Human papillomavirus: Opportunity to eradicate gynecologic dysplasia and cancer

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Presenter

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Disclosures

- Army Maj. Erica Hope, M.D. has no relevant financial or non-financial relationships to disclose relating to the content of this activity.
- The views expressed herein are those of the author and do not reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Defense Health Agency, the Department of the Army and Air Force, the Department of Defense or the U.S. Government.
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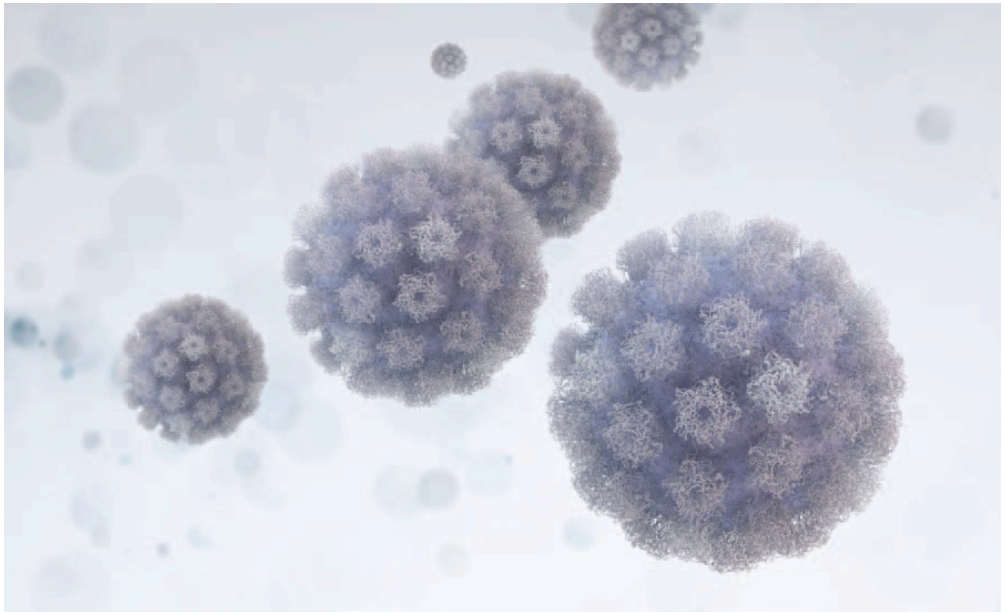
Learning Objectives

At the end of the presentation, the participants will be able to:

1. Identify human papillomavirus (HPV) as a cause of gynecologic dysplasia and malignancy.
2. Summarize the burden of HPV-related dysplasia and cancer on the healthcare system.
3. Evaluate HPV vaccine as a cancer prevention method.
4. Assess avenues to increase HPV vaccination rates.

Human Papillomavirus

- Circular double-stranded DNA virus
- >200 subtypes
- Low vs high risk
- Viral oncogenes
- Persistent infections



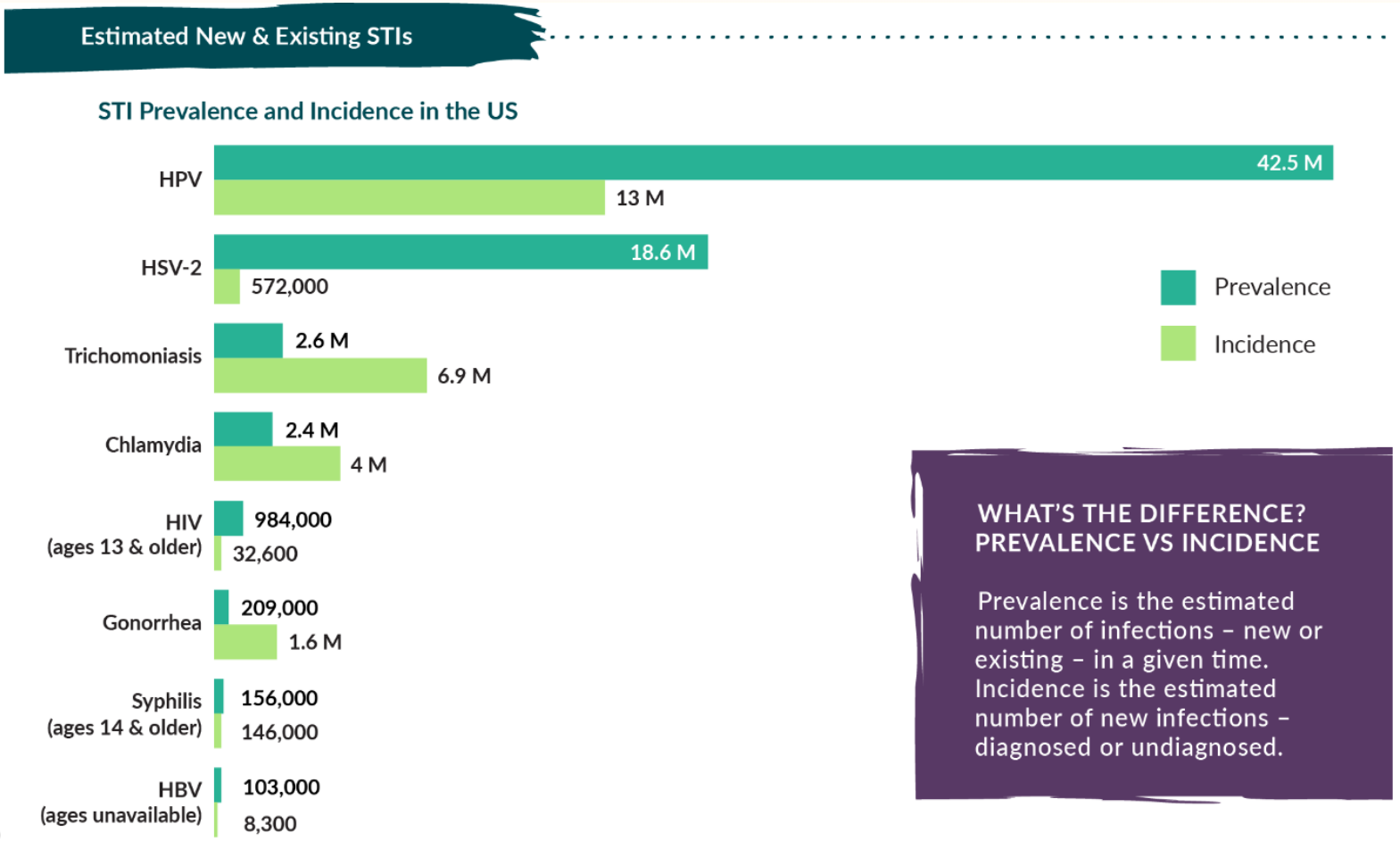
(Narisawa-Saito & Kiyono, 2007)
(CDC.org, 2020)

Human Papillomavirus

- Most common sexually transmitted infection (STI)
- High rate of new infection
- Asymptomatic
- Risk of dysplasia and malignancy
- No cure

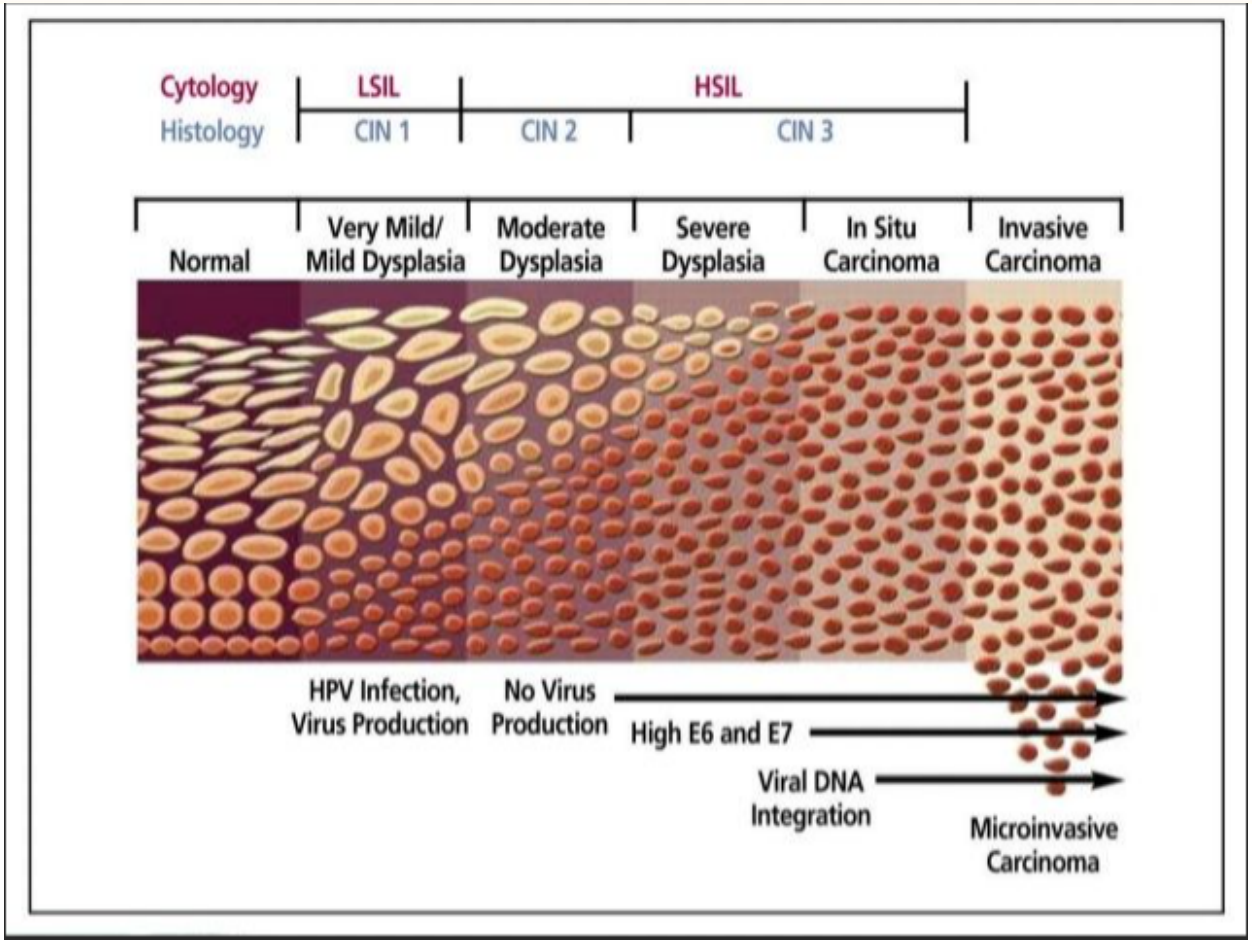
(Dunne et al., 2007)
(Satterwhite et al., 2013).

HPV Disease Burden



(CDC, 2021)

HPV Infection



(Pgneet.co, n.d.)

Cervical Cancer Screening

Population*	Recommendation	Recommendation Grade†
Women aged <21 years	No screening	D
Women aged 21 – 29 years	Cervical cytology alone every 3 years	A
Women aged 30 – 65 years	Cervical cytology alone every 3 years **OR** hrHPV testing‡ alone every 5 years **OR** Co-testing (hrHPV testing‡ and cervical cytology) every 5 years	A
Women aged >65 years with adequate prior screening	No screening	D
Women who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade cervical precancerous lesion or cervical cancer	No screening	D

(USPSTF, 2018)

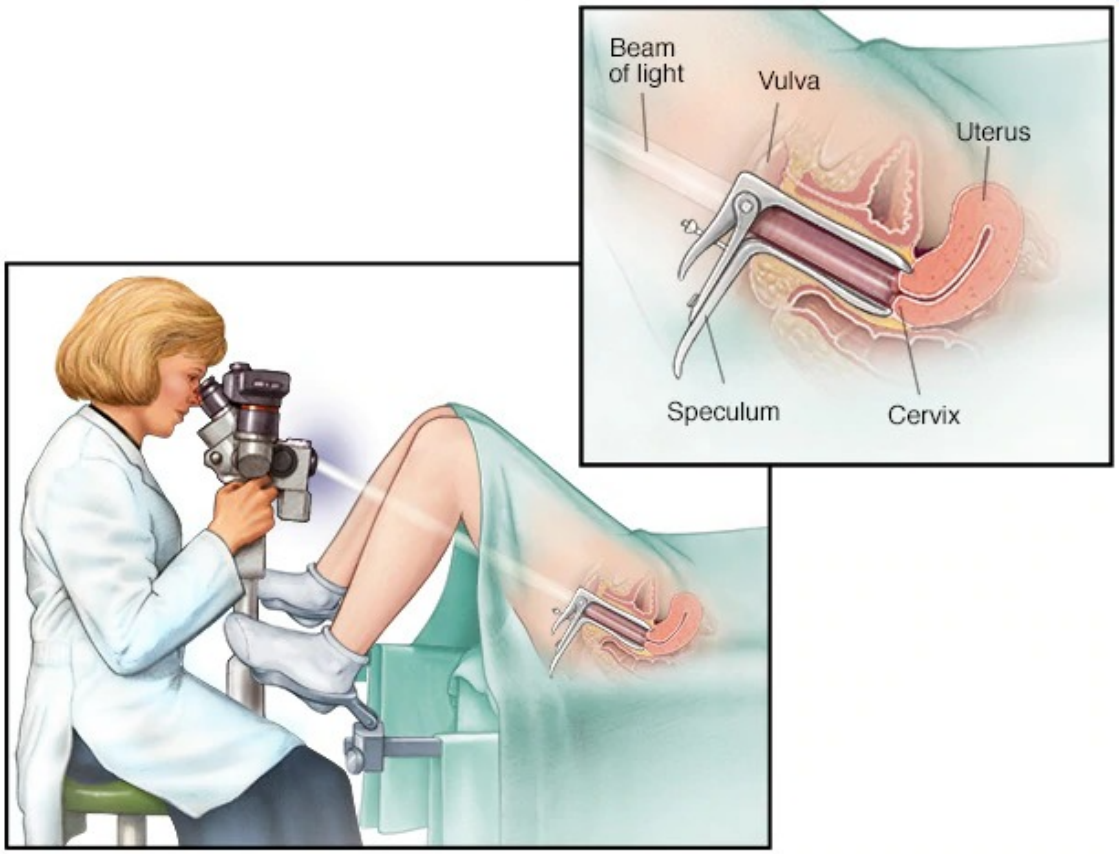
HPV Testing

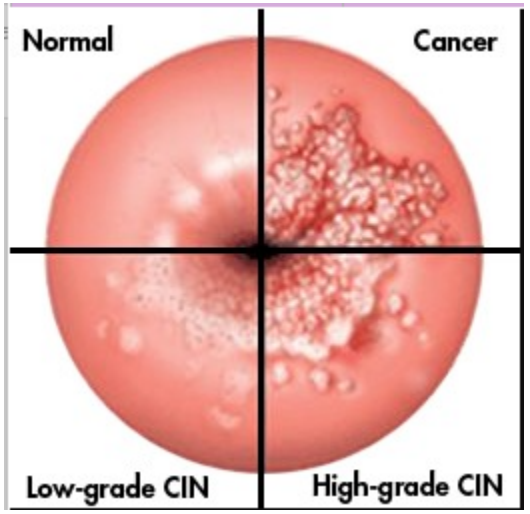
Table 1 Comparison of the 5 FDA-approved testing platforms.

Test	Hybrid Capture II	Cervista	cobas	Aptima	BD Onclarity
Manufacturer	Qiagen	Hologic	Roche	Gen Probe (Hologic)	Becton Dickinson
Year FDA approved for reflex HPV testing and HPV/Papanicolaou co-testing	2001	2009	2011	2011	2018
Year approved for primary screening	N/A	N/A	2014 (ThinPrep only)	N/A	2018 (SurePath only)
Method	DNA (non-PCR based) Signal amplification: full genome probe	DNA (non-PCR based) Signal amplification: L1, E6, and E7 genes	DNA (PCR based); Target amplification: L1 gene target	mRNA (PCR based); Target amplification: *E6/E7* gene target	DNA (PCR based); Target amplification: *E6/E7* gene target
Genotypes detected	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 with genotyping of 16 and 18	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68; genotyping as separate test (16, 18/45)	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68; simultaneous, discrete identification of 16, 18, and 45
Clinical trial	ASC-US/LSIL Triage Study (ALTS), 2006 CAP	Cervista HPV HR	ATHENA[12]	CLEAR trial	Onclarity trial (baseline phase)[13]
Clinical validation	Extensive	Limited	Limited	Limited	Limited
Sensitivity for CIN2/3	63.6%-100%[2,14-24]	92.8%-100%[25]	71.1%-99%[2,15-21,26]	55.3%-100%[2,14,17-20,22-24,26-30]	85.7%-100%[18,31-33]
Specificity for CIN2/3	6.2%-98.4%[2,14-24]	–	24%-86.2%[2,15-21,26]	28.8%-99.2%[2,14,17-20,22-24,26-30]	17%-98.8%[18,31-34]
Built-in internal control	No	Yes (HIST2H2BE)	Yes (ß-globin)	Yes, an internal control	Yes (ß-globin)

(FDA Executive Summary, 2019)
(Salazar et al., 2019)

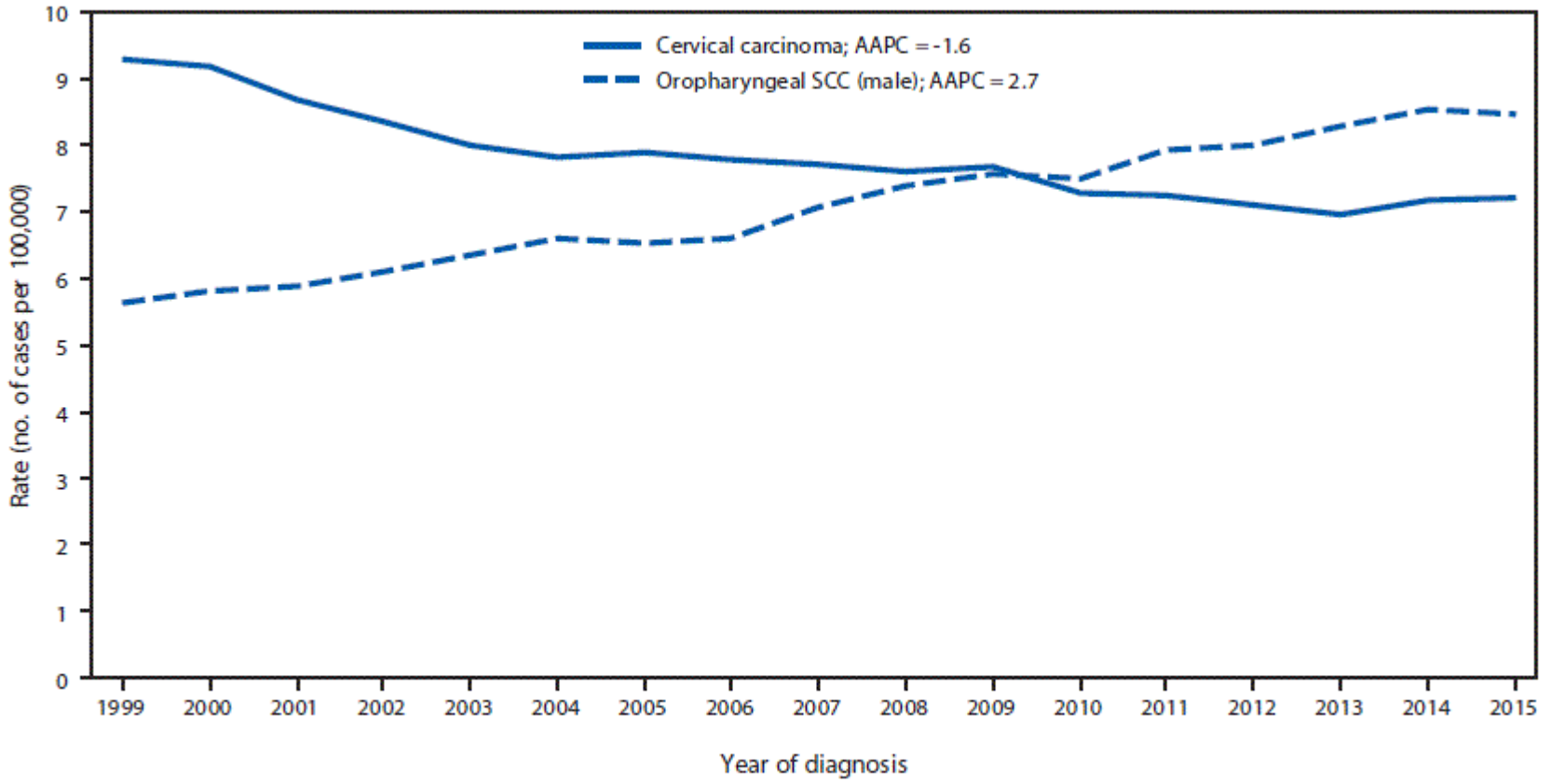
Abnormal Cervical Cancer Screening





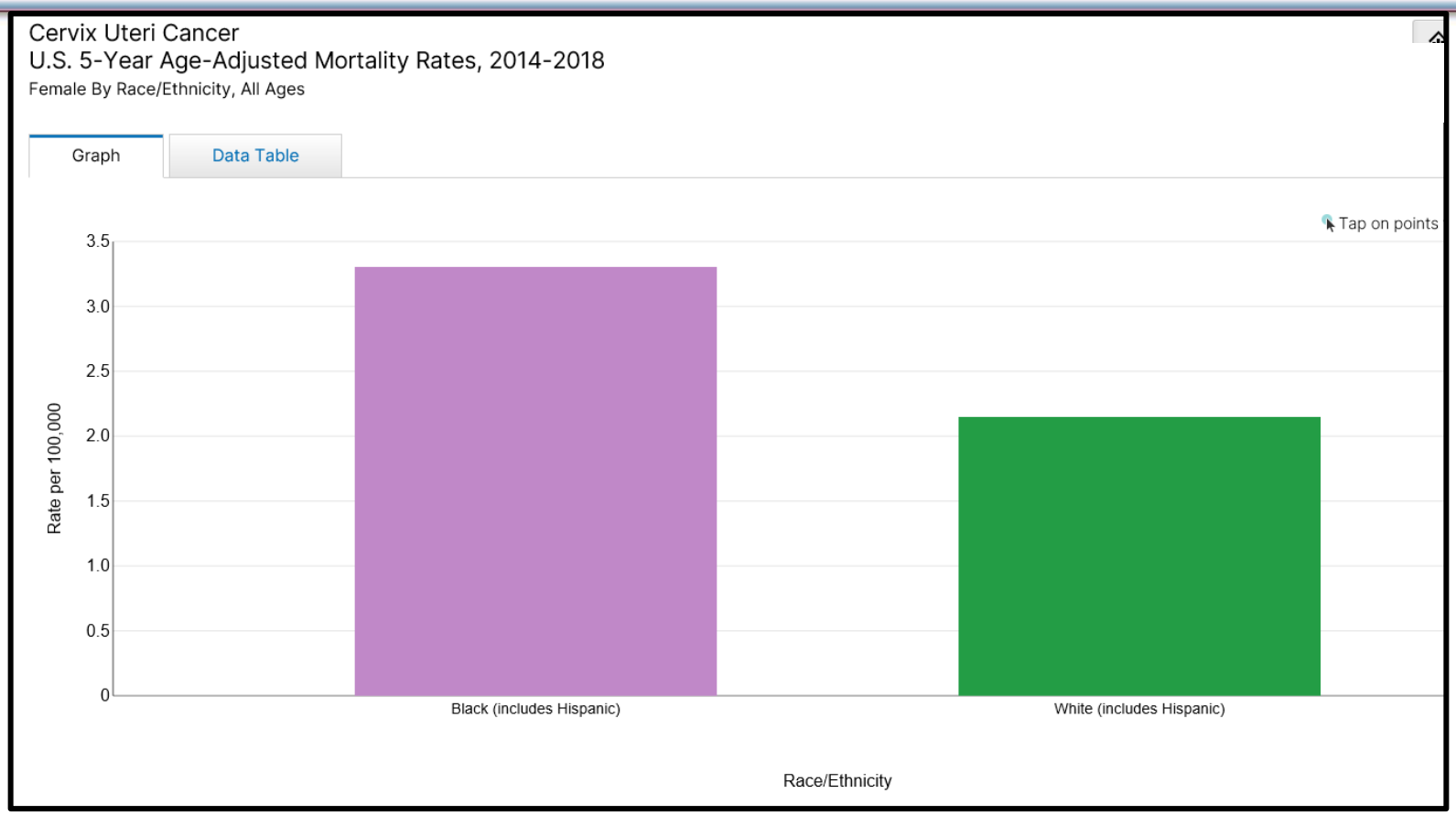
(Mayoclinic.org, n.d.)
(FDA Executive Summary, 2019)

HPV Related Cancers



(CDC.org, n.d.)
(VanDyne et al, 2018)

Cervical Cancer Racial Disparities

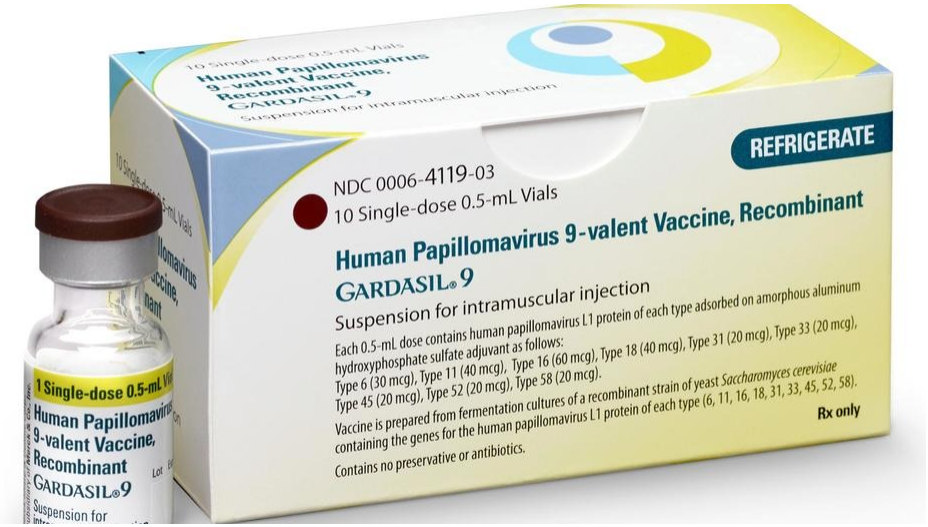


(Seer.cancer.gov, 2021)
(Dalton & Farley, 2017)

HPV Vaccine

- 2006 - Gardasil® HPV4
- 2009 - Cervarix HPV2
- 2014 - Gardasil®9 HPV9

- Viral-like particle
- Non-infectious



(The History of Vaccines, n.d.)
(Taberna et al., 2017)
(Meites et al., 2016)
(Merck, n.d.)

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HPV Vaccine

TABLE 1. Characteristics of the three human papillomavirus (HPV) vaccines licensed for use in the United States

Characteristic	Bivalent (2vHPV)*	Quadrivalent (4vHPV)†	9-valent (9vHPV)§
Brand name	Cervarix	Gardasil	Gardasil 9
VLPs	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Manufacturer	GlaxoSmithKline	Merck and Co., Inc.	Merck and Co., Inc.
Manufacturing	*Trichoplusia ni* insect cell line infected with L1 encoding recombinant baculovirus	*Saccharomyces cerevisiae* (Baker's yeast), expressing L1	*Saccharomyces cerevisiae* (Baker's yeast), expressing L1
Adjuvant	500 μg aluminum hydroxide, 50 μg 3-O-desacyl-4′ monophosphoryl lipid A	225 μg amorphous aluminum hydroxyphosphate sulfate	500 μg amorphous aluminum hydroxyphosphate sulfate
Volume per dose	0.5 ml	0.5 ml	0.5 ml
Administration	Intramuscular	Intramuscular	Intramuscular

Abbreviation: L1 = the HPV major capsid protein; VLPs = virus-like particles.

(Petrosky et al, 2015)

Vaccine Dosing Schedule

TABLE. Recommended number of doses and intervals for human papillomavirus (HPV) vaccine, by age at series initiation and medical conditions — United States, 2016

Return

Population	Recommended number of HPV vaccine doses	Recommended interval between doses
Persons initiating HPV vaccination at ages 9 through 14 years,* except immunocompromised persons†	2	0, 6–12 months§
Persons initiating HPV vaccination at ages 15 through 26 years¶ and immunocompromised persons† initiating HPV vaccination at ages 9 through 26 years	3	0, 1–2, 6 months**

*ACIP recommends routine HPV vaccination for adolescents at age 11 or 12 years; vaccination may be given starting at age 9 years.

† Persons with primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity (see also: Medical conditions)

§ In a 2-dose schedule of HPV vaccine, the minimum interval between the first and second doses is 5 months.

¶ For persons who were not adequately vaccinated previously, ACIP recommends vaccination for females through age 26 years and for males through age 21 years; males ages 22 through 26 years may be vaccinated. Vaccination is recommended for some persons aged 22 through 26 years; see Medical conditions and Special populations.

** In a 3-dose schedule of HPV vaccine, the minimum intervals are 4 weeks between the first and second doses, 12 weeks between the second and third doses, and 5 months between the first and third doses.

(Meites et al., 2016)
(Kreimer et al., 2018)
(Chesson et al., 2008)

Vaccine Safety

- >100 million doses given
- Overall well tolerated
- Similar safety profiles in 4vHPV vs 9vHPV
- No serious adverse events reported
  - Vaccine Adverse Events Reporting System (VAERS)
  - Vaccine Safety Datalink (VSD)

(CDC.org, n.d.)

Vaccine Efficacy

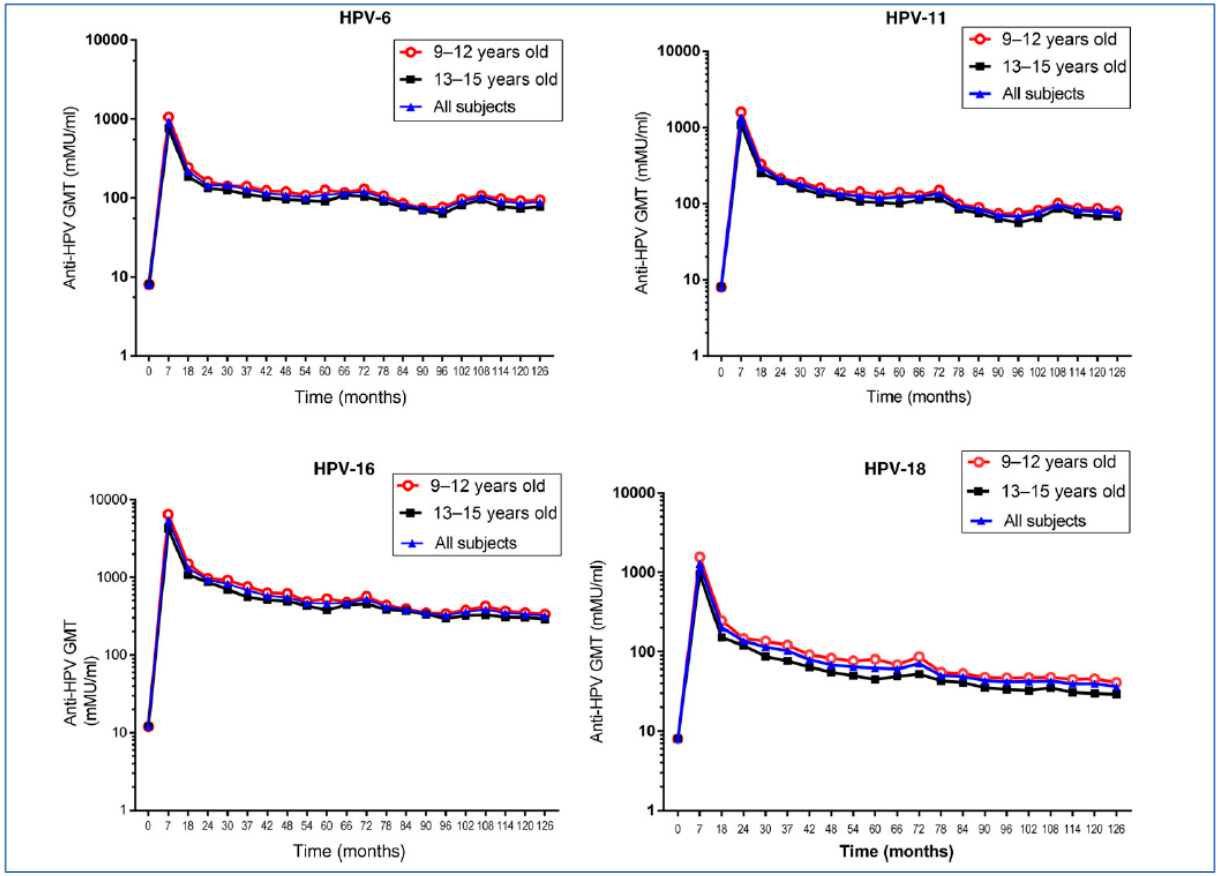
TABLE 2. Results of a Phase III efficacy trial comparing 9-valent human papillomavirus (HPV) vaccine (9vHPV) with quadrivalent HPV vaccine (4vHPV), per protocol population* in females aged 16 through 26 years†

		9vHPV		4vHPV		Vaccine efficacy	
Endpoint-related types	Endpoint	No. participants	Cases	No. participants	Cases	%	(95% CI)
HPV 31, 33, 45, 52, 58	≥CIN2, VIN2/3, ValN2/3	6,016	1	6,017	30	96.7	(80.9–99.8)
	≥CIN2	5,948	1	5,943	27	96.3	(79.5–99.8)
	6-month persistent infection	5,939	35	5,953	810	96.0	(94.4–97.2)
HPV 6, 11, 16, 18	≥CIN2§	5,823	1	5,832	1	—	—
	Anogenital warts	5,876	5	5,893	1	—	—

Abbreviations: CI = confidence interval; ≥CIN2 = cervical intraepithelial neoplasia grade 2 or 3 or adenocarcinoma in situ; ValN2/3 = vaginal intraepithelial neoplasia grade 2 or 3; VIN2/3 = vulvar intraepithelial neoplasia grade 2 or 3.

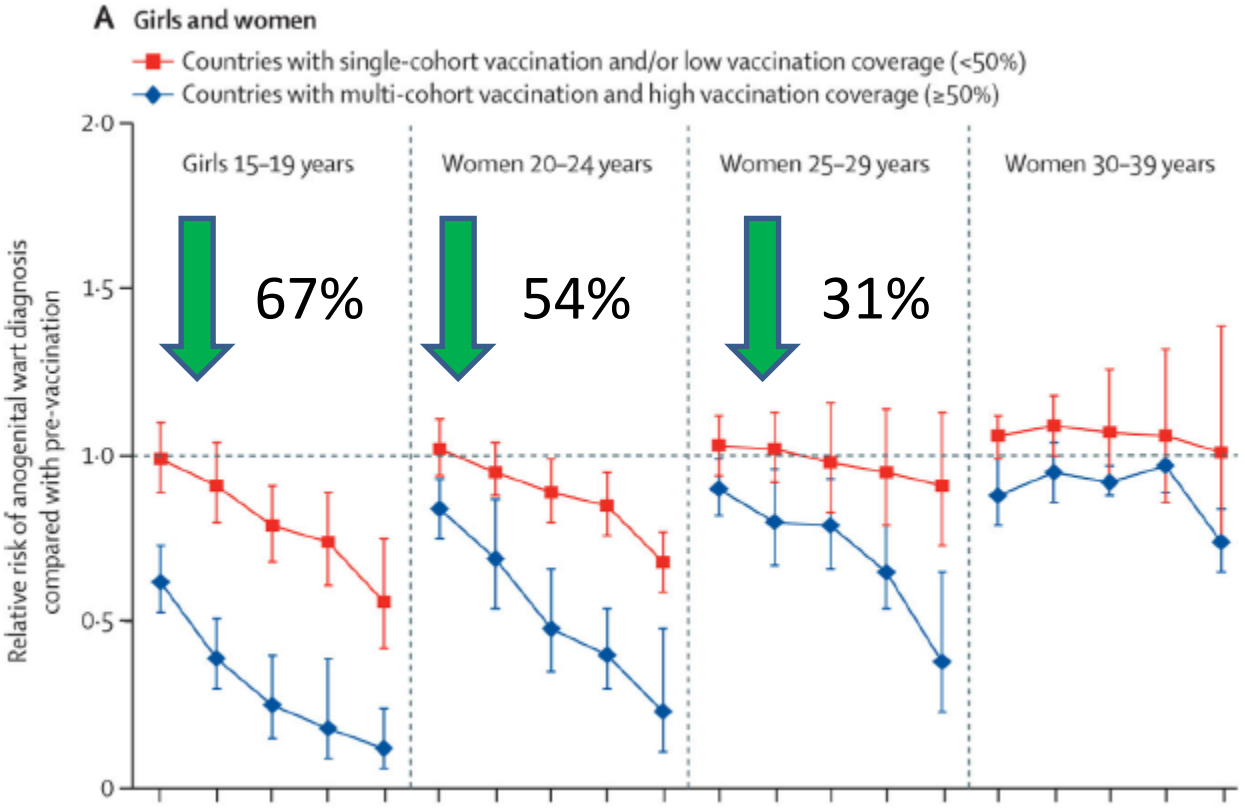
(Meites E et al, 2019)

Vaccine Efficacy



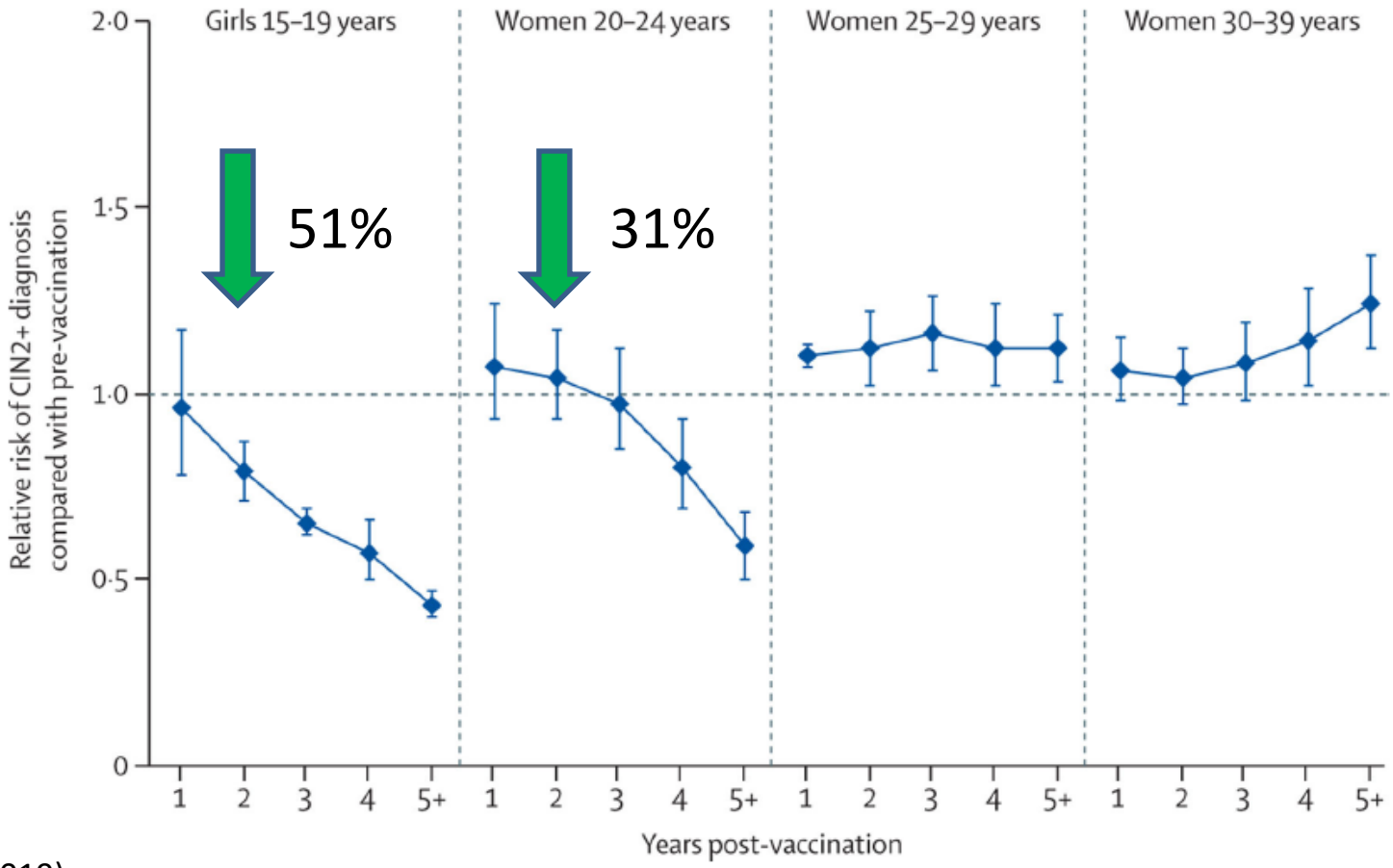
(Ferris et al, 2017)

Vaccine Efficacy



(Drolet et al, 2019)

Vaccine Efficacy



(Drolet et al, 2019)

Vaccine Efficacy – United States

- HPV-IMPACT
  - Five US communities
  - Data from 2008 and 2016
  - Decreased incidence of CIN2+
- Few studies have reported on decline in adenocarcinoma in situ (AIS)
  - 22% decrease in 20-24 year olds

(McClung et al., 2019)
(Cleveland et al., 2019)

Cancer Prevention

- Sweden
- >1.6 million females
- Ages 10-30 from 2006-2017
- 4vHPV vaccine
- **First study with decreased cervical CANCER incidence after vaccination

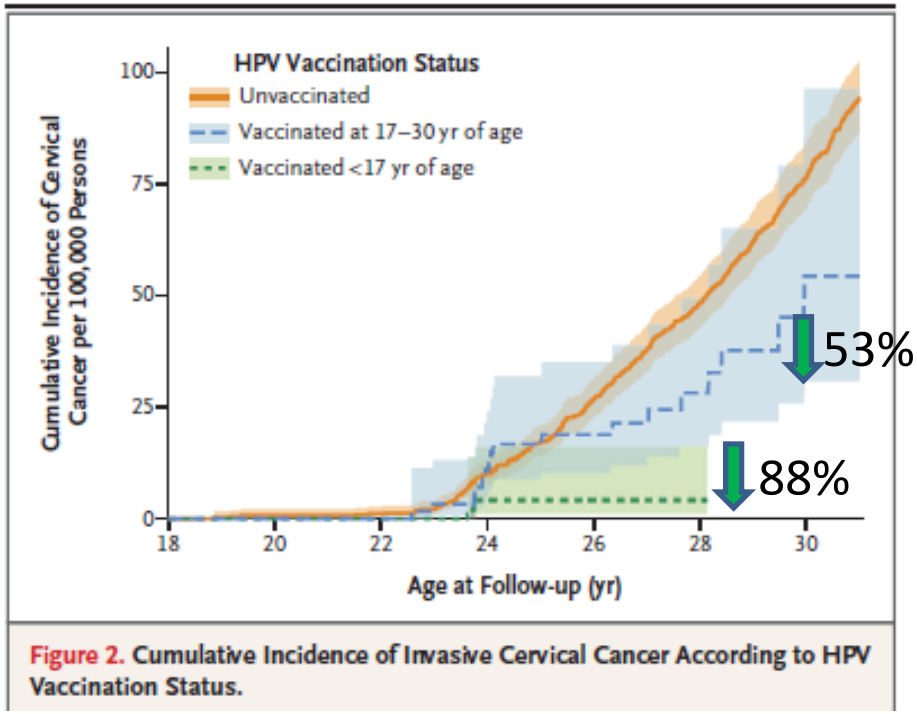


Figure 2. Cumulative Incidence of Invasive Cervical Cancer According to HPV Vaccination Status.

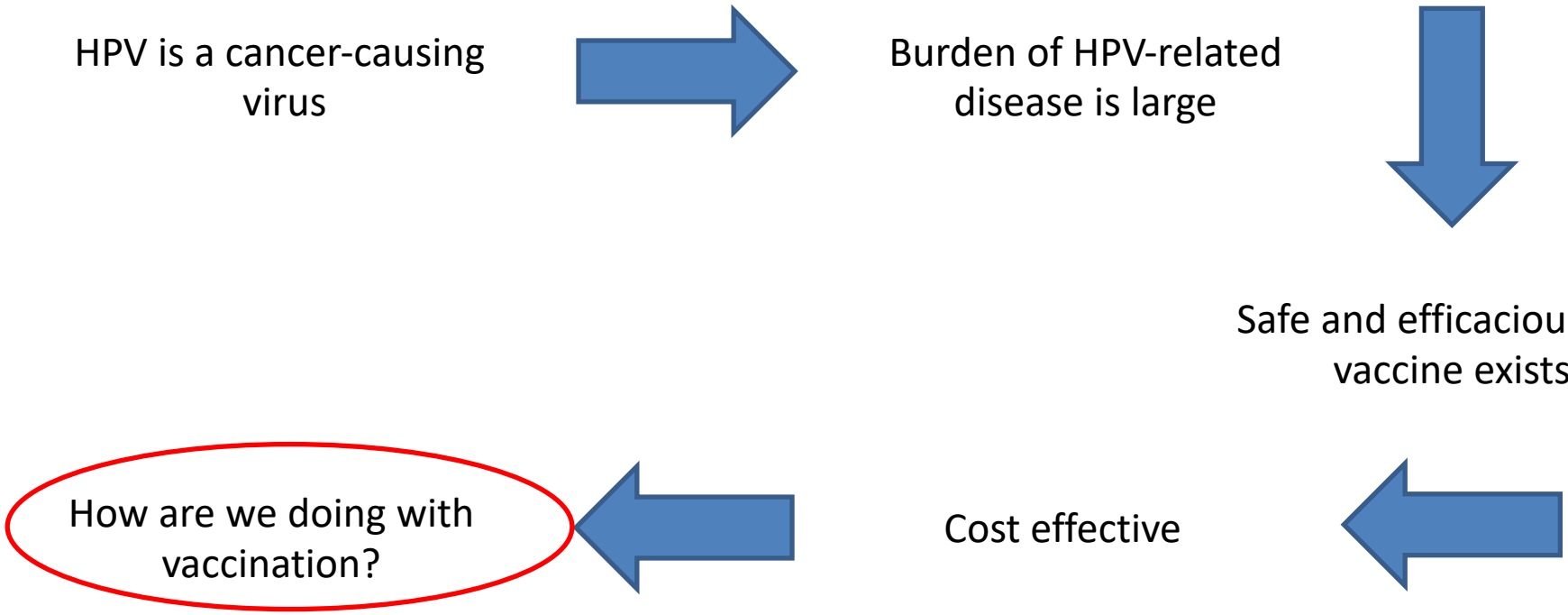
(Lei et al., 2020)

Vaccine Cost

- Merck vaccine assistance program
- Vaccines for Children
- Children's Health Insurance Programs
- Grants
- Universities or health departments
- Affordable Care Act

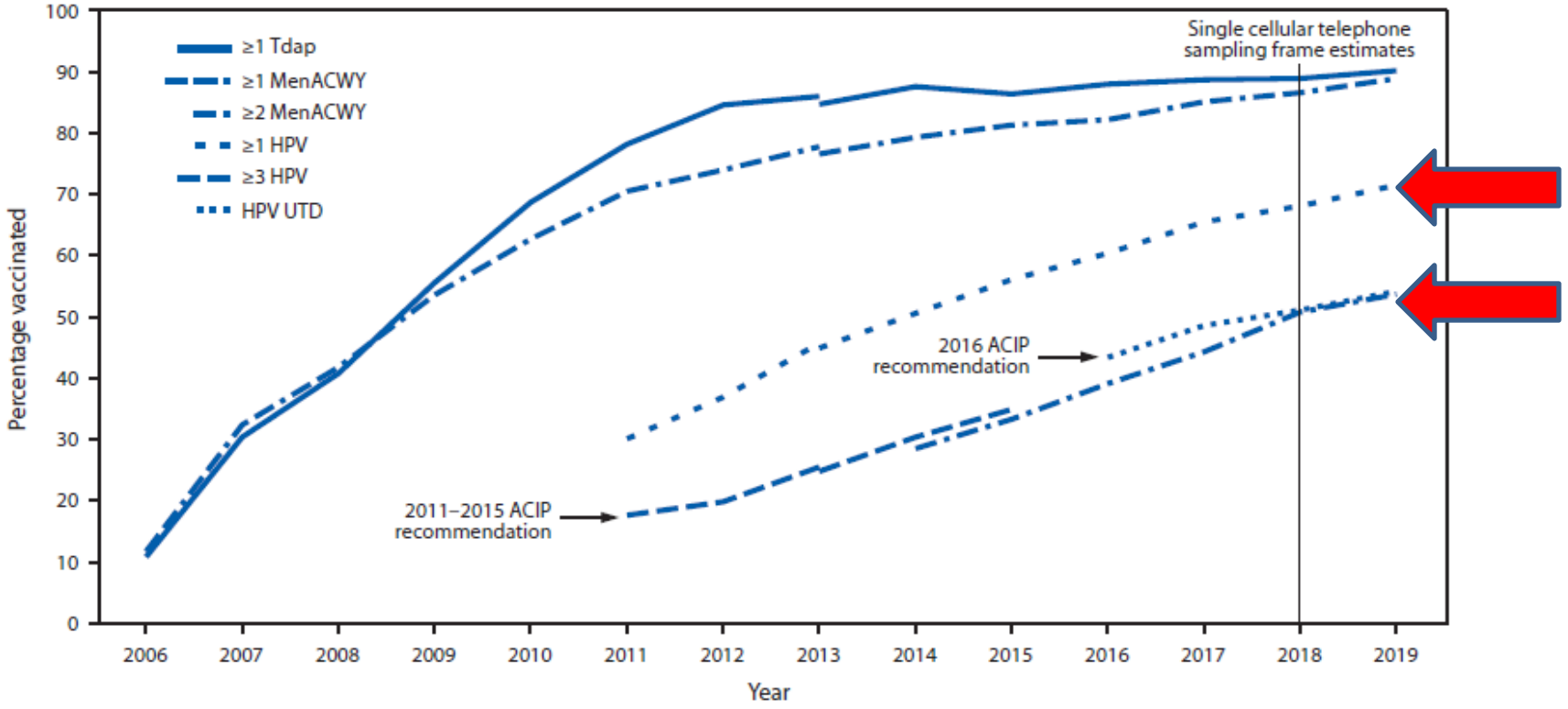
(Chesson et al., 2008)
(Petrosky et al., 2015)
(Ng et al., 2018)

Cancer Prevention



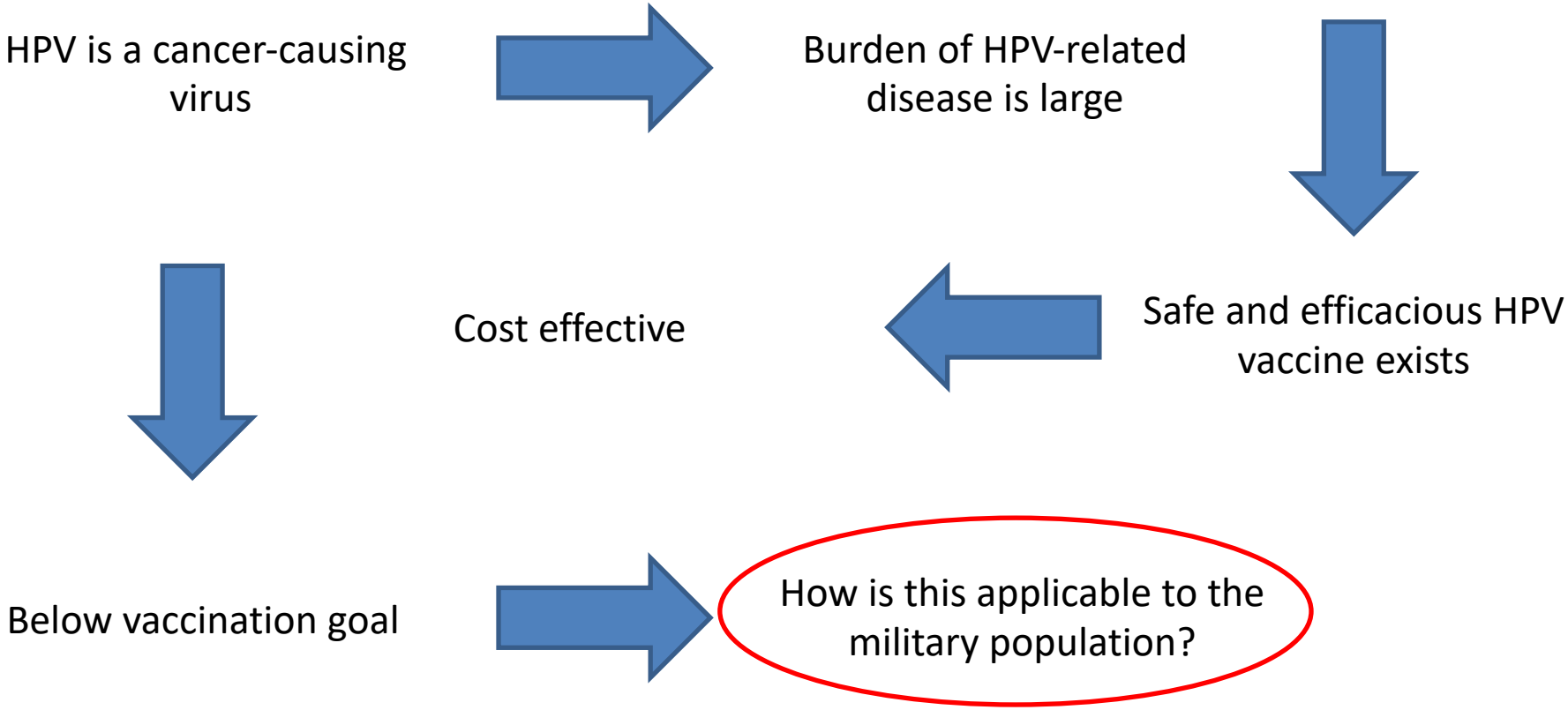
HPV Vaccination Rates

FIGURE. Estimated vaccination coverage with selected vaccines and doses* among adolescents aged 13–17 years, by survey year and Advisory Committee on Immunization Practices (ACIP) recommendations† — National Immunization Survey-Teen (NIS-Teen)§,¶ — United States, 2006–2019



Elam-Evans et al, 2020; World Health Organization, 2017; Spencer et al, 2019; Chen et al, 2020.

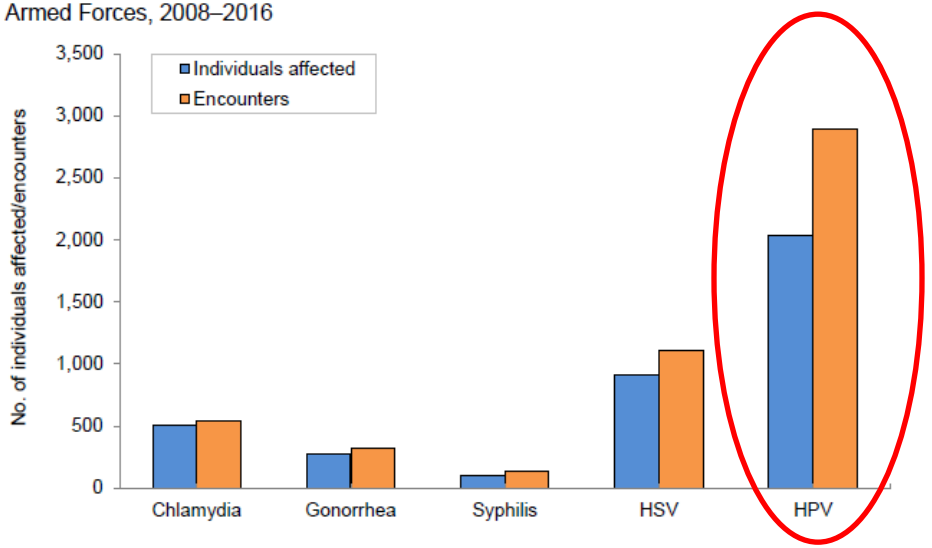
Cancer Prevention



HPV in Military

- One of the most common STIs in ADSM
- More encounters during deployments
- Higher prevalence than in general population

FIGURE 9. Individuals affected by sexually transmitted infections (STIs), and encounters for STIs, during deployment to U.S. Central Command operations, active component, U.S. Armed Forces, 2008–2016

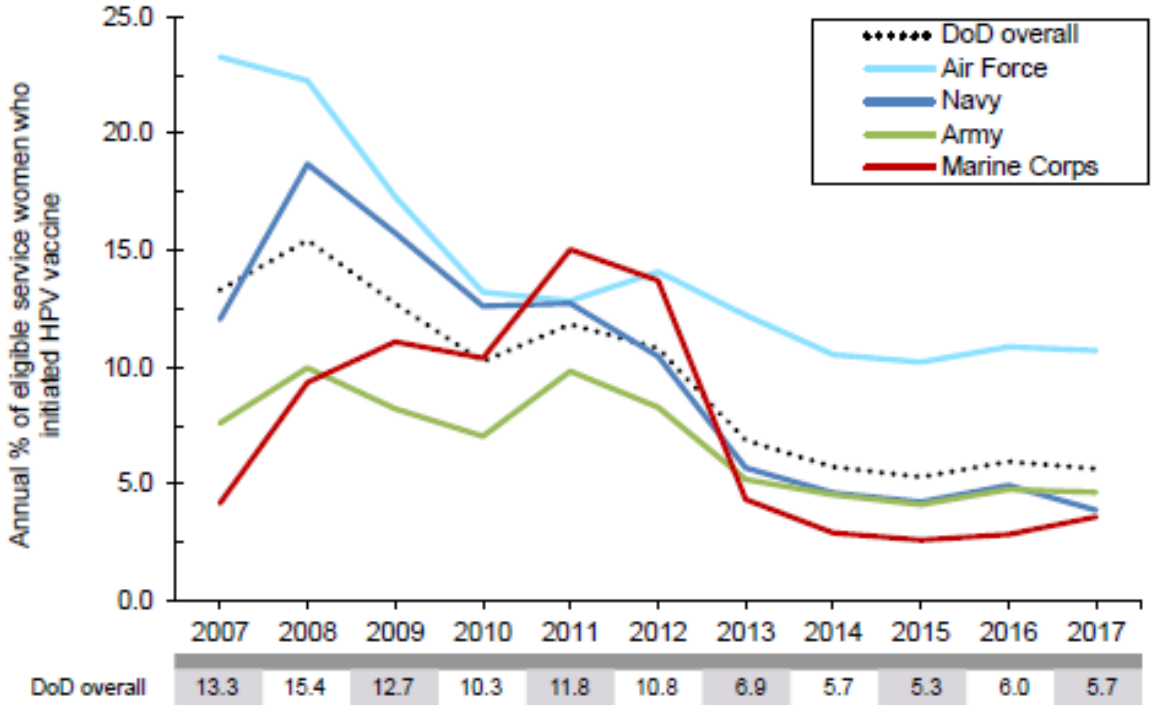


HSV, herpes simplex virus; HPV, human papillomavirus

(Deiss et al., 2015)
(Stahlman & Oetting, 2007)
(Masel et al., 2015)

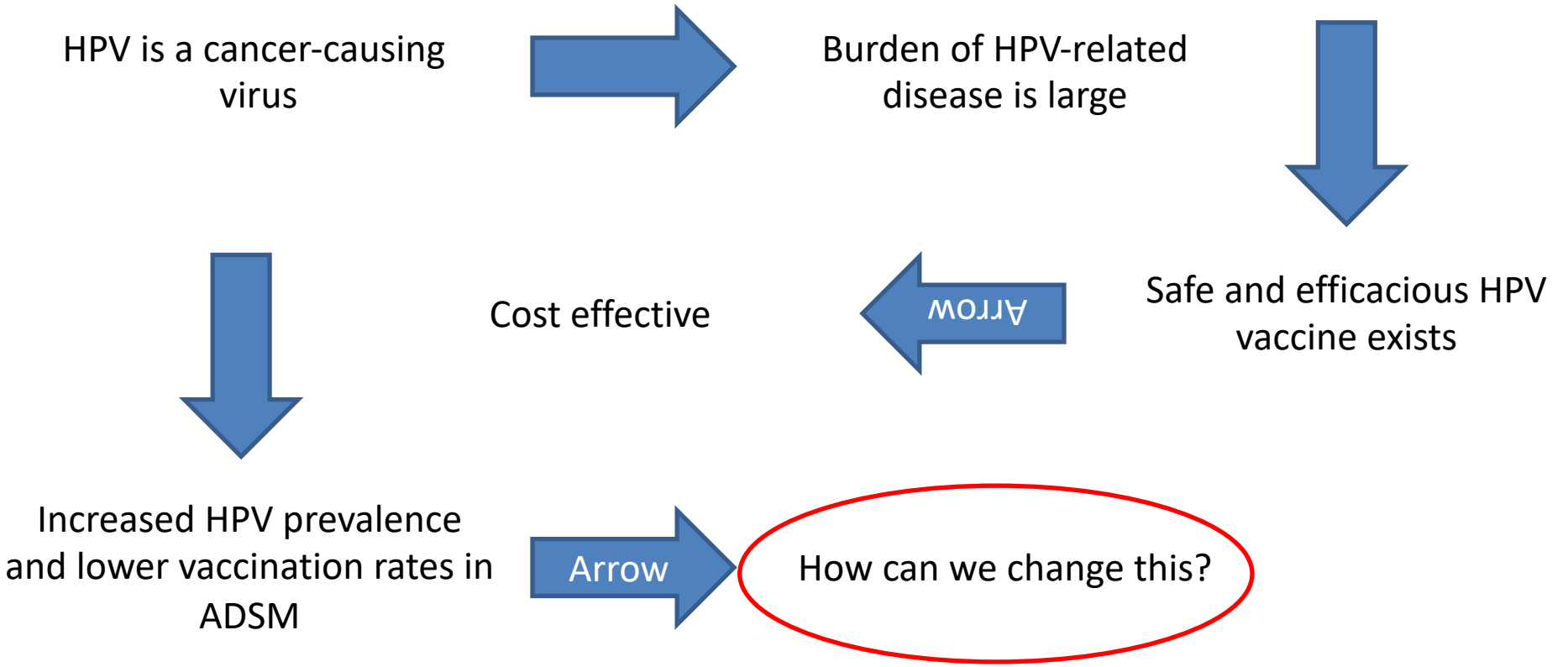
Military Vaccination Rates

FIGURE 1. Annual percentage of eligible active component service women who initiated human papillomavirus (HPV) vaccine, U.S. Armed Forces, 2007–2017



(Clark et al., 2018)
(Porter et al., 2020)
(Shen-Gunther et al., 2011)

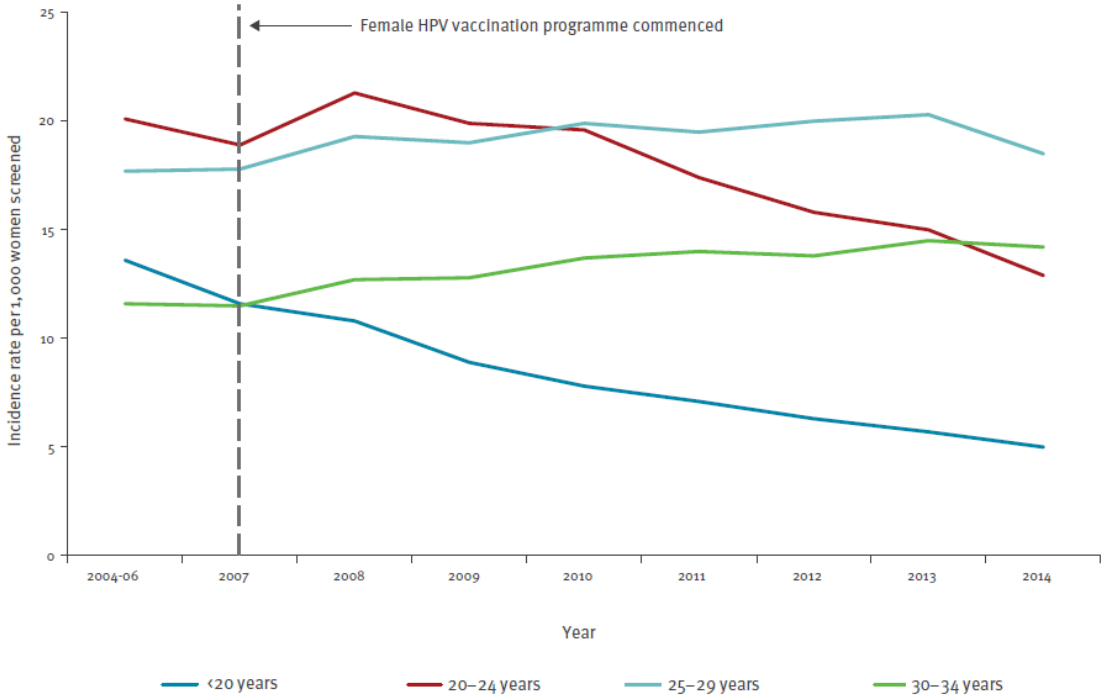
Australia Vaccination Program



Australia Vaccination Program

FIGURE

Trends in high-grade cervical abnormalities in women by age group before and after commencement of the female HPV vaccination programme, Australia, 2004–2014



HPV: human papillomavirus.

(Patel et al., 2018)
(Drolet et al., 2017)
(Hall et al., 2019)

Australia Vaccination Program

Cervical Cancer Incidence

Cervical Cancer Mortality

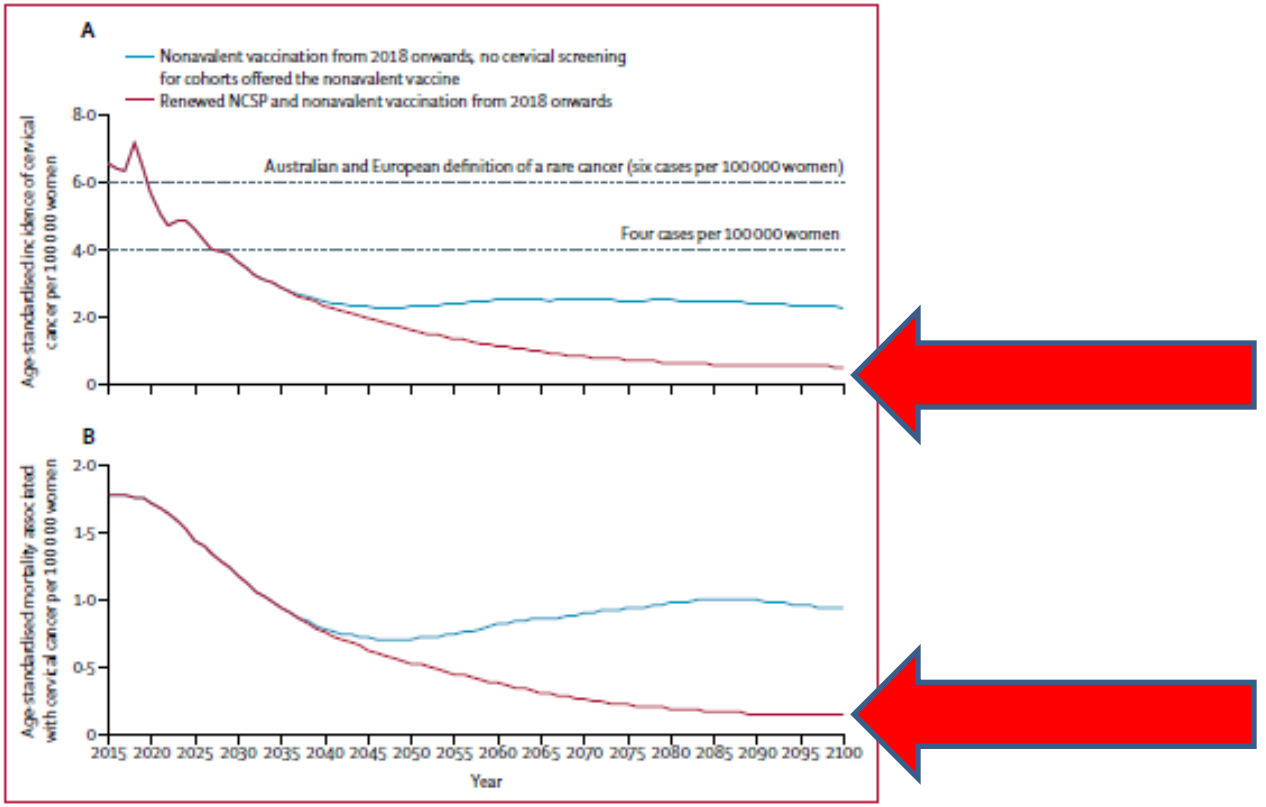


Figure 1: **The (A) age-standardised annual incidence of invasive cervical cancer and (B) associated mortality**
Data are the model predictions for rates from 2015 to 2100, accounting for the transition to primary human papillomavirus screening in 2017 (the renewed NCSP) and the switch to nonavalent vaccine in 2018.
NCSP=National Cervical Screening Programme.

(Hall et al., 2019)

Vaccination Programs

- Required for school attendance
- Five US jurisdictions
  - Virginia
  - Washington DC
  - Hawaii
  - Rhode Island
  - Puerto Rico
- No changes in adolescent sexual behavior

(Cook et al., 2018)

Ways to Increase Vaccination Rates

- Educational programs
- Required training
- Mandatory vaccination for adolescents and ADSM
- Maximize access
- Reminders, standardized information system
- Discuss at routine health visits or periodic health assessments

(Spencer et al., 2019)
(Nobel et al., 2019)
(Clark et al., 2018)
(Buechel, 2018)

New Directions

- Trivalent 16/18/58 vaccine
  - Asia-Pacific region
- L2-based vaccine
- Dosing strategies
  - 1 vs 2-dose regimen
- Long term efficacy
- Decreases in cancer rates

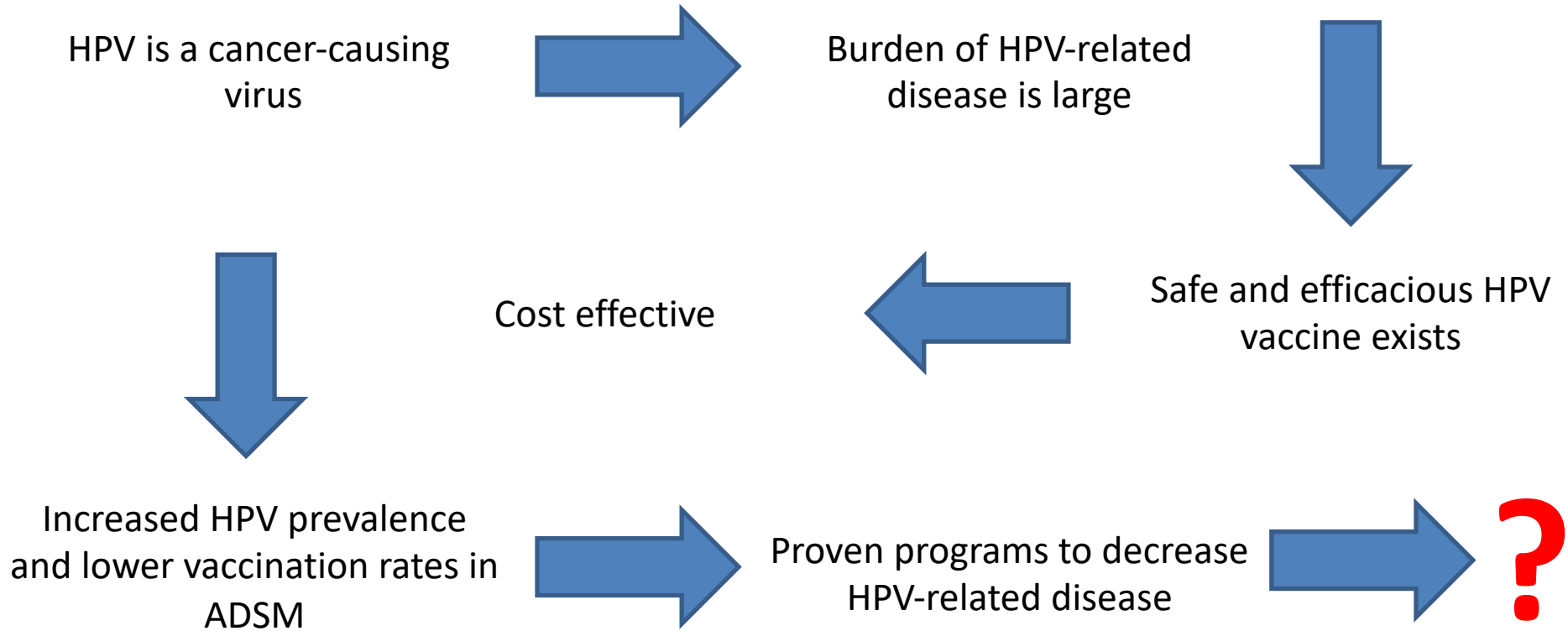
(Dilley, Miller, Huh, 2020)

WHO Call to Action

- Elimination as a public health program
- 2030 targets
  - 90% of girls fully vaccinated by age 15
  - 70% of women screened two times per life by age 35 and 45
  - 90% with cervical disease receive treatment and care
- Low and middle income countries
- Significantly reduce disease and mortality

(Gultekin et al, 2020)

Cancer Prevention



Next Steps

- Mandatory free vaccination
- Widely available, eliminate barriers
- Reminder and tracking system
- Patient and healthcare provider education
- Reduce healthcare burden
- Increase medical readiness

Key Takeaways

- HPV is the most common STI
- Causes the vast majority of all gynecologic dysplasia and cancer
- No cure for HPV
- Vaccination against HPV is safe and efficacious
- US and ADSM vaccination rates are increasing but remain low overall
- Mandatory vaccination could eradicate HPV-related dysplasia and cancer

Thank you for your time!

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Resources

- www.cdc.gov/hpv
- www.vaccines.gov
- www.cancer.gov
- www.hpvinfo.ca
- www.hpv.com
- www.acog.org
  - Committee Opinion 809, HPV Frequently Asked Questions

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