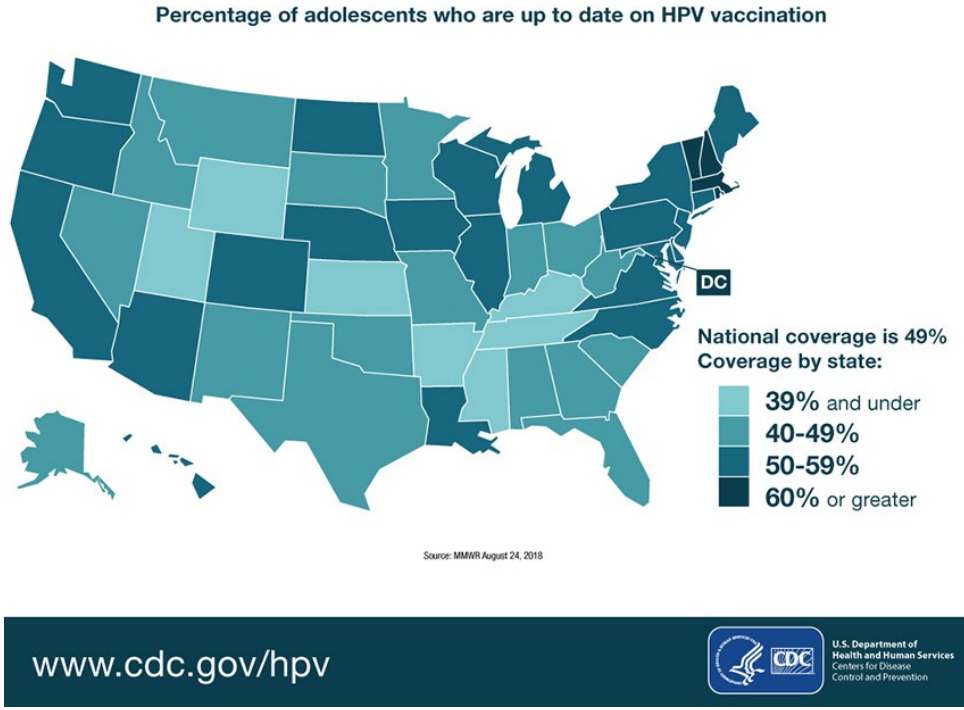
MMWR Vol 67 No 33 August 24, 2018

South has High Rates of Cervical Cancer, Low Rates of HPV Vaccination

New Cervical Cancer Diagnoses



HPV Vaccination Coverage



Lowest/Highest: HI, WA, OR, CO, AZ, NE, MI, NH, MA, VA

Highest/Lowest: AR, MS, KY

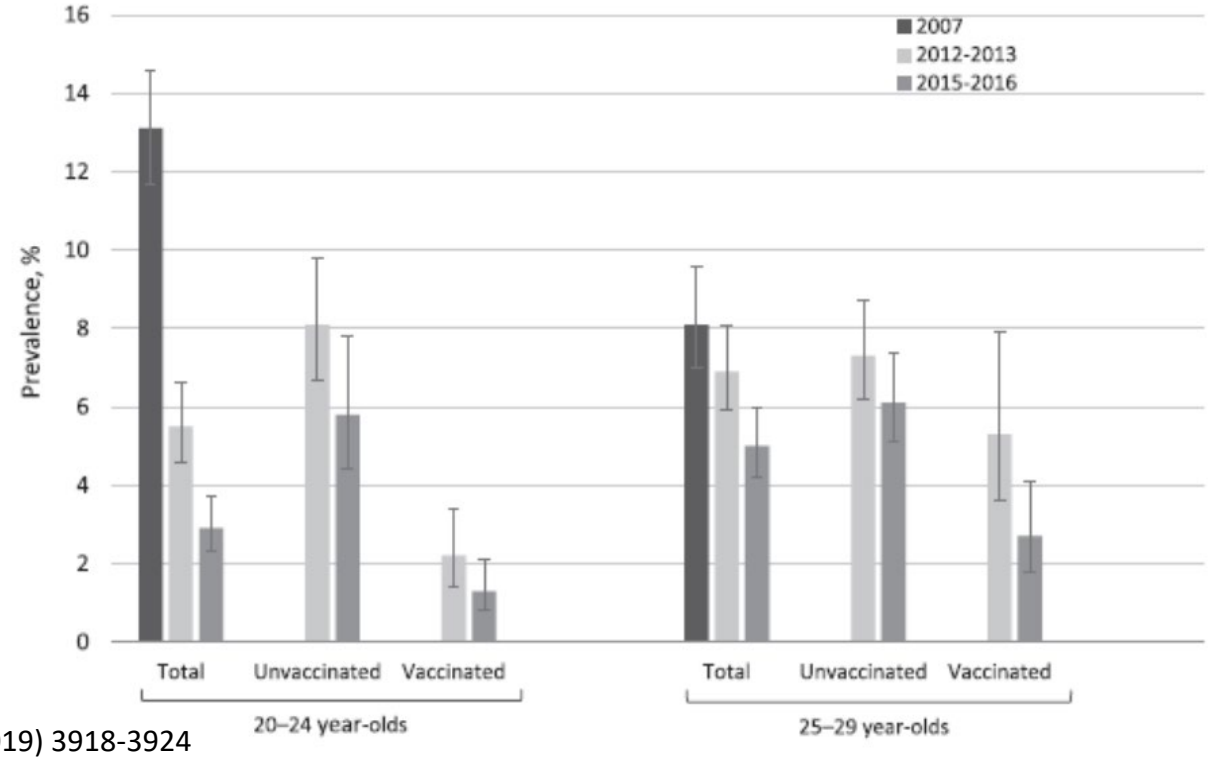
Declines in HPV Vaccine Types

- 12,788 residual cervical cytology specimens, Kaiser Permanente Northwest (Portland, OR)
- 20-24yo and 25-29yo
- 3 time periods: 2007 (baseline, unvaccinated), 2012-2013 and 2015-2016
- 69-72% were non-Hispanic White women

Markowitz et al. Vaccine. 37 (2019) 3918-3924

Evidence of Herd Effects Among Unvaccinated

4vHPV Type Prevalence:	Baseline 2007	2012-2013	2015-2016
20-24yo total	13.1%	5.5%* (↓58%)	2.9%* (↓78%)
20-24yo, unvaccinated	13.1%	8.1%* (↓38%)	5.8%* (↓55%)
20-24yo, ≥1 dose vaccine	N/A	2.2%* (↓83%)	1.3%* (↓90%)
25-29yo total	8.1%	6.9%	5.0%* (↓38%)
25-29yo, unvaccinated	8.1%	7.3%	6.1%* (↓25%)
25-29yo, ≥1 dose vaccine	N/A	6.1%* (↓25%)	2.7%* (↓67%)



Markowitz et al. Vaccine. 37 (2019) 3918-3924

Meta-Analysis of Population-Level Impact of HPV Vaccination

- HPV Vaccination Impact Study Group
- 2015: first systematic review & meta-analysis
- Update published in *Lancet* online 6/26/19
- Included 65 articles from 14 high-income countries
- Data from 60 million individuals up to 8 years post-vaccination follow-up

Drolet et al. Lancet. August 10, 2019

Meta-Analysis: Changes in HPV Prevalence

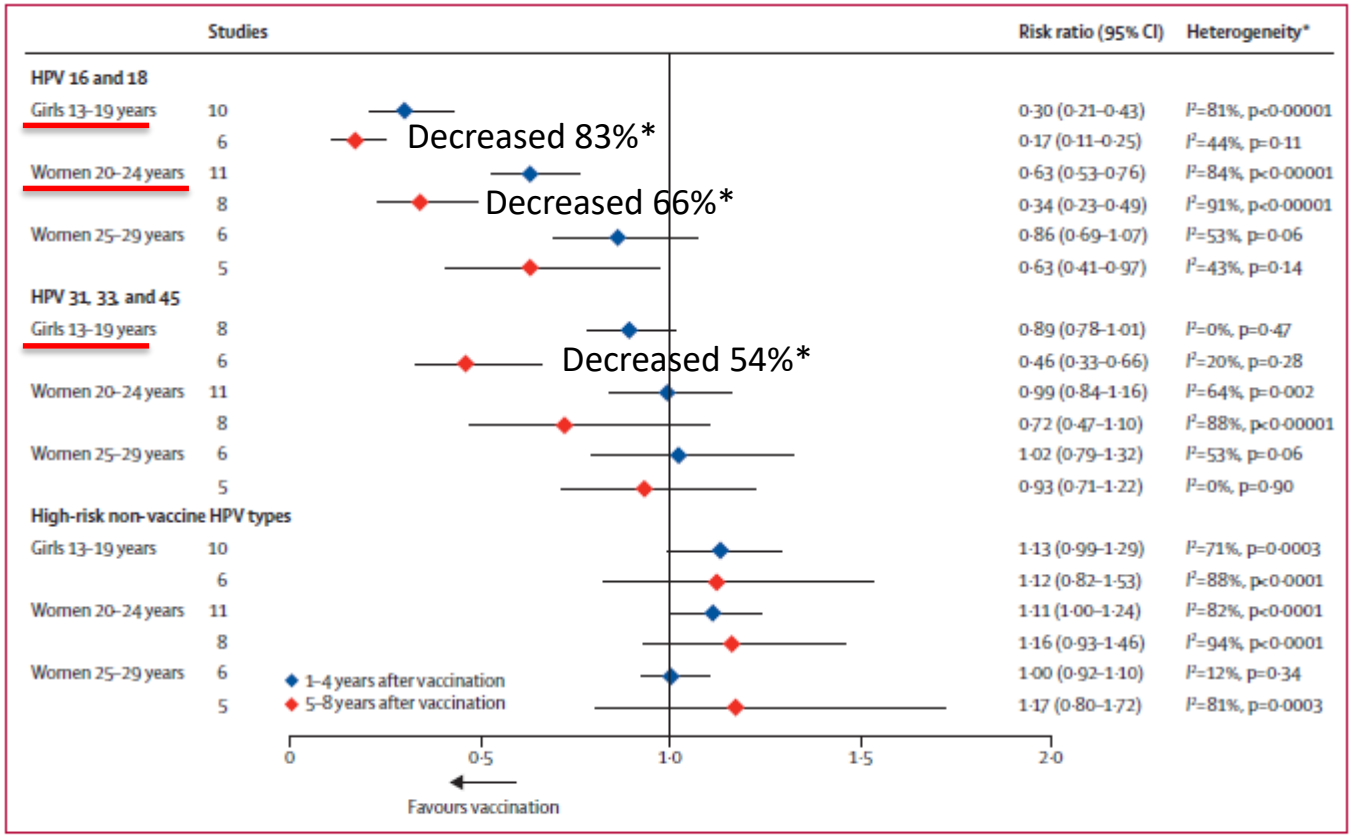


Figure 2: **Changes in the prevalence of HPV infections between pre-vaccination and post-vaccination periods**
HPV=human papillomavirus. *p values are associated with the χ^2 statistic.

Drolet et al. Lancet. August 10, 2019

Meta-Analysis: Changes in Anogenital Wart Diagnosis

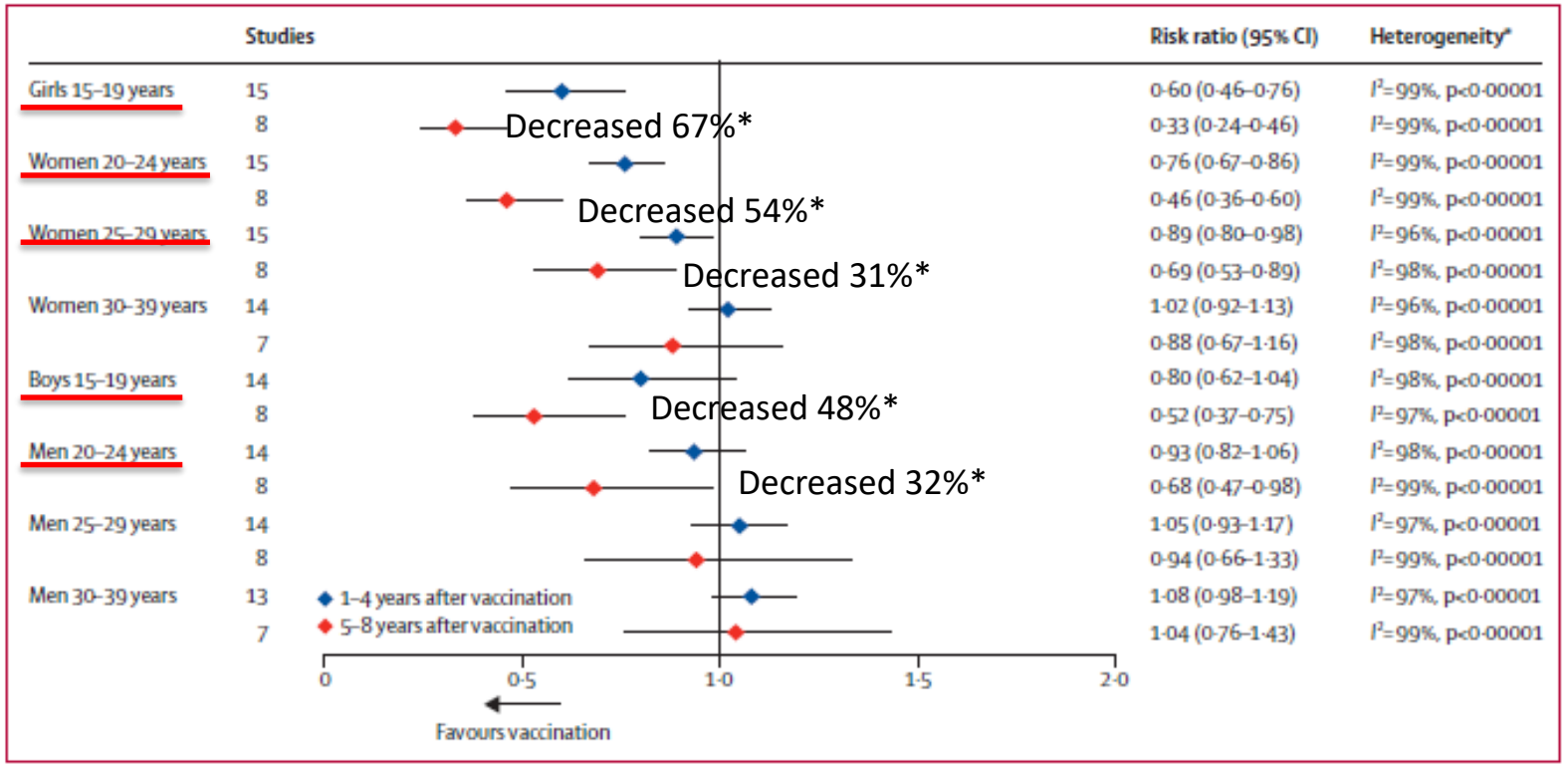


Figure 3: Changes in anogenital wart diagnoses between pre-vaccination and post-vaccination periods in countries using the quadrivalent vaccine
*p values are associated with the χ^2 statistic.

Drolet et al. Lancet. August 10, 2019

Meta-Analysis: Changes in CIN2+

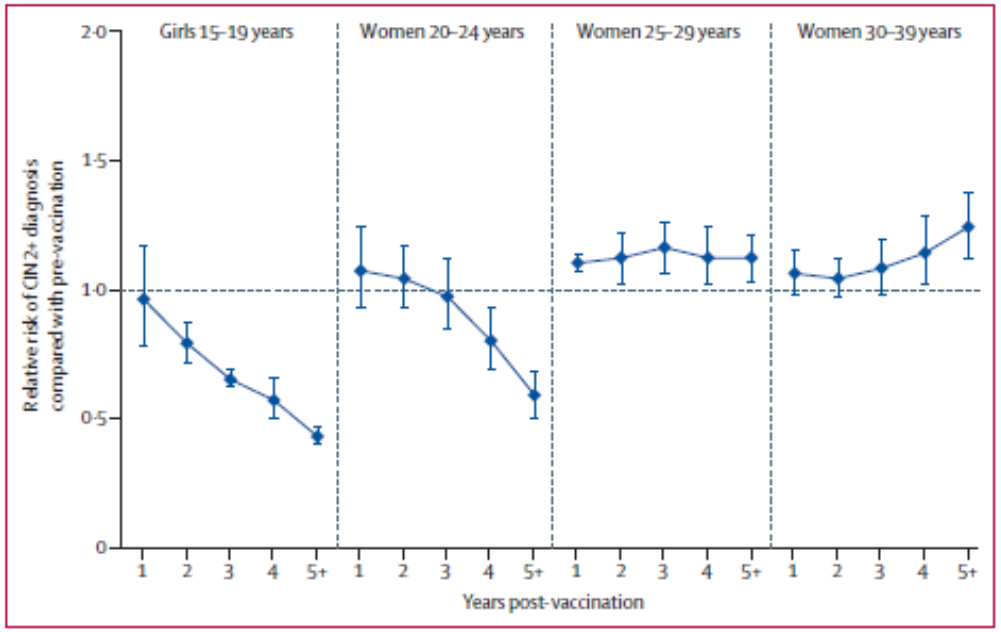


Figure 6: Changes in CIN2+ among screened girls and women during the first 7 years after the introduction of girls-only human papillomavirus vaccination, in countries with multi-cohort vaccination and high vaccination coverage

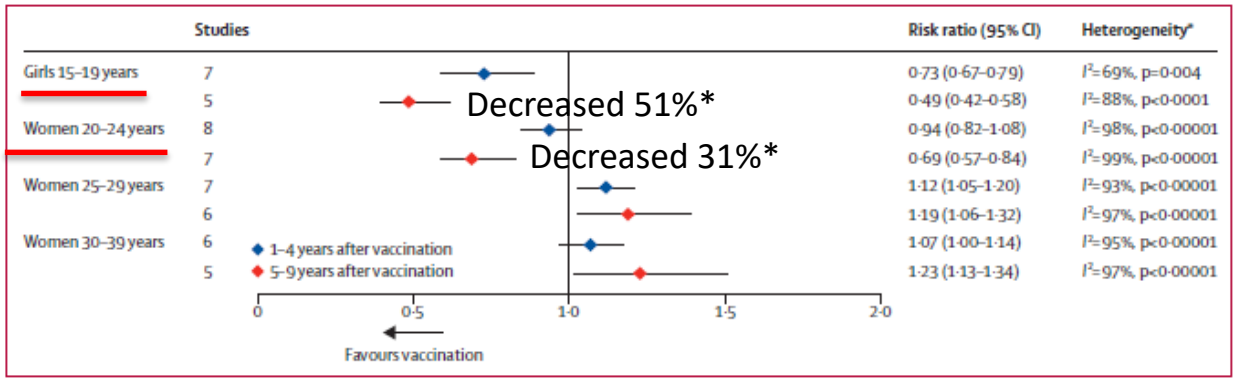


Figure 5: Changes in CIN2+ among screened girls and women between the pre-vaccination and post-vaccination periods
CIN2+=cervical intraepithelial neoplasia grade 2+. *p values are associated with the χ^2 statistic.

Countries with multi-cohort vaccination and high coverage (≥50%) were Australia, Canada (British Columbia), Denmark, Scotland, and the USA.

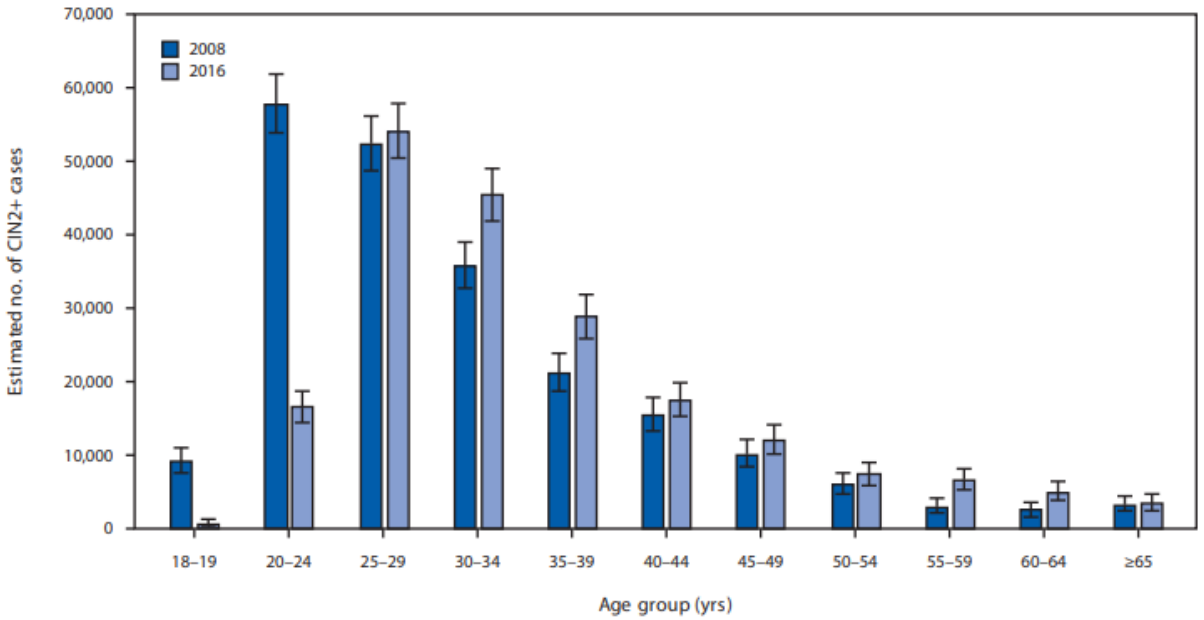
The authors noted that USA was included in this analysis because of data indicating an association between screening participation and HPV vaccination, noting that this coverage is likely to be higher than the overall vaccination coverage in the population. They did a sensitivity analysis excluding the USA and results were unchanged.

Drolet et al. Lancet. August 10, 2019

Estimated CIN2+ Cases in US, 2008 & 2016

- HPV-IMPACT (HPV vaccine impact monitoring project)
- Rates decreased significantly for women 18-24yo
- Rates increased significantly for women 40-64yo

FIGURE 1. Estimated number of diagnosed CIN2+ cases,* by age group — United States, 2008 and 2016

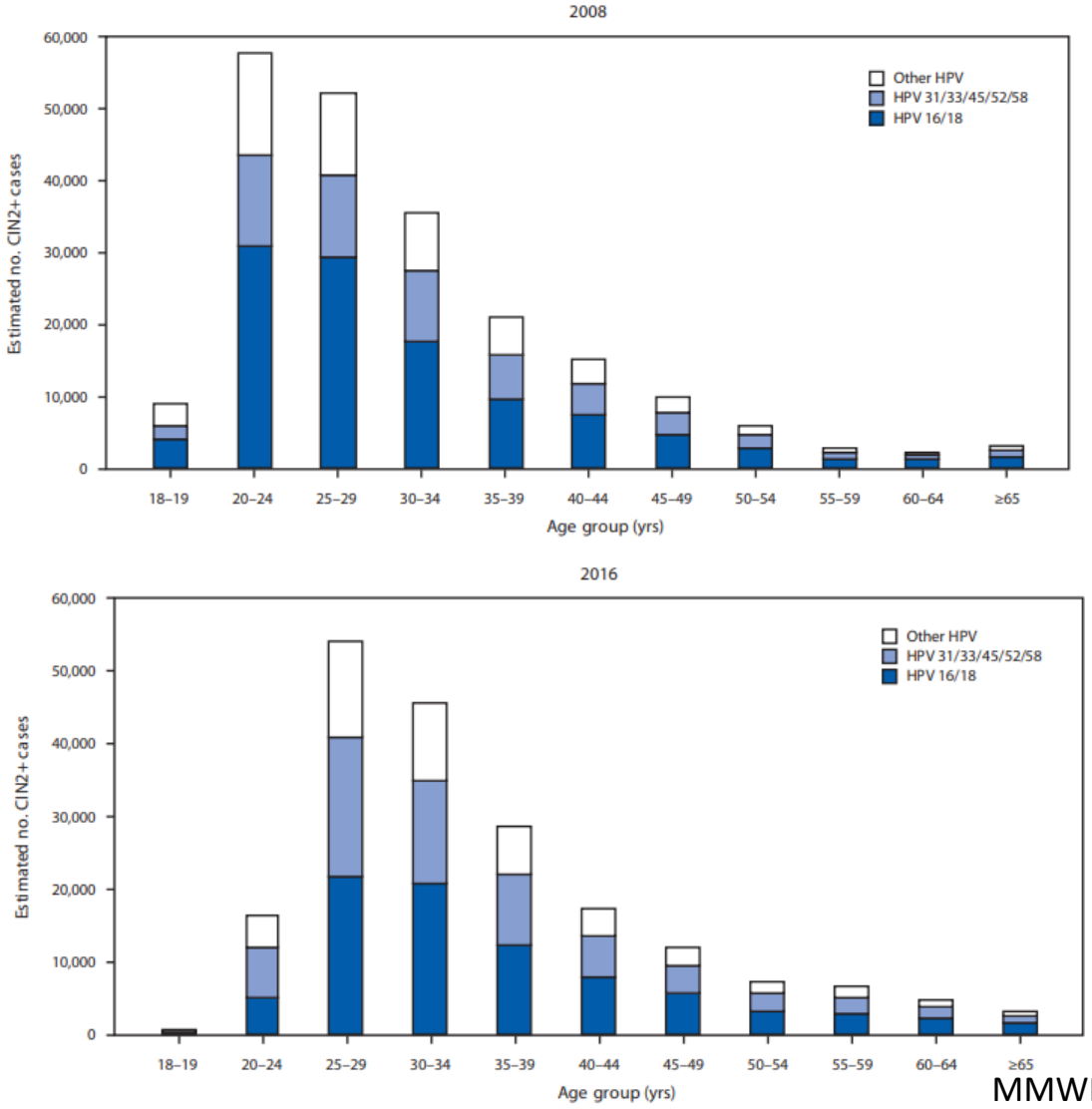


Abbreviation: CIN2+ = cervical intraepithelial neoplasia grades 2, 3, and adenocarcinoma in situ.
* Error bars indicate 95% confidence intervals, which were calculated by applying the upper and lower limits of CIN2+ rates to the age-specific U.S. population.

Average annual percentage change (AAPC)
18-19yo: -38.5
20-24yo: -14.9

MMWR Vol 68 No 15 April 19, 2019

Estimated CIN2+ Cases by Age and HPV Type, 2008 & 2016



In both 2008 & 2016, an estimated 76% of CIN2+ cases were due to HPV types in the 9-valent vaccine

HPV-16/-18 decreased from 52% to 43%

MMWR Vol 68 No 15 April 19, 2019

BE LIKE AUSTRALIA

Australian HPV Vaccination Campaign

- April 2007 – started fully government-funded program administering 4vHPV
- April 2007 – December 2009
  - Vaccinated all girls 12-17yo through school program
  - Vaccinated women up to 25yo through community providers
- Ongoing school vaccination program – give at 12-13yo (first year of high school)
  - Boys added to program in 2013
  - Catch-up program for boys up to 15yo through 2015

Hall et al. Lancet Public Health. January 2019

Australia's Successes

- 2016: by 15yo 78.6% of girls and 72.9% of boys were fully vaccinated
- Australia already had among the lowest incidence and mortality rates for cervical cancer
    - 1991 – introduced National Cervical Screening Program (NCSP) → incidence decreased by 50% in women >25yo
    - 83% coverage from 2011-2015
    - 2017: transitioned to primary HPV screening model
- 2018: changed to 9vHPV vaccine, 2-dose course

Hall et al. Lancet Public Health. January 2019

"The early adoption of both HPV vaccination and HPV-based cervical screening, high uptake of the vaccine, and high participation in screening position ***Australia as the first country that is likely to eliminate cervical cancer*** as a public health issue."

Hall et al. Lancet Public Health. January 2019

Cervical Cancer Elimination in Australia

- Potential elimination thresholds:
  - Rare cancer threshold: annual age-standardized incidence of 6 new cases/100K women
  - Lower threshold: 4 new cases/100K women
- Model assumed 82% of girls and 76% of boys would have completed HPV series (based on midpoint of observed 2- and 3-dose coverage in 2017)

Hall et al. Lancet Public Health. January 2019

Cervical Cancer Elimination in Australia

- Assuming ongoing high rates of vaccination and screening:
- In 2020 the rare cancer threshold will be reached (6 new cases/100K)
- Stricter definition of 4 new cases/100K would be reached in 2028

Hall et al. Lancet Public Health. January 2019

St. Jude Children's Research Hospital
HPV Cancer Prevention Initiative

St. Jude's Role in HPV Cancer Prevention

- As the only NCI-designated Comprehensive Cancer Center dedicated solely to children, St. Jude has important responsibility to promote cancer prevention in youth
- St. Jude is located in an area of the country with high HPV-related cancer incidence, and low rates of HPV vaccination
- St. Jude's goal is to reduce cancer deaths locally and nationally through increased uptake of HPV vaccination

St. Jude Children's Research Hospital

Will pursue goals across geographic areas:

- Memphis area
- Tennessee
- Regionally, including catchment areas of St. Jude affiliates:
  - Baton Rouge, LA
  - Charlotte, NC
  - Huntsville, AL
  - Johnson City, TN
  - Peoria, IL
  - Shreveport, LA
  - Springfield, MO
  - Tulsa, OK
- Nationally

St. Jude HPV Initiative Planning

- HPV Vaccine Strategy Workshop held at St. Jude May 2019 – invited leading national experts/key stakeholders
- September 2019 – will begin interviewing candidates for Director
- FY2020 – planning and pre-implementation, develop administrative core team

Stay tuned!

Audience Participation

- True/False

Over 90% of HPV-associated cancers are preventable through HPV vaccination

Thank you!