

# HPV Related Gynecologic Cancer Prevention

Immunize Arkansas 2024 HPV Summit  
Wyndham Hotel, North Little Rock, AR  
May 3, 2024

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Arkansas Department of Health

# Objectives

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At the end of this presentation the learner will be able to:

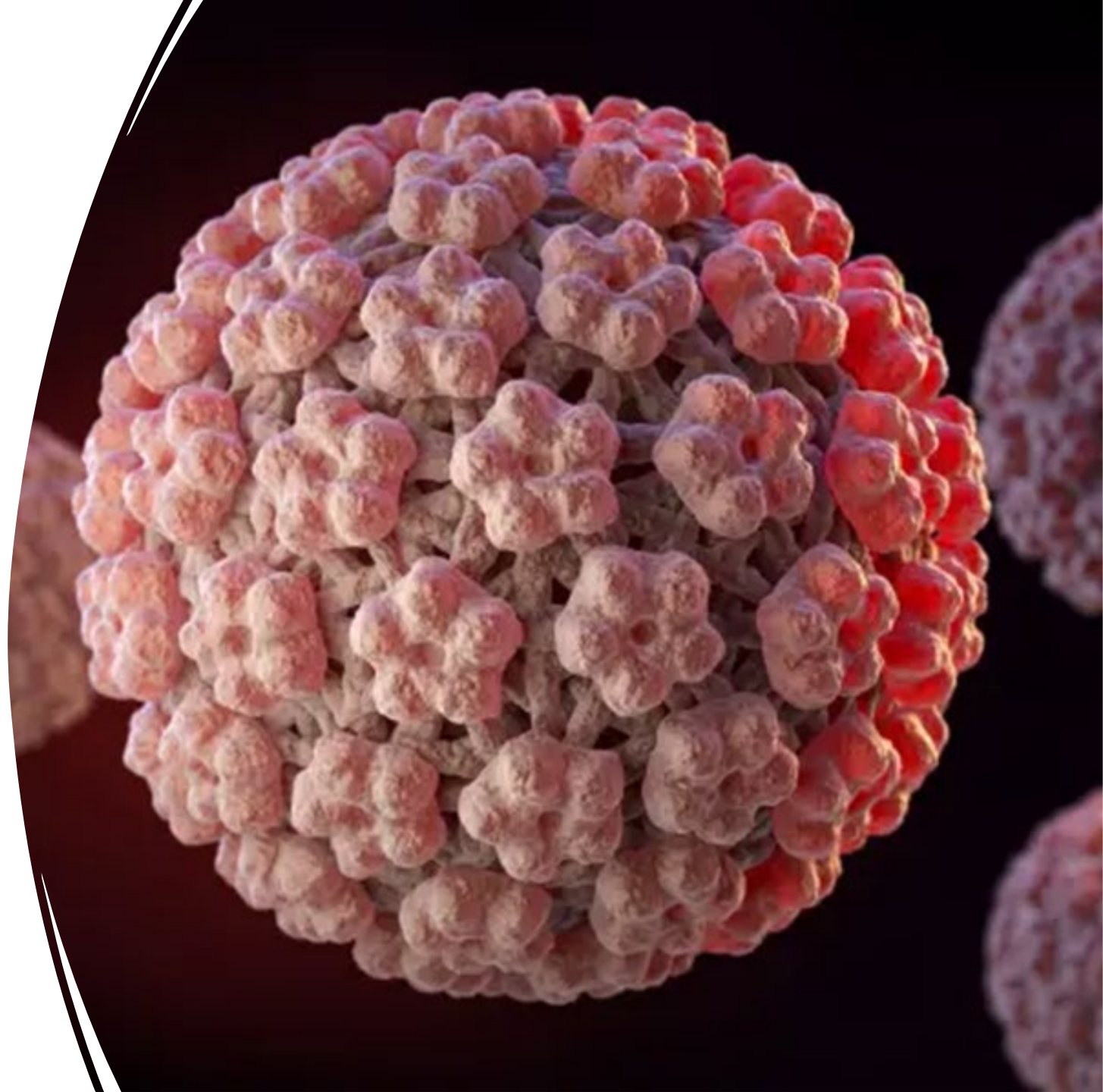
1. Describe the biologic relationship between HPV and Gynecologic Cancer
2. Discuss epidemiology of HPV associated cancers
3. Describe strategies to prevent HPV related Gynecologic Cancer

# What is HPV?

human Papillomavirus

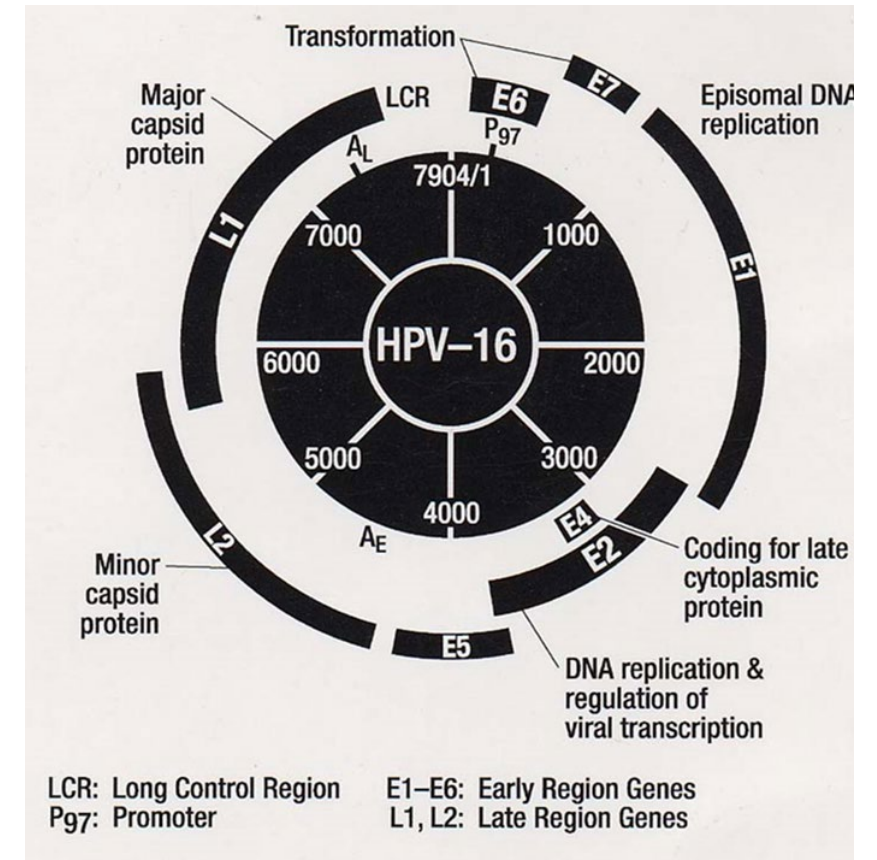
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- double-stranded DNA viruses
- Over 200 HPV subtypes
- Over 40 can infect genital areas
- 13 subtypes considered high risk
- Cancers of mucosal epithelium
- Most common STI in U.S.
  - Nearly all sexually active people infected
  - Within months to a few years of first activity
  - Approximately half are with high-risk HPV



# HPV Genome & Oncoproteins

- **E6 Protein**
  - -Binds and degrades p53
  - -Inhibits apoptosis
  -
- **E7 Protein**
  - -Binds and degrades Rb tumor suppressor gene product
  - -Stimulates cell proliferation



# Four major steps in cervical cancer development

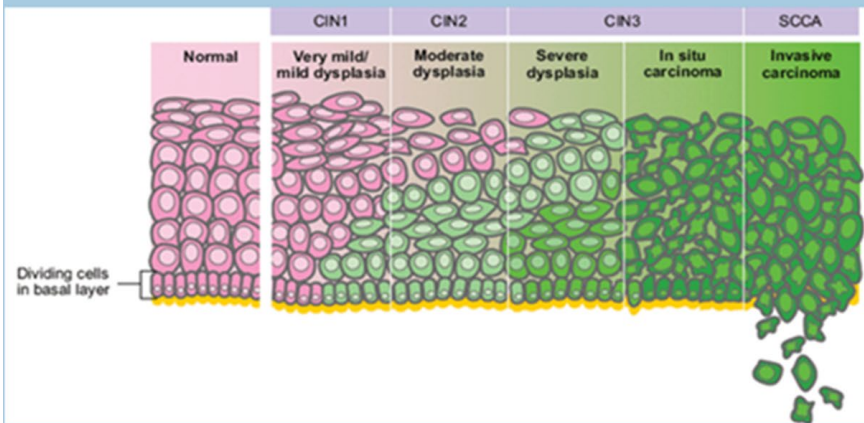
## Human papillomavirus: High- and low-risk types for causing cervical cancer

High-risk (oncogenic or cancer-associated) types
Common types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 82
Low-risk (non-oncogenic) types
Common types: 6, 11, 40, 42, 43, 44, 54, 61, 72, 81

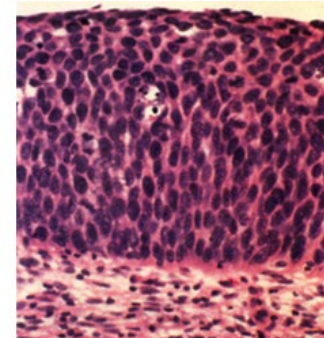
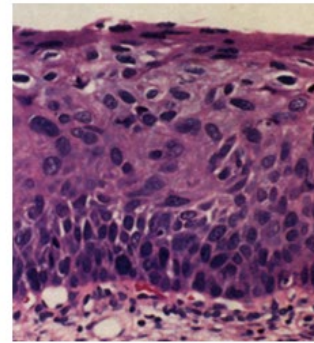
Data from: Centers for Disease Control and Prevention. National Cancer Institute Factsheet. Human papillomavirus and cancer: Questions and answers (Accessed on June 11, 2012).

UpToDate

- Oncogenic HPV infection of the metaplastic epithelium at the cervical transformation zone
- Persistence of the HPV infection
- Progression of a clone of epithelial cells from persistent viral infection to precancer
- Development of carcinoma and invasion through the basement membrane.



High-Grade Lesion → Cancer



Courtesy: UAMS Dept of Pathology

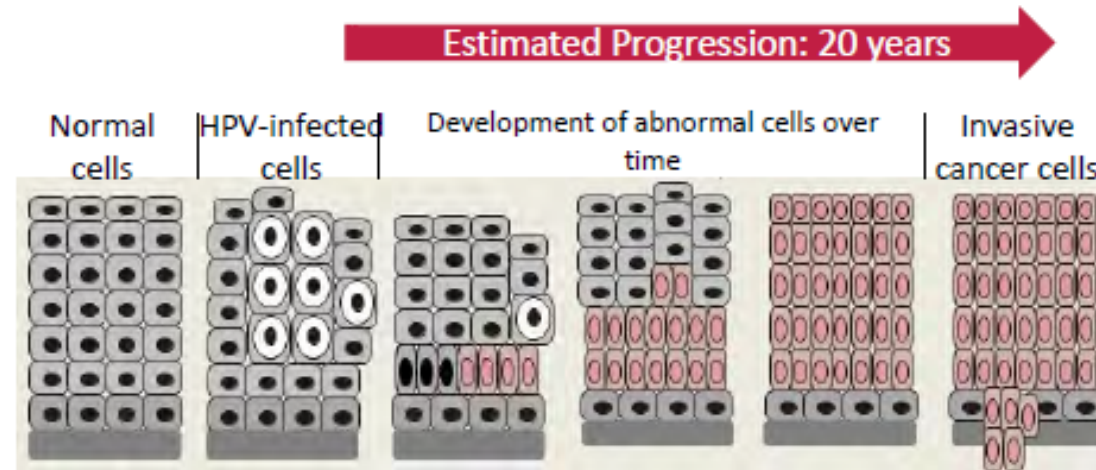
# About HPV and Cervical Cancer in the US



- Most people can fight off HPV infection
- CDC: About 90% of cervical cancer cases are due to HPV infections
- ACCR does not collect data on the presence or absence of HPV in cancer tissue.
  - Collects on the cells types that are more likely to be caused by HPV in order to calculate the approximate burden in the state.

Human Papillomavirus-Associated Cancers<sup>3, 8-11</sup>

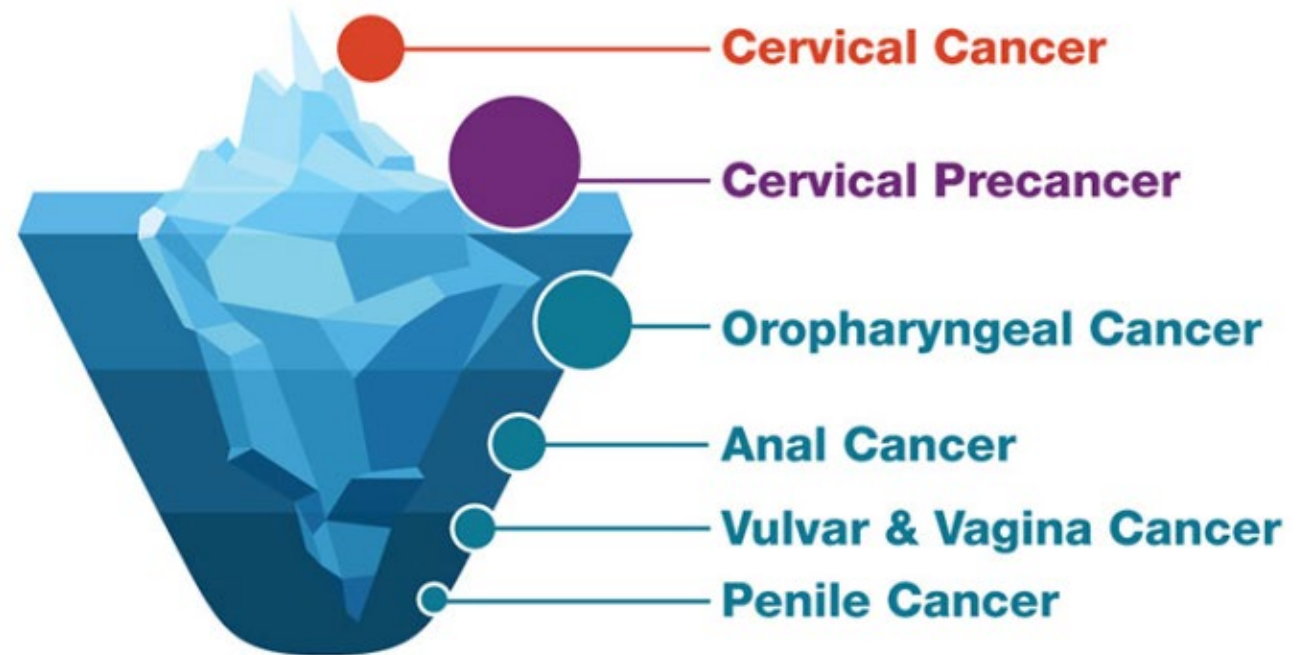
Cancer	ICD-O-3 site codes	ICD-O-3 histology codes	Additional restrictions
Cervical carcinoma	C53.0-53.9	8010-8071, 8240-8241	Restrict to females and restrict to microscopically confirmed



# Background

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- Estimated 43 million HPV infections in U.S
- Most infections are transient
- Persistent infection can lead to cancer
- Progression from infection to invasive cervical cancer: 10-20 years





# How is HPV Transmitted?

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- Transmission
  - intimate skin-to-skin contact
  - use of sex toys or other objects
- Condoms and dental dams
  - can lower transmission
  - does not prevent it completely.

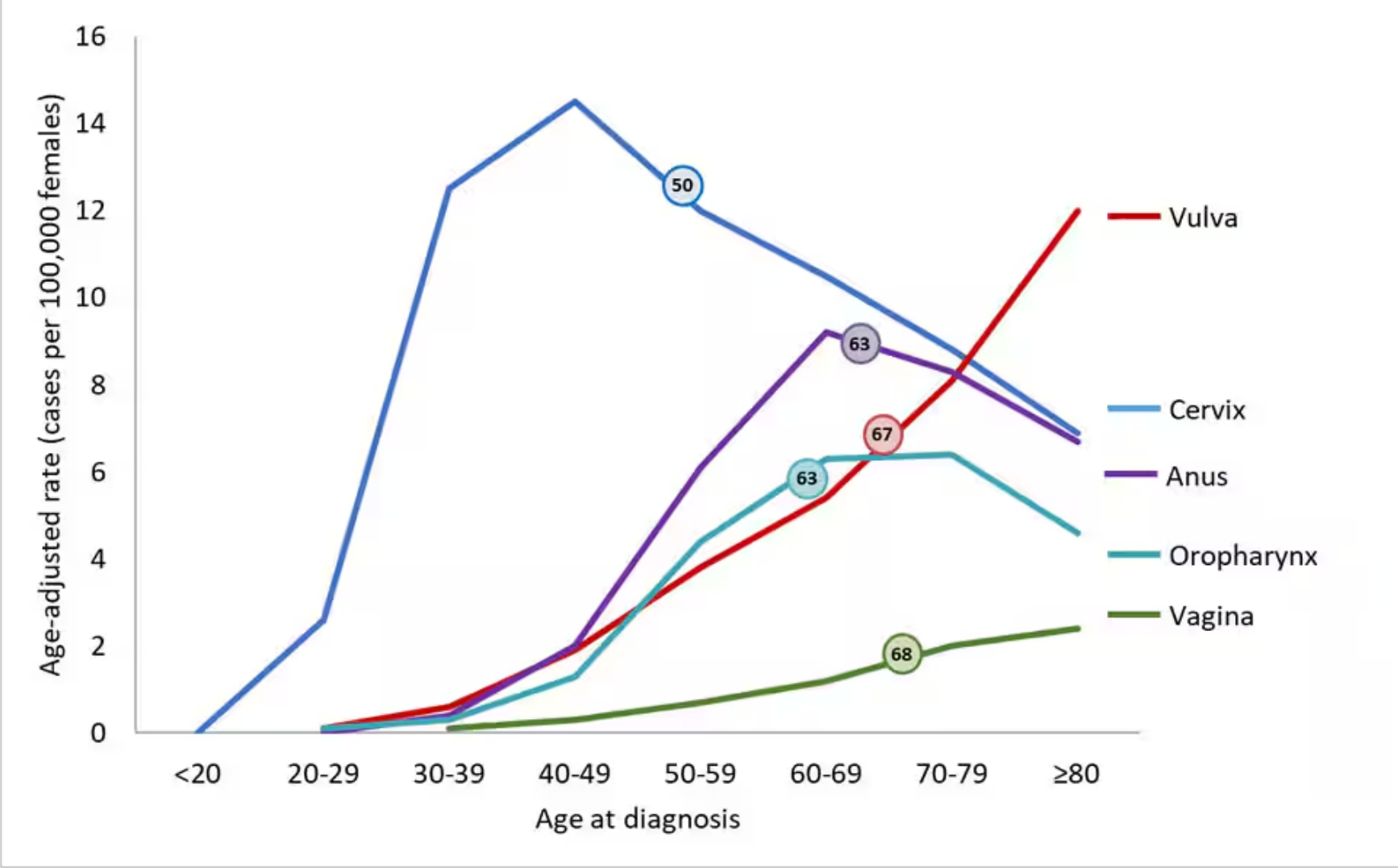


## Number of HPV-Associated and Estimated Number of HPV-Attributable Cancer Cases per Year

- Approximately 46,711 new cases of cancer in areas where HPV is often found
- 25,689 among women
- 21,022 among men
- HPV causes about 37,000 of these cancers

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 <sup>a</sup>	Estimated number probably caused by any HPV type <sup>a</sup>
Cervix	11,869	91%	10,800
Vagina	875	75%	700
Vulva	4,238	69%	2,900
Penis	1,364	63%	900
Anus <sup>b</sup>	7,560	91%	6,900
Female	5,150	93%	4,800
Male	2,410	89%	2,100
Oropharynx	20,805	70%	14,800
Female	3,557	63%	2,300
Male	17,248	72%	12,500
<b>TOTAL</b>	<b>46,711</b>	<b>79%</b>	<b>37,000</b>
<b>Female</b>	<b>25,689</b>	<b>84%</b>	<b>21,500</b>
<b>Male</b>	<b>21,022</b>	<b>74%</b>	<b>15,500</b>

# Rates of HPV-Associated Cancers and Age at Diagnosis Among Women in the United States per Year, 2016–2020



# Vulvar Cancer

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# Vulvar Cancer

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Squamous cell carcinoma the most common histologic type

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1,466 deaths from vulvar cancer

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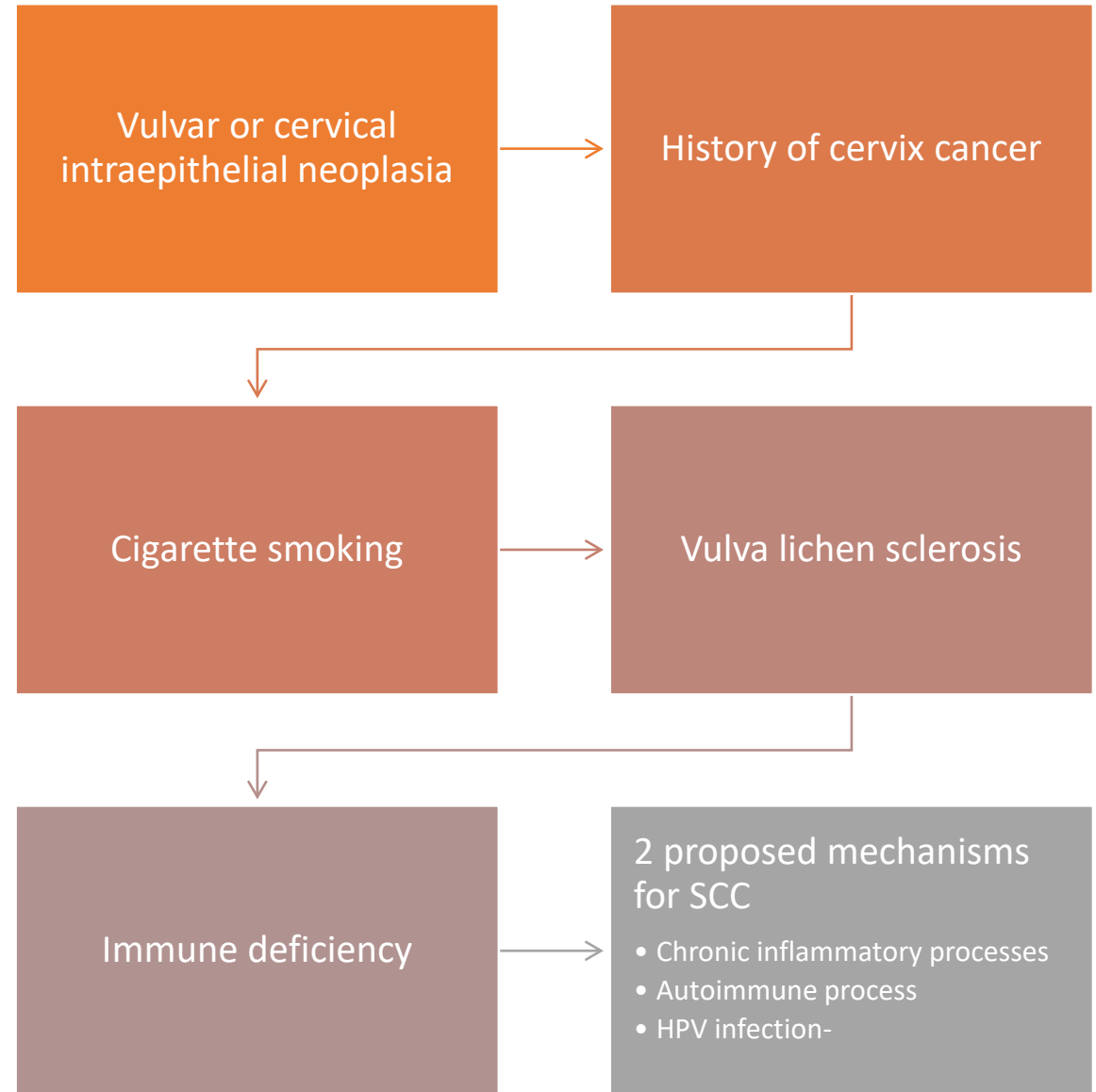
Average age at diagnosis is 68

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72% five-year survival after diagnosis in US

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# RISK FACTORS AND ETIOLOGY



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# CLINICAL PRESENTATION

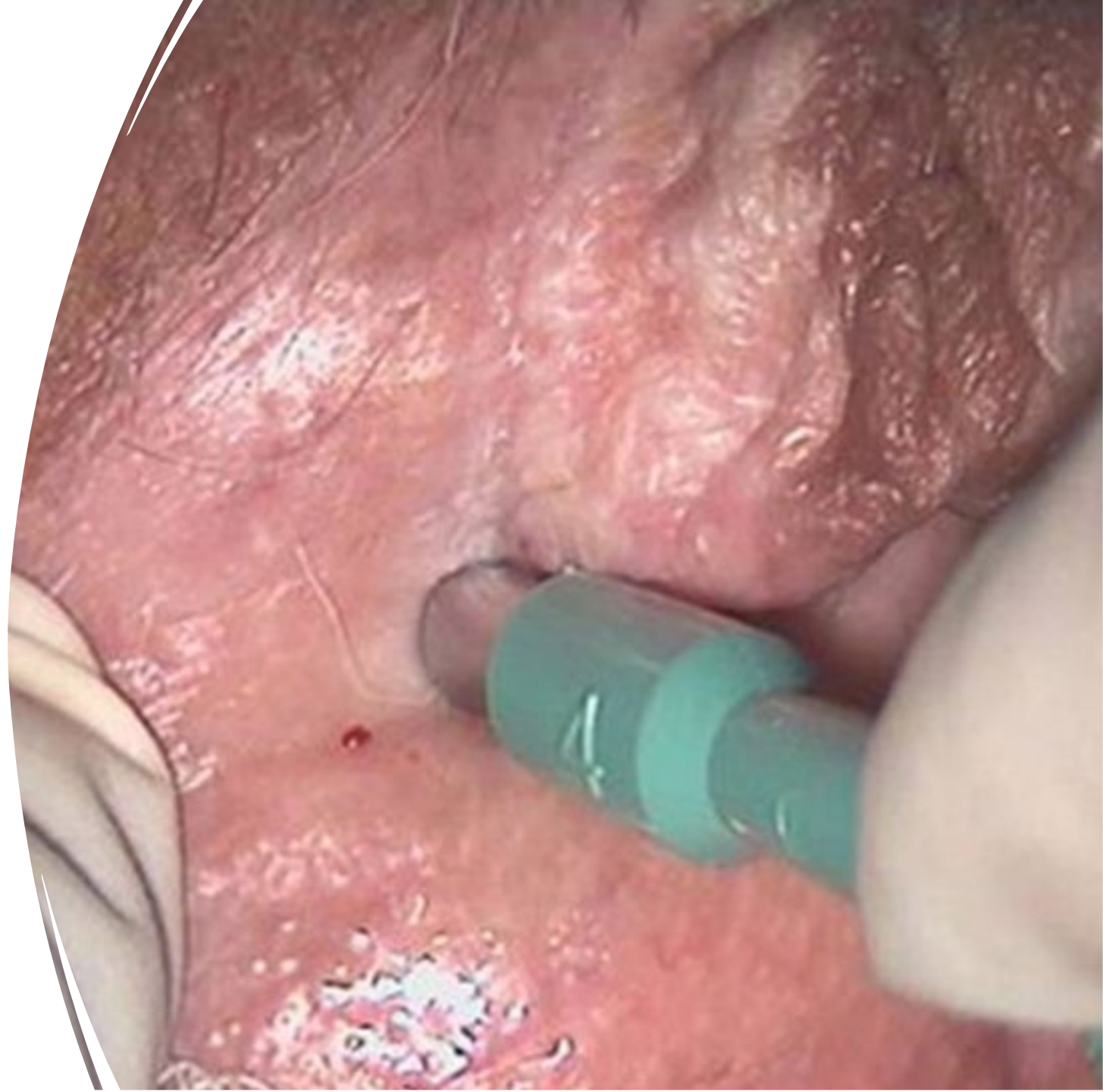
- Vulvar lesion
- Vulvar pruritus
- Bleeding
- Pain



# DIAGNOSTIC EVALUATION

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- History of risk factors/symptoms
- Complete pelvic exam
- Color changes
- Masses
- Ulceration
- Colposcopy of vulva
- Biopsy





# Histologic Types

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- Squamous cell carcinoma
  - 75% of cases
  - 2 subtypes
    - Keratinizing-
      - Not HPV related
      - Older patients
      - Associated with vulvar dystrophy
    - Bowenoid type
      - Associated with HPV 16,18, 33
      - Younger patients
      - Risk factors-first intercourse, multiple partner, cigarette smoking
- Less common subtypes
  - Basal Cell- Melanoma-Paget disease of vulva



# Vaginal Cancer

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# INTRODUCTION

- Less common than uterine, ovarian, and cervical
- More common than vulvar cancer
- Most are squamous cell carcinomas
- Majority of vaginal malignancies are metastatic
- Often arising from the endometrium, cervix, vulva, ovary, rectum

# RISK FACTORS AND EPIDEMIOLOGY

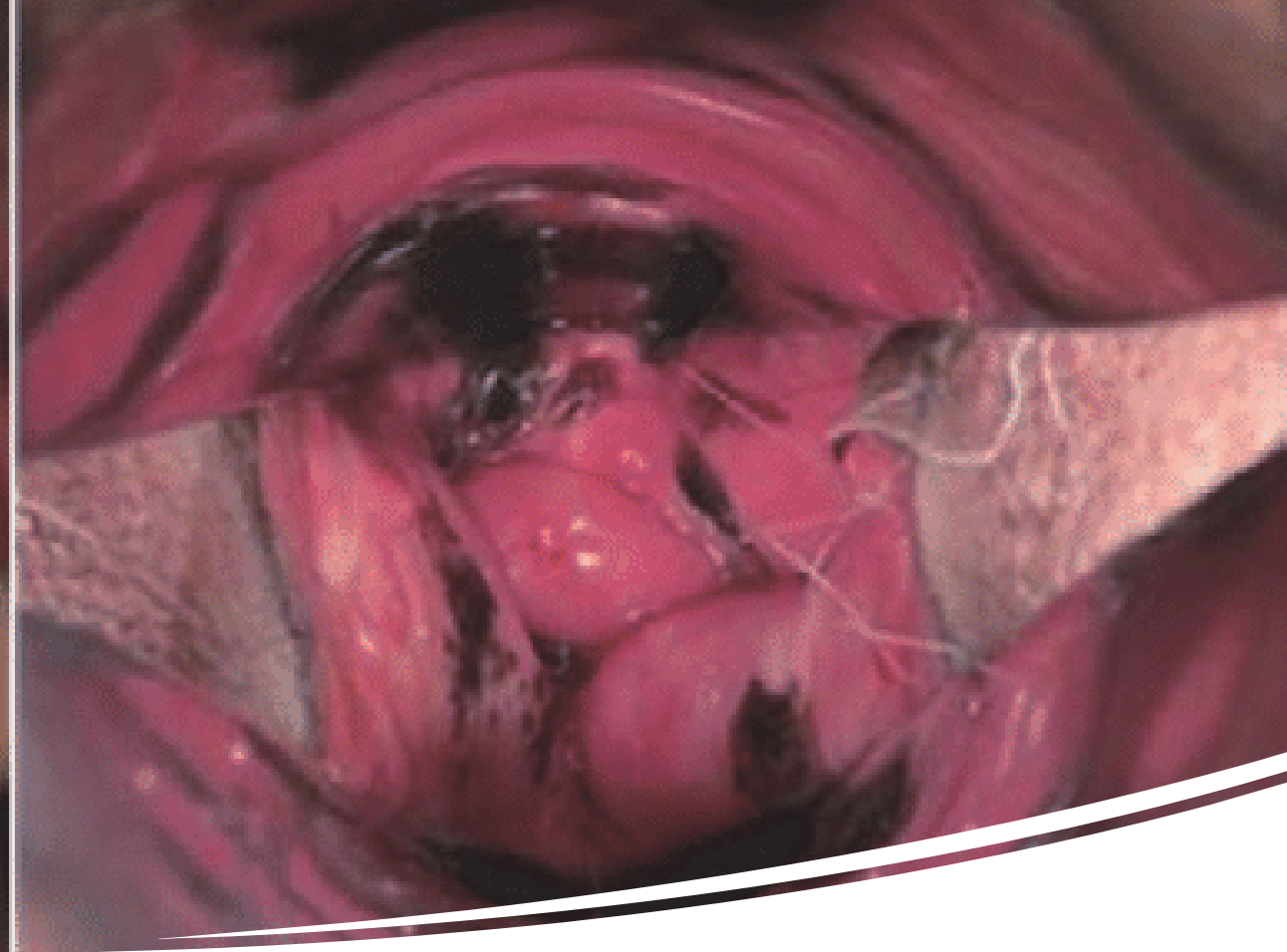
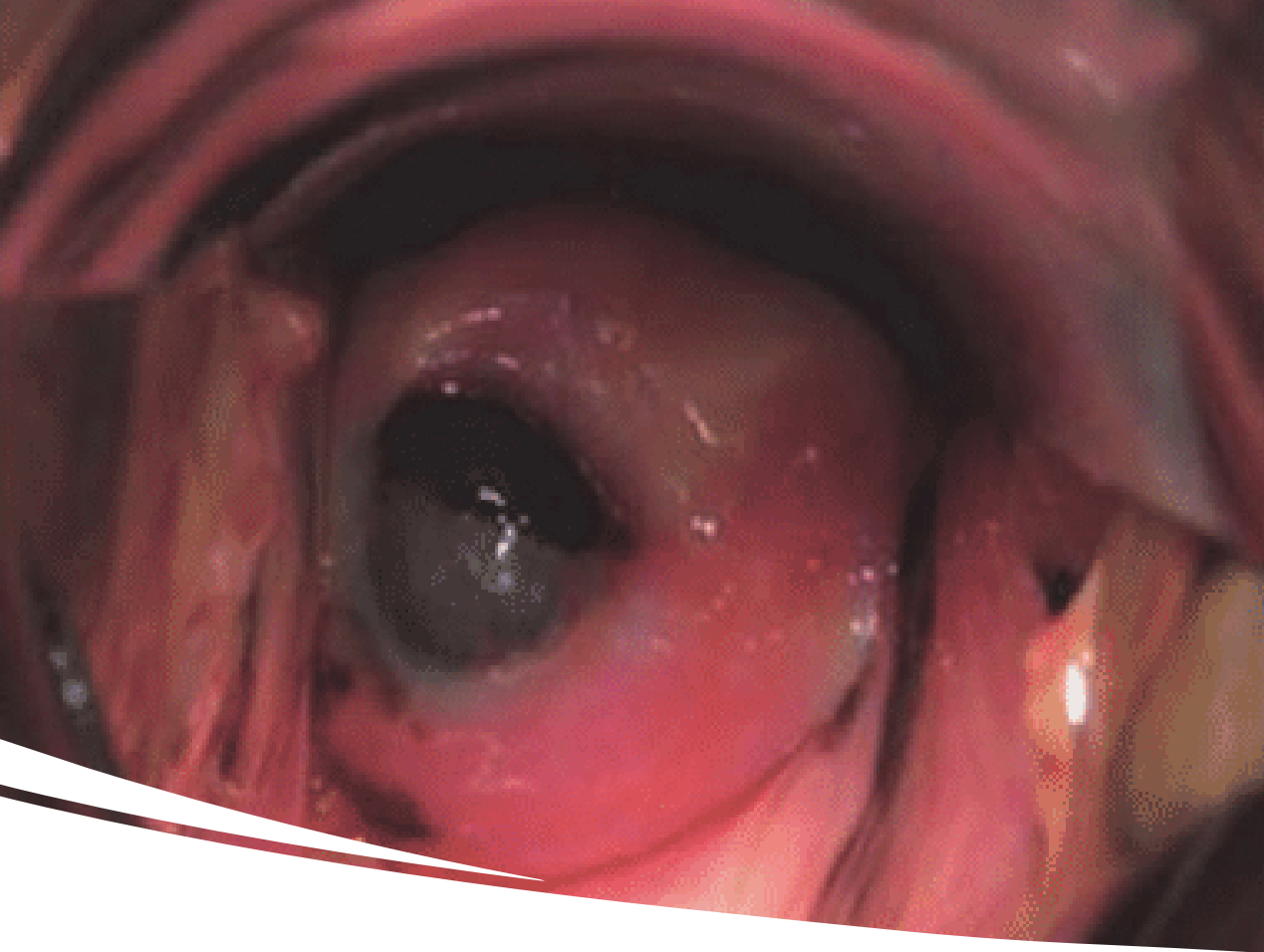
- Approximately 1 in 100,00 diagnosed with in-situ or invasive vaginal cancer
- Most cases of are likely mediated by HPV infection
- Same risk factors as cervical neoplasia:
  - multiple lifetime sexual partners
  - early age at first intercourse
  - current smoker

# CLINICAL PRESENTATION

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- Asymptomatic
- Vaginal bleeding is the most common clinical presentation of vaginal cancer
  - Postcoital
  - Postmenopausal
  - Blood tinged-watery-malodorous
- Vaginal mass may also be discovered
- Symptoms related to local extension
  - urinary symptoms
  - gastrointestinal complaints
  - pelvic pain from extension of disease



# HISTOPATHOLOGY

- Squamous cell carcinoma
- Verrucous carcinoma
- Adenocarcinoma
- Sarcoma
- Melanoma

# PROGNOSIS



The most important variable affecting prognosis is the stage at the time of presentation



The size and depth of tumor penetration



5 survival 65 versus 84 percent in tumors  $\leq 4$  cm  
mortality 51 percent higher in women with melanoma compared with SCC vaginal cancer

# Invasive Cervical Cancer





# Key facts

- Two human papillomavirus (HPV) types (16 and 18) are responsible for nearly 50% of high grade cervical pre-cancers
- Women living with HIV are 6 times more likely to develop cervical cancer compared to women without HIV.
- Vaccination against HPV and screening and treatment of pre-cancer lesions is a cost-effective way to prevent cervical cancer.
- Cervical cancer can be cured if diagnosed at an early stage and treated promptly.
- Comprehensive cervical cancer control includes
  - **primary** prevention (vaccination against HPV)
  - **secondary** prevention (screening and treatment of pre-cancerous lesions)
  - **tertiary** prevention (diagnosis and treatment of invasive cervical cancer)
  - **palliative** care



# Cervical Cancer Risk Factors

## Cannot be modified:

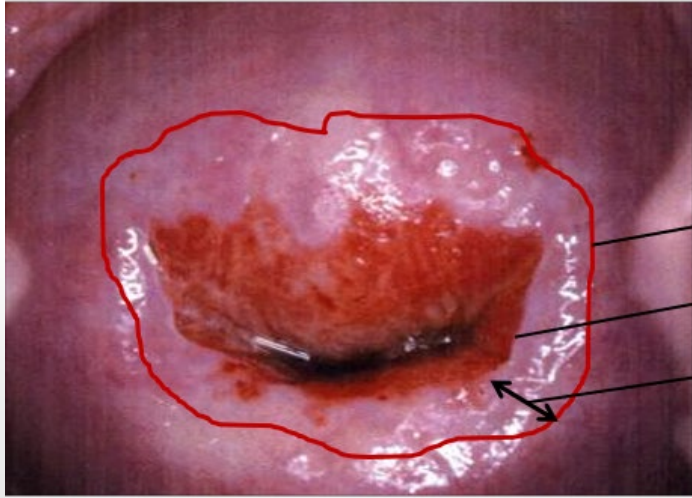
1. “DES Daughters” (40x more likely to develop a rare cancer called clear cell adenocarcinoma of the vagina and cervix)
2. Family history of cervical cancer (mother and/or sister)

## Can be modified:

1. Long-term use of oral contraceptives (OCs) (ceasing use can decrease risk)
2. Young age at 1st full-term pregnancy (<20 years old)
3. Smoking (damages DNA of cervix cells)
4. Chlamydia (current or past infection)
5. Multiple full-term pregnancies (Females who have had 3 or more)
6. Weakened immune system (HIV, or drugs to treat autoimmune disease/organ transplant recipients)
7. Economic status: Limited access to healthcare to cervical cancer screenings and cervical pre-cancer treatments
8. Poor diet and nutrition (low intake of fruits and vegetables *may* increase risk for cervical cancer)

**NOTE: Several risk factors can increase the chance of developing cervical cancer**

**9. Human papillomavirus (HPV)**  
**Major cause of cervical cancer**



OSCJ

NSCJ

TZ



# Introduction



Third most common gynecologic cancer diagnosis



Human papillomavirus

central to the development of cervical neoplasia  
can be detected in 99.7 percent of cervical cancers



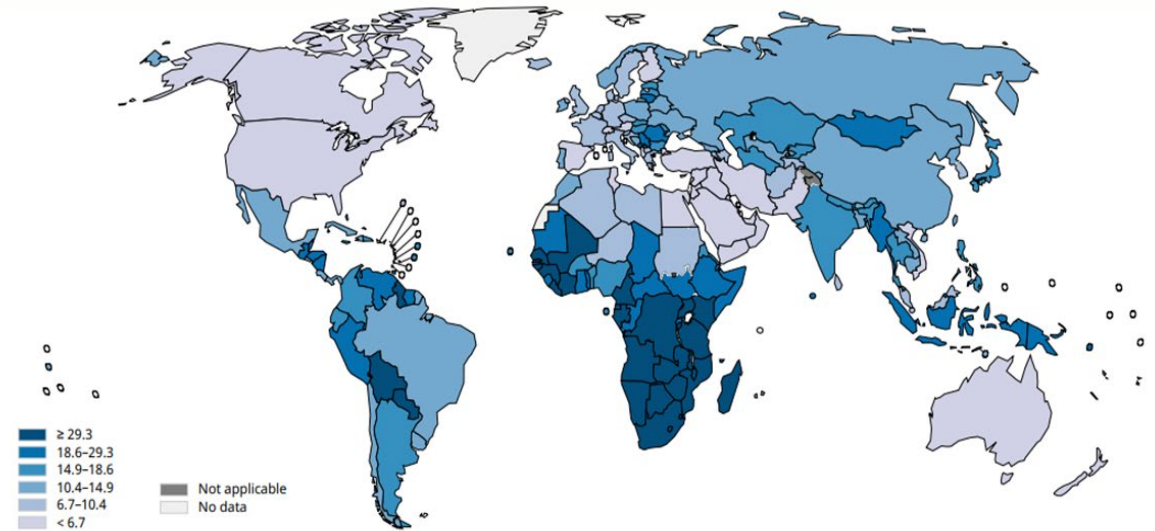
Common histologic types of cervical cancer

Squamous Cell 70-75%  
Adenocarcinoma 25%

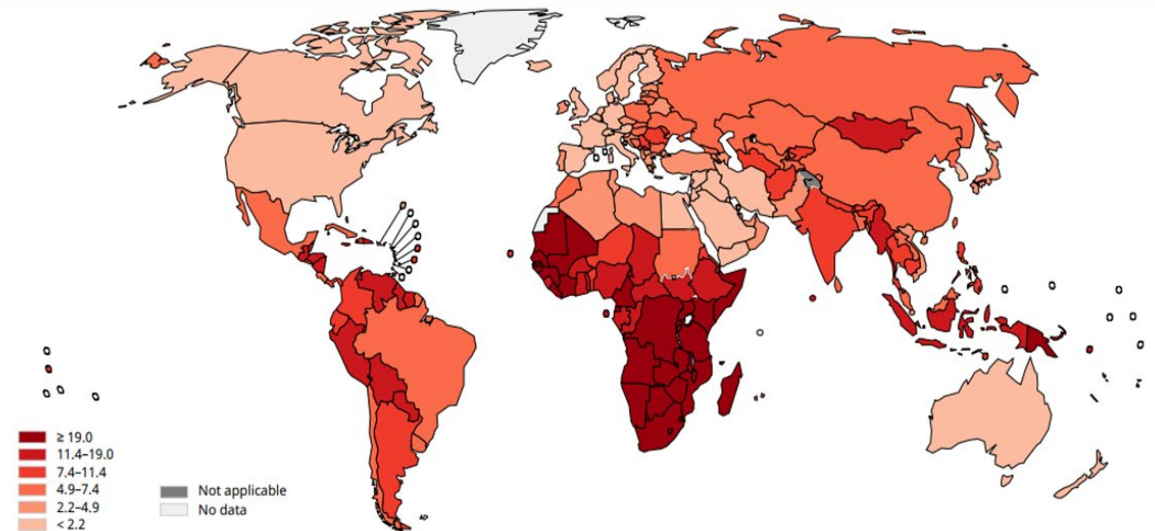
# Cervical Cancer

- Fourth most common cancer among women globally
- 660,000 new cases 2022
- 350,000 deaths 2022
- Highest rates of new cases and deaths worldwide in low- and middle-income countries

Age standardized (World) incidence rates, cervix uteri, all ages



Age standardized (World) mortality rates, cervix uteri, all ages



Data source: GLOBOCAN 2020  
Graph production: IARC (<https://gco.iarc.fr/today>)  
World Health Organization

# Epidemiology

## Worldwide 2020

- 604,000 new cancer cases
- 342,000 deaths

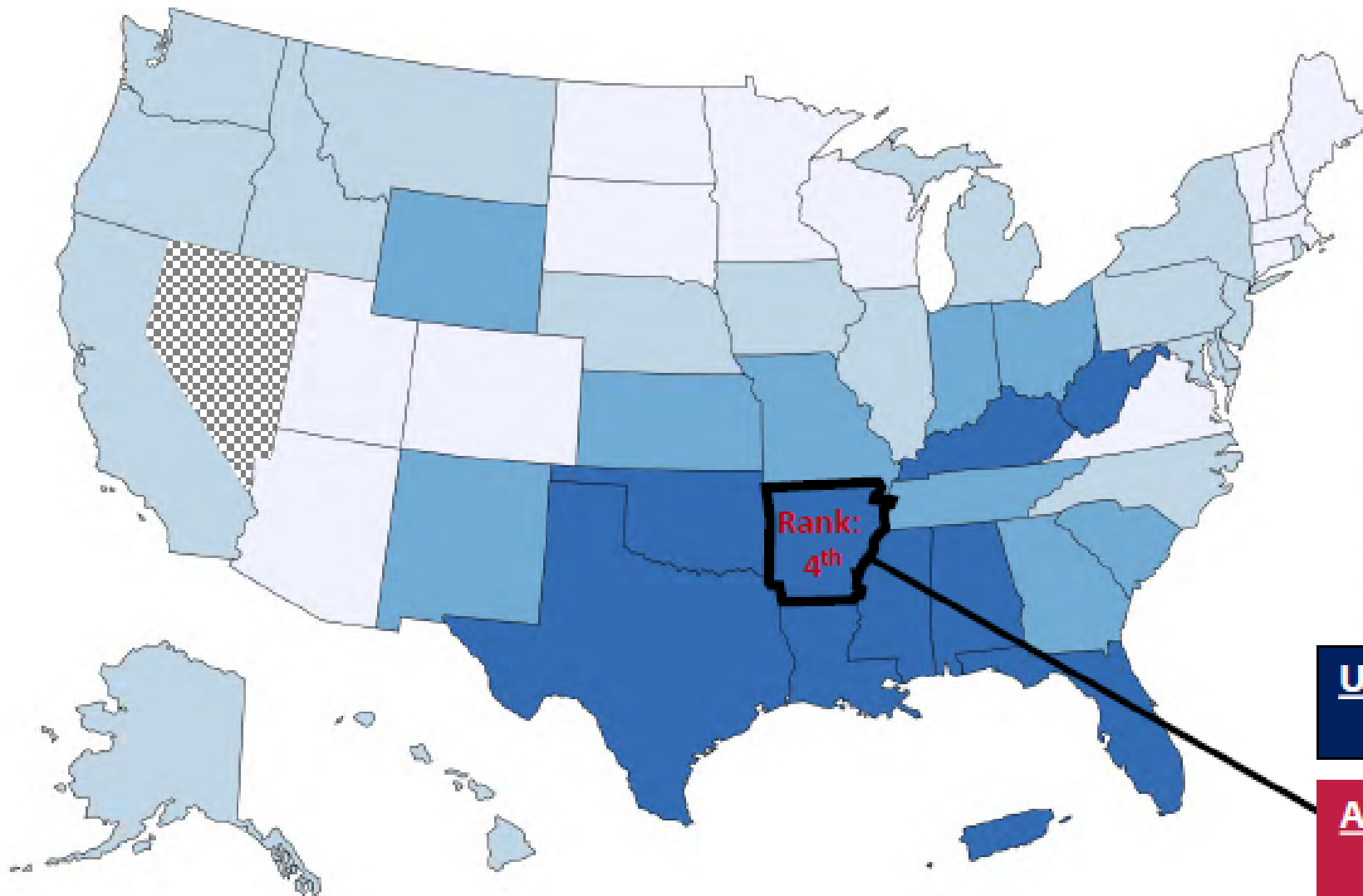
## United States 2020

- 11,542 new cases of invasive cervical cancer
- 4272 cervical cancer-related deaths occur each year

## Global incidence and mortality rates

- Depends on the presence of screening programs
- Cervical precancer and cancer detection
- Human papillomavirus (HPV) vaccination

# US Map Overview of Cervical Cancer Rate, 2015-2019

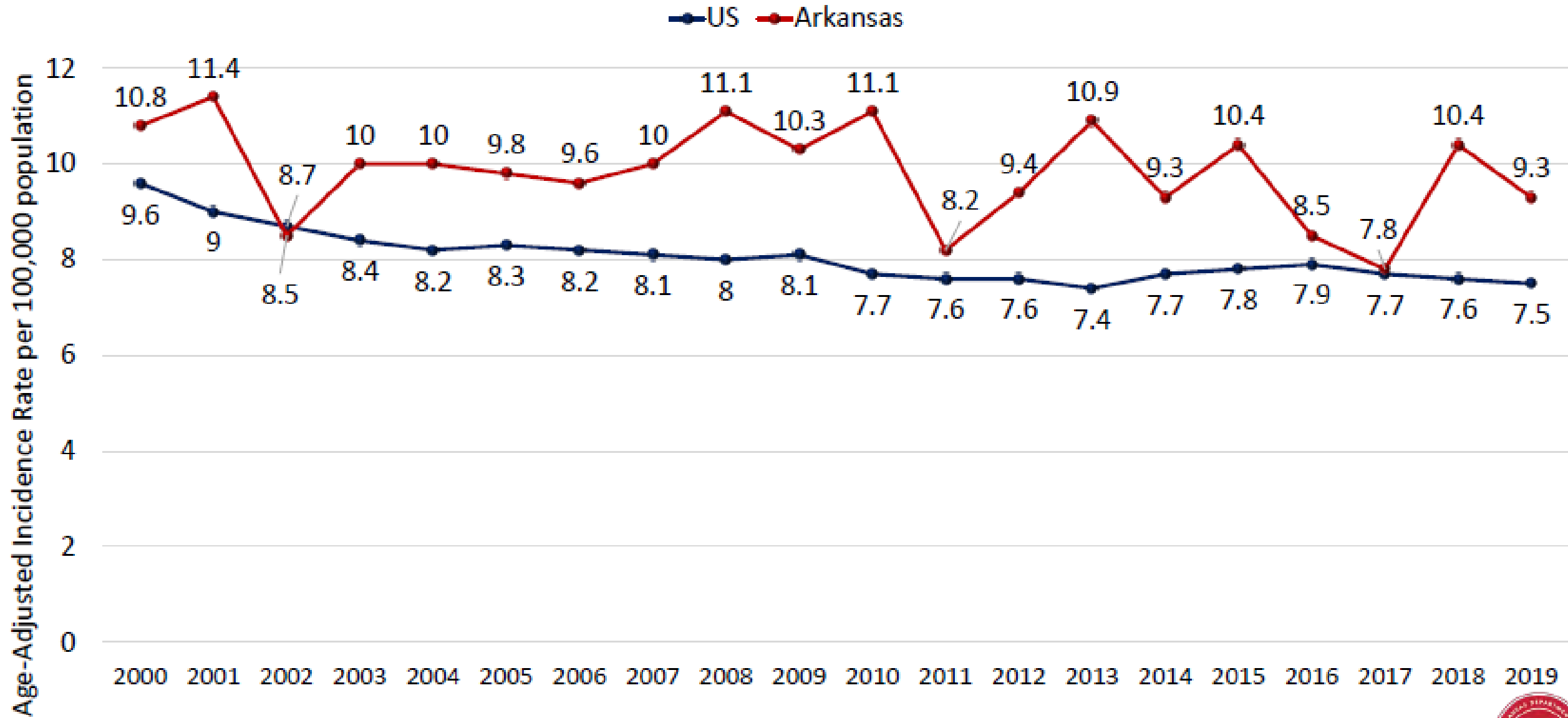


Age-adjusted incidence rate per 100,000 population	
Lightest Blue	4.8 – 6.5
Light Blue	6.7 – 7.7
Medium Blue	7.8 – 8.4
Dark Blue	9.2 – 12.6
Checkered	No data/data suppressed

**US rate: 7.7 age-adjusted incidence rate**

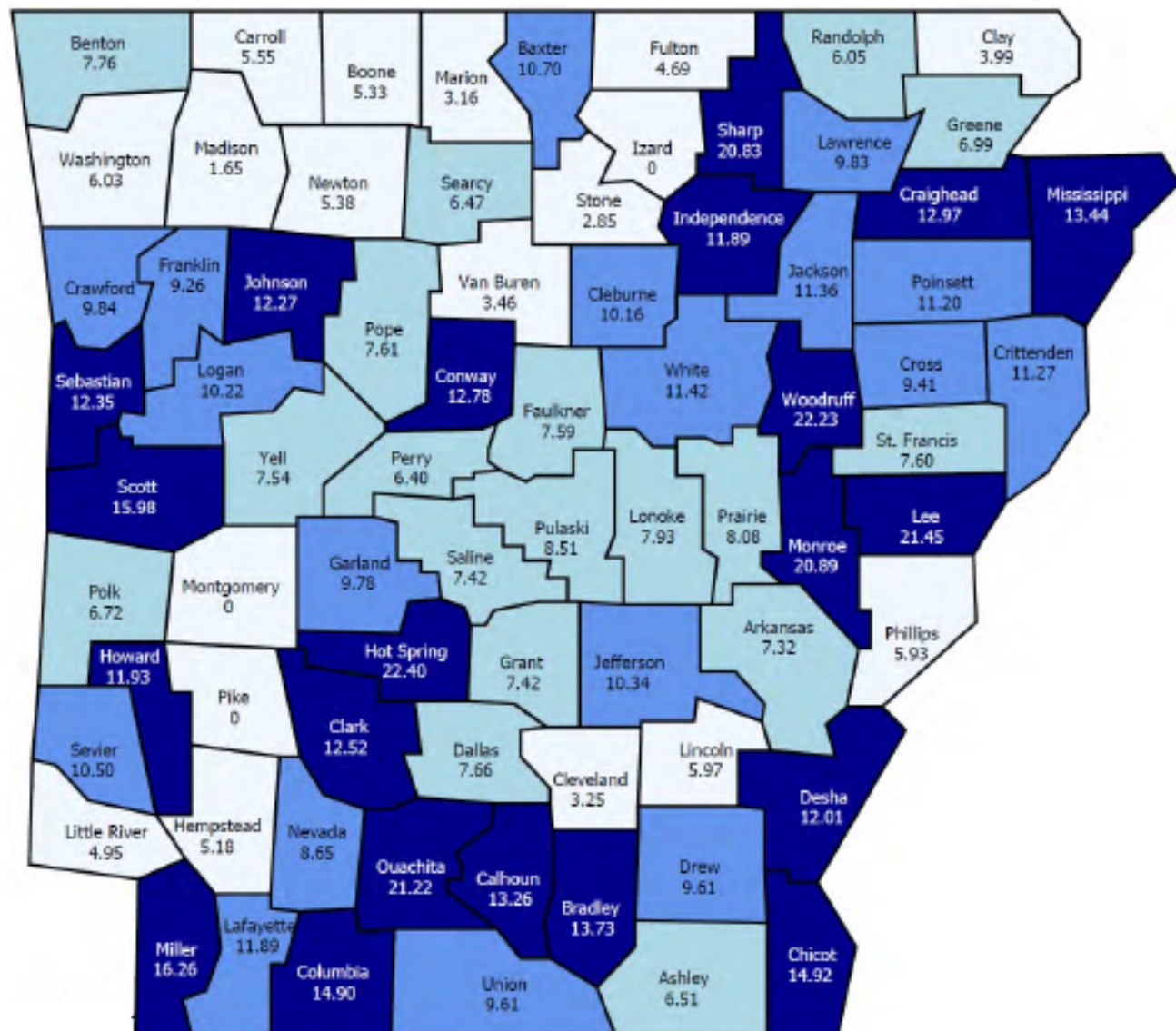
**Arkansas rate: 9.5 age-adjusted incidence rate**

# Age-Adjusted Incidence Trend for Cervical Cancer US and Arkansas 1997 - 2019





## Map of cervical cancer incidence rate among Arkansas females by county, 2015-2019



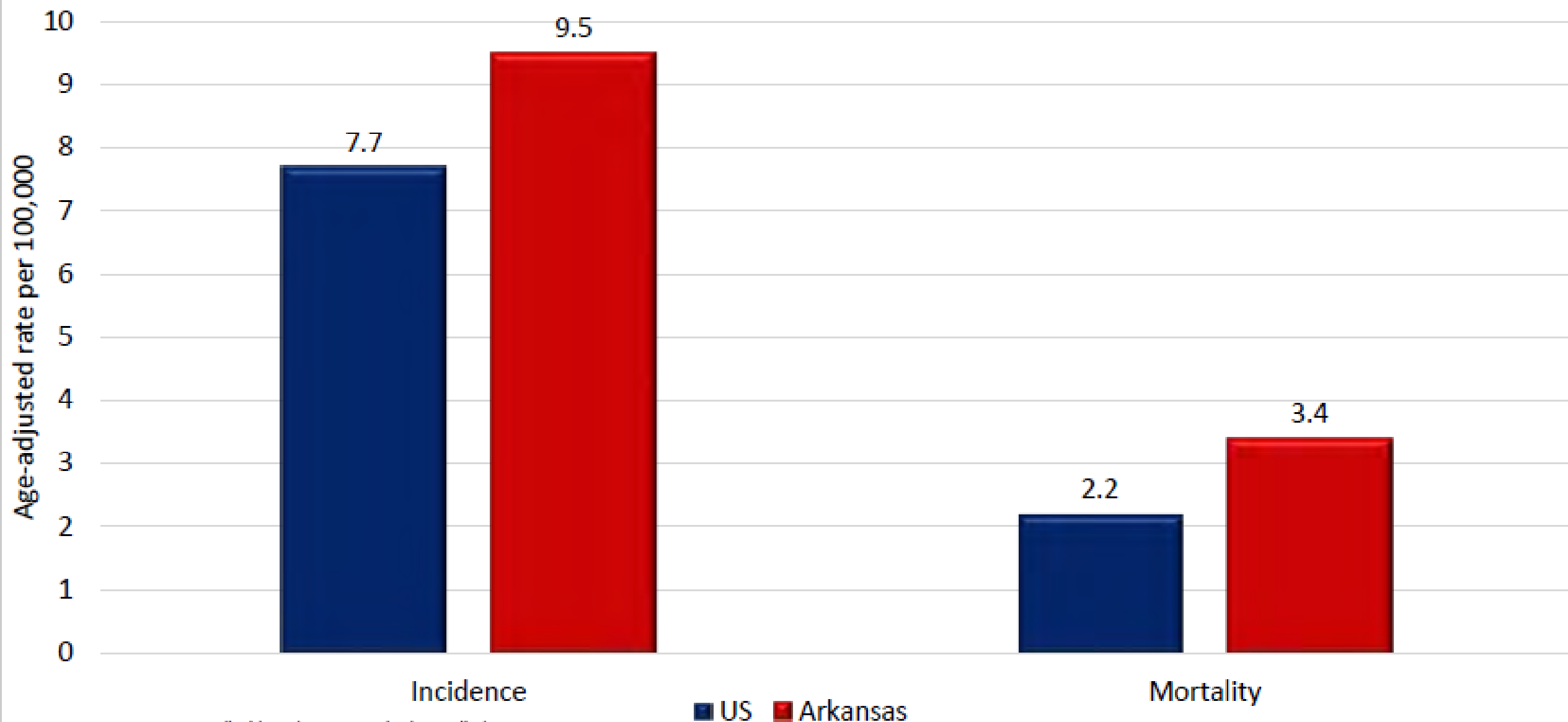
**State age-adjusted incidence rate:  
9.29 per 100,000 population**

Age-adjusted incidence rate per 100,000 female population	
	6.00 – 6.04
	6.05 – 8.64
	8.65 – 11.88
	11.89 – 22.40

Source: AR Cancer Rates Query

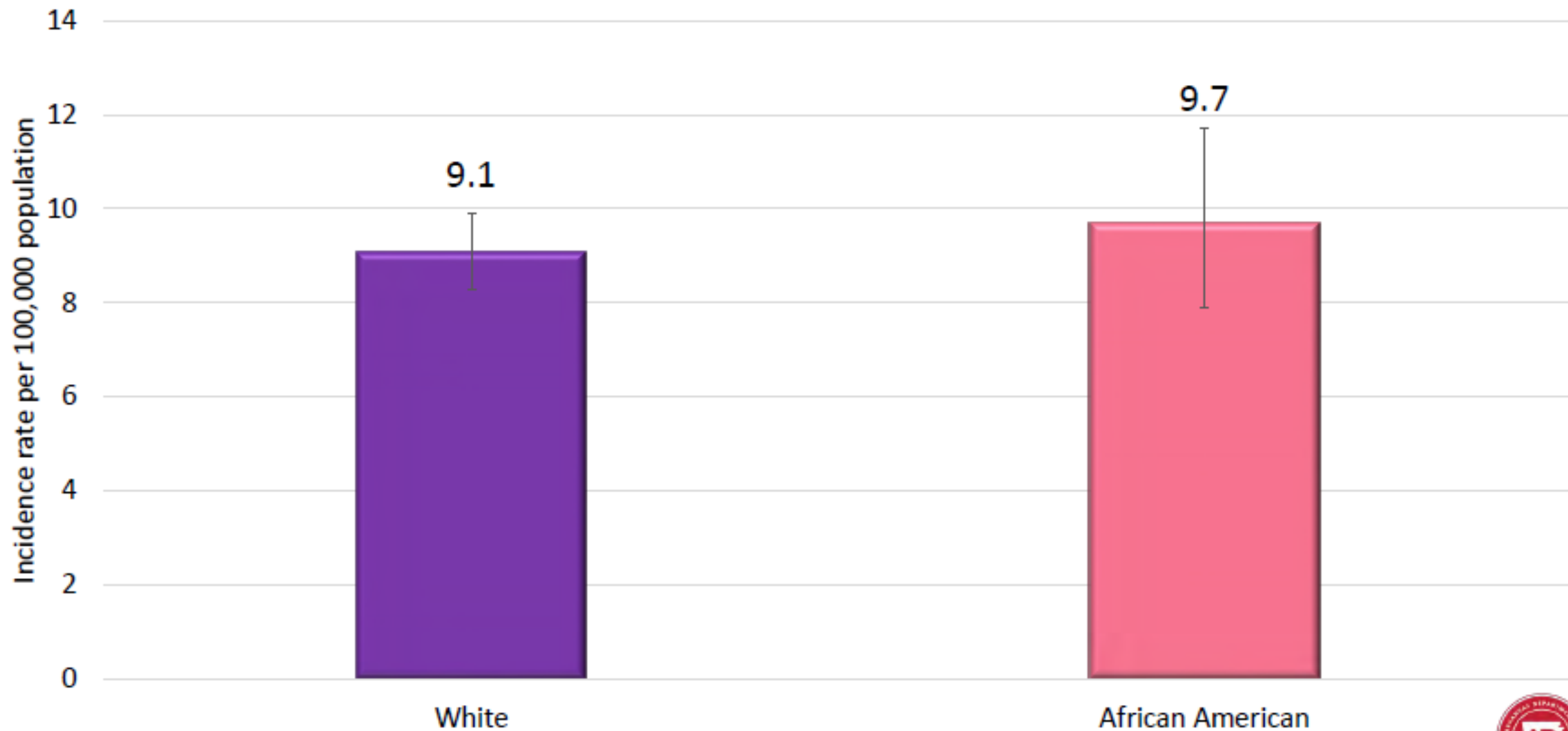


# Overall incidence and mortality rate of cervical cancer among females in US and Arkansas, 2015-2019

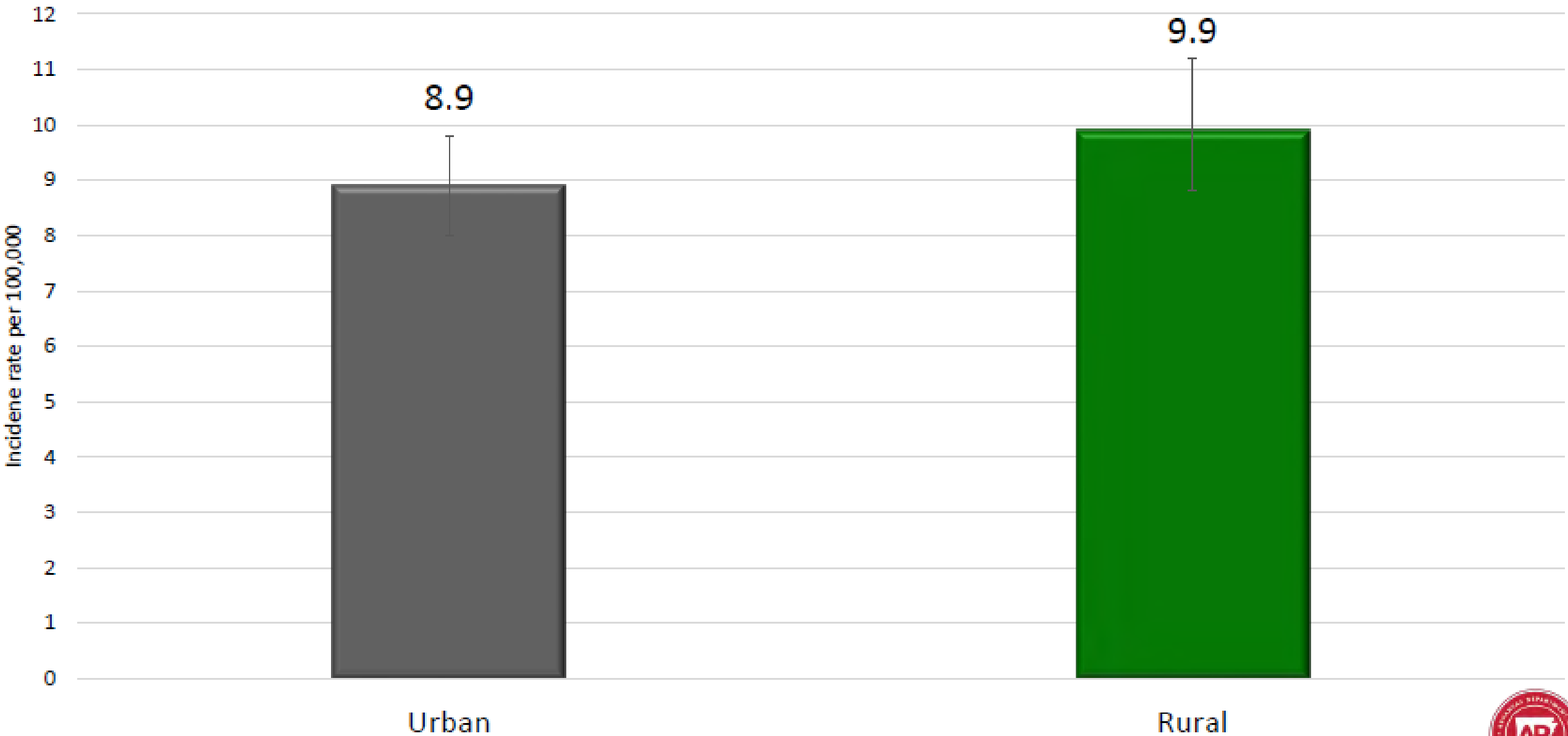


Source: ACCR Query System (incidence), CDC Wonder (mortality)

## Cervical cancer incidence rate among females by race Arkansas, 2015-2019



# Cervical cancer incidence rate among females by urban/rural Arkansas, 2015-2019



# Cervical Cancer Prevention Methods





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ORIGINAL ARTICLE



# Condom Use and the Risk of Genital Human Papillomavirus Infection in Young Women

**Authors:** Rachel L. Winer, Ph.D., James P. Hughes, Ph.D., Qinghua Feng, Ph.D., Sandra O'Reilly, B.S., Nancy B. Kiviat, M.D., King K. Holmes, M.D., Ph.D., and Laura A. Koutsky, Ph.D. [Author Info & Affiliations](#)

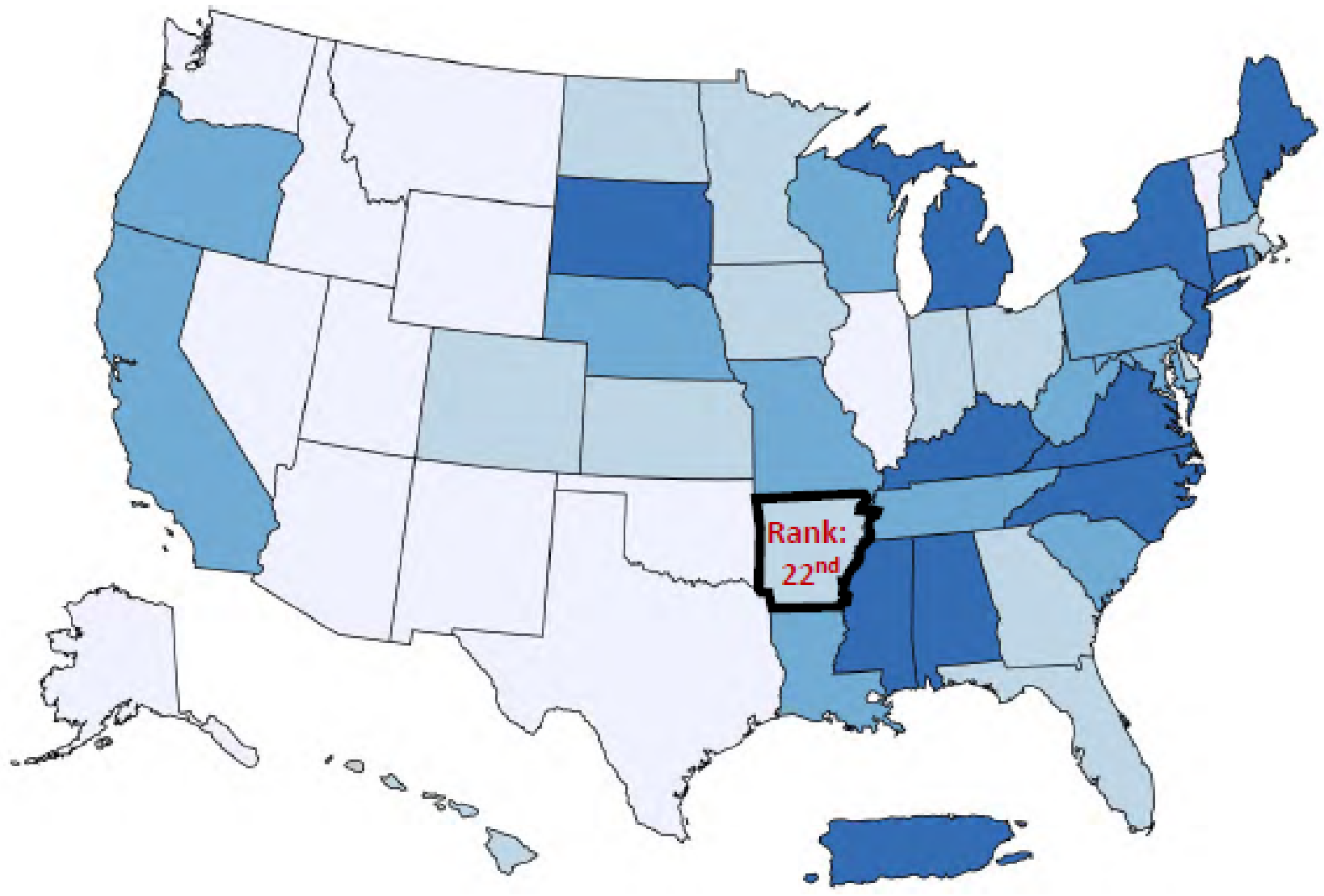
Published June 22, 2006 | N Engl J Med 2006;354:2645-2654 | DOI: 10.1056/NEJMoa053284 | [VOL. 354 NO. 25](#)

# United States Preventive Services Task Force (USPSTF) Screening Recommendations



Screenings for females 21 to 29 years of age	Perform screenings every 3 years with cytology (pap test) alone
Screenings for females 30 to 65 years of age	Perform screenings every 3 years with cytology (pap test) alone Or, Perform screenings every 5 years with hrHPV testing alone Or, Perform co-testing (pap test and hrHPV) every 5 years
Female less 21 years of age & females older than 65 years of age with adequate prior screening, and women who have had a hysterectomy	Do not screen for cervical cancer
Risk Assessment	All women aged 21 to 65 years are at risk for cervical cancer because of potential exposure to high-risk HPV types (hrHPV) through sexual intercourse and should be screened. Certain risk factors further increased risk for cervical cancer, including HIV infection, a compromised immune system, in utero exposure to diethylstilbestrol, and previous treatment of a high-grade precancerous lesion or cervical cancer. <b><u>Women with these risk factors should receive individualized follow-up.</u></b>

# Percent of females who reported receiving a pap test within the past 3 years, US Map, 2020



Age-adjusted prevalence percent per 100,000 population	
Lightest blue	68.4 – 80.8
Light blue	80.1 – 81.7
Medium blue	81.8 – 83.2
Darkest blue	83.3 – 87.7

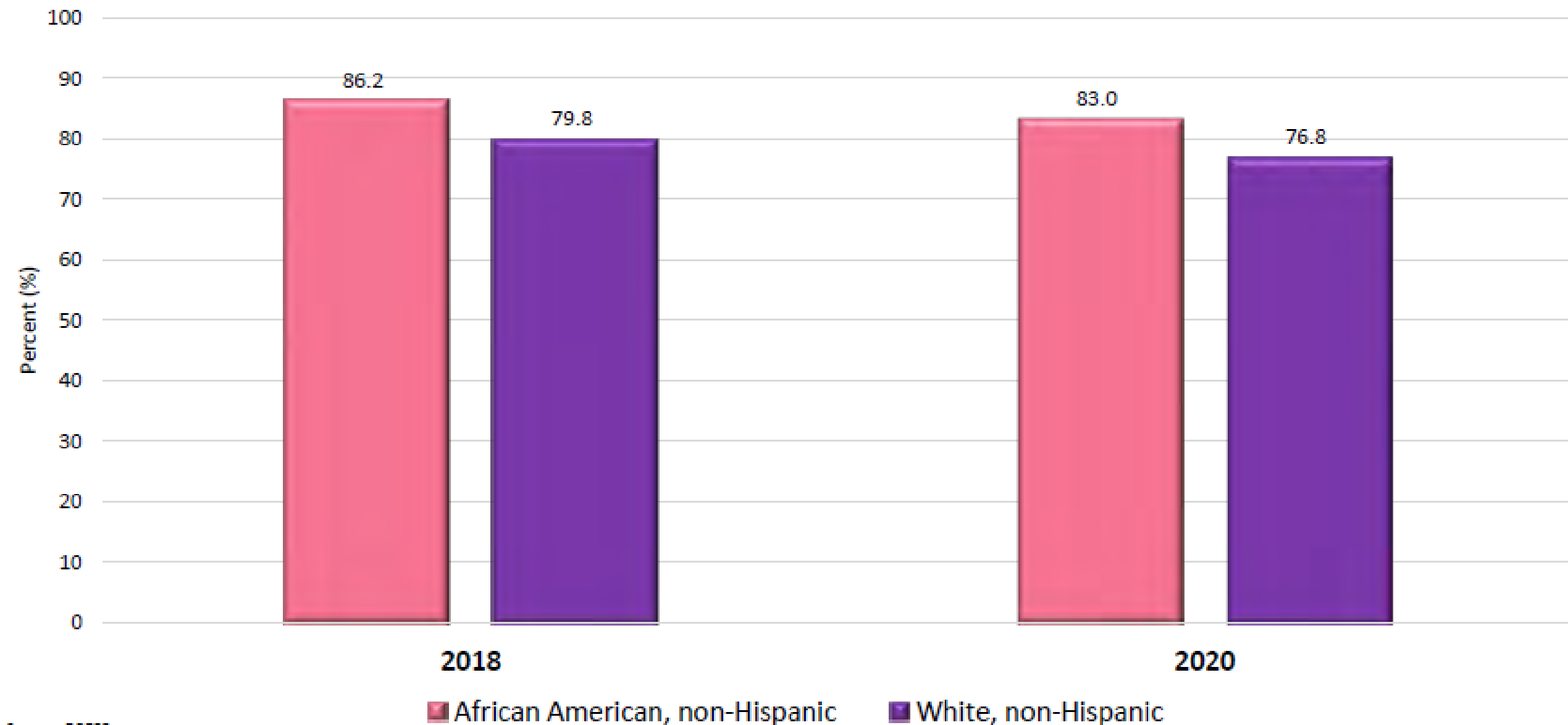
- DC
- ND
- DE
- NJ
- CT
- RI
- MA
- VT
- NH

**Arkansas:**  
77.6% reported receiving a pap test within the past 3 years

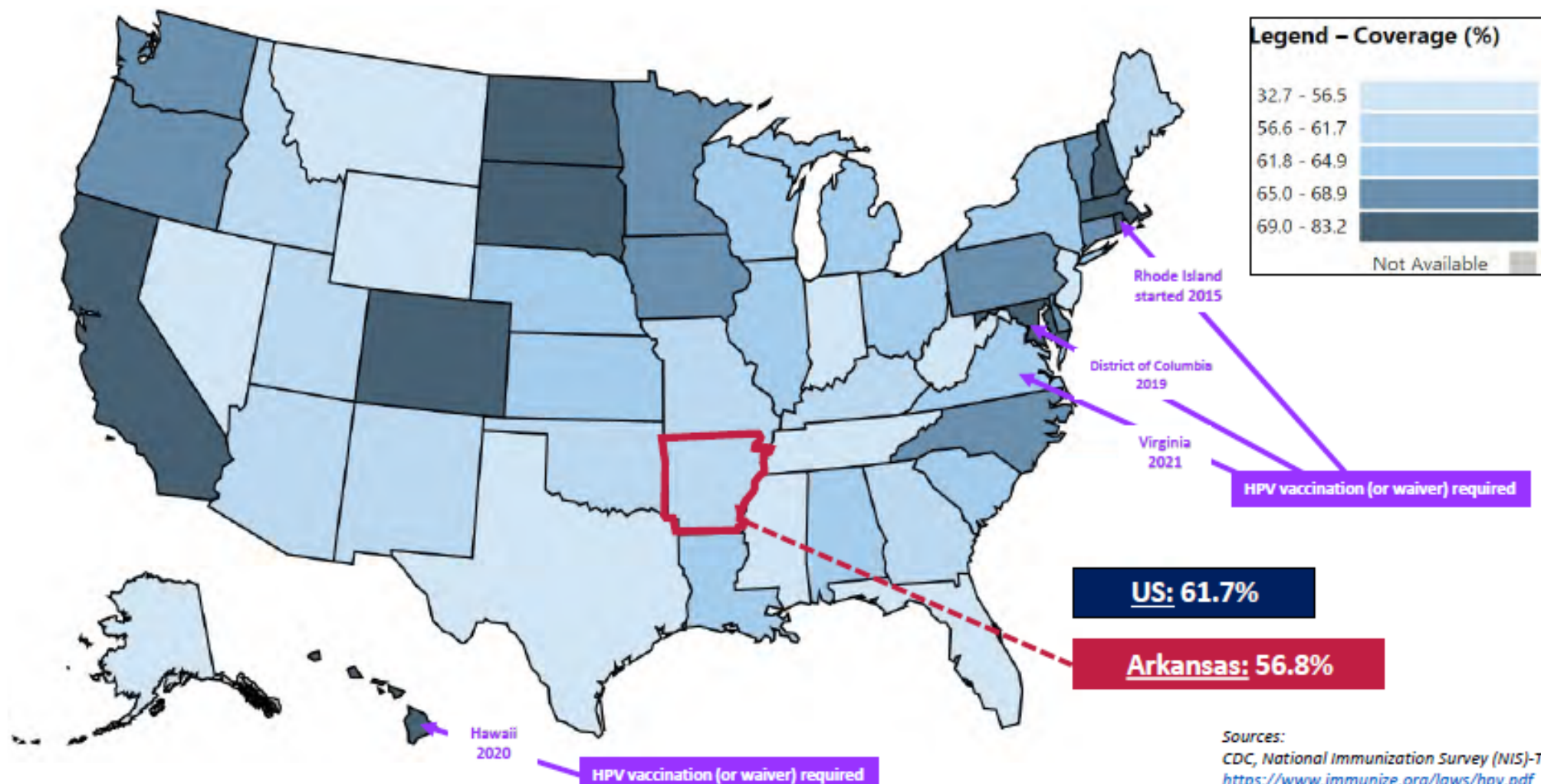
Source: USCS Data Visualization, extracted crude prevalence from BRFSS



# Percent of females who reported receiving a Pap test within the past 3 years by race/ethnicity, Arkansas, 2018-2020



## Up-to-date HPV Vaccine Rate per County for Children Ages 13-17, All Males and Females US Map, 2021



# ACIP Vaccine Recommendations

Morbidity and Mortality Weekly Report

## **Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices**

Elissa Meites, MD<sup>1</sup>; Peter G. Szilagyi, MD<sup>2</sup>; Harrell W. Chesson, PhD<sup>3</sup>; Elizabeth R. Unger, PhD, MD<sup>4</sup>; José R. Romero, MD<sup>5</sup>;  
Lauri E. Markowitz, MD<sup>1</sup>

# ACIP Vaccine Recommendations

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- **Children and adults aged 9 through 26 years.** HPV vaccination is routinely recommended at age 11 or 12 years; vaccination can be given starting at age 9 years. Catch-up HPV vaccination is recommended for all persons through age 26 years who are not adequately vaccinated.



# ACIP Vaccine Recommendations

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- **Adults aged >26 years.**
- Catch-up HPV vaccination is not recommended for all adults aged >26 years.
- Instead, shared clinical decision-making regarding HPV vaccination is recommended for some adults aged 27 through 45 years who are not adequately vaccinated.
- HPV vaccines are not licensed for use in adults aged >45 years.



# ACIP Vaccine Recommendations

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- **Special populations and medical conditions.** These recommendations for children and adults aged 9 through 26 years and for adults aged >26 years apply to all persons, vaccination should be delayed until after pregnancy;
- however, pregnancy testing is not needed before vaccination.
- Persons who are breastfeeding or lactating can receive HPV vaccine.





# ACOG Recommendations (1)

- The Advisory Committee on Immunization Practices and ACOG recommend routine human papillomavirus (HPV) vaccination for girls and boys at the target age of 11–12 years (but it may be given from the age of 9 years) as part of the adolescent immunization platform.



# ACOG Recommendations (2-4)

- Obstetrician–gynecologists and other health care professionals should:
  - strongly recommend HPV vaccination to eligible patients and stress the benefits and safety of the HPV vaccine.
  - assess and vaccinate adolescent girls and young women with the HPV vaccine during the catch-up period (ages 13–26 years), regardless of sexual activity, prior exposure to HPV, or sexual orientation, if they were not vaccinated in the target age of 11–12 years
  - educate parents in their decision making regarding vaccinations for their daughters and sons.



# ACOG Recommendations (5-8)

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For some women aged 27–45 years who are previously unvaccinated, obstetrician–gynecologists and other health care professionals may use shared clinical decision making regarding the HPV vaccination, considering the patient’s risk for acquisition of a new HPV infection and whether the HPV vaccine may provide benefit.



The American College of Obstetrician–Gynecologists does not recommend that an individual who received the quadrivalent HPV vaccine be revaccinated with 9-valent HPV vaccine, including those aged 27–45 years who previously completed some, but not all, of the vaccine series when they were younger.



Obstetrician–gynecologists are encouraged to stock and administer HPV vaccine in their offices when feasible.




Vaccination is recommended for women through age 26 years even if the patient is tested for HPV DNA and the results are positive.

# ACOG Recommendations (9-12)


Testing for HPV DNA is not recommended before vaccination.



Human papillomavirus vaccination is not recommended during pregnancy; however, routine pregnancy testing is not recommended before vaccination.



The HPV vaccine can and should be given to breastfeeding women age 26 years and younger who have not previously been vaccinated.



In children with a history of sexual abuse or assault, the HPV vaccine should be given as early as possible, starting at age 9 years

## Immunogenicity and Vaccine Efficacy (Does it Work?)

HPV vaccines are highly immunogenic

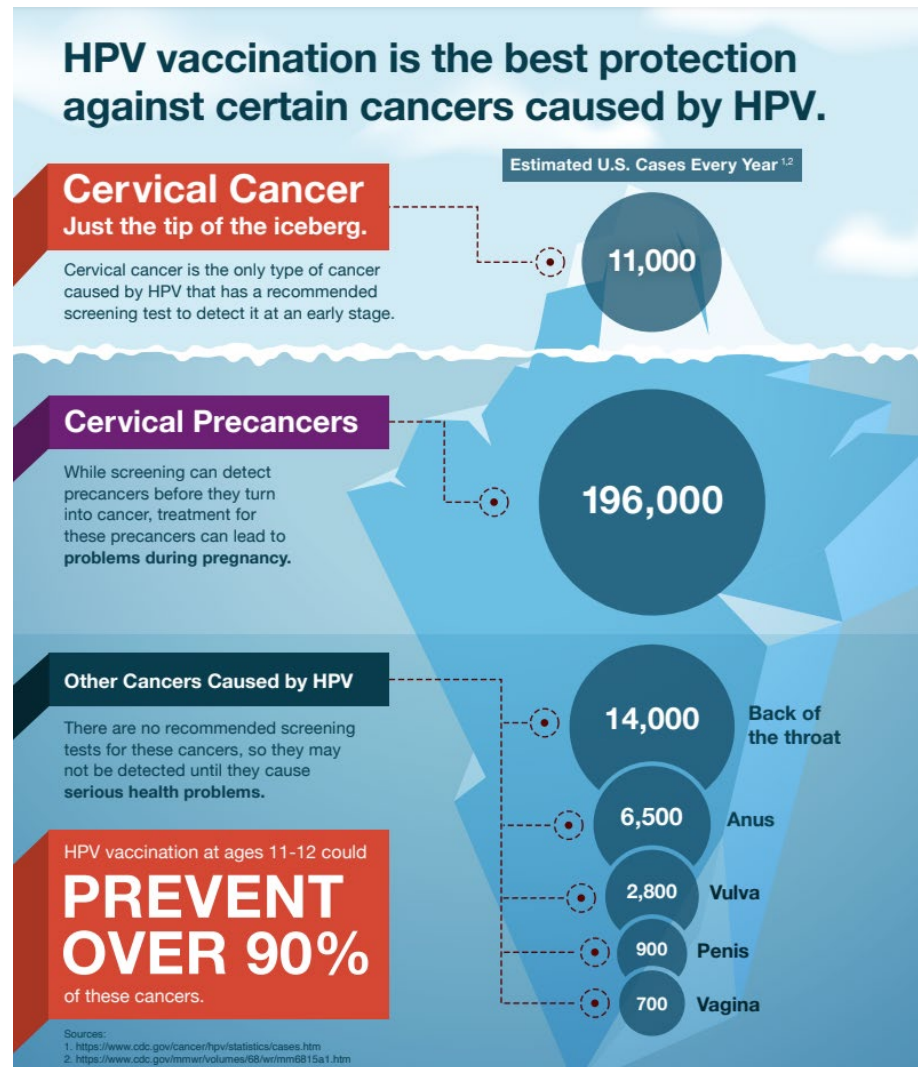
All HPV vaccines have been found to have high efficacy (close to 100%) for prevention of HPV vaccine type-related persistent infection, cervical intraepithelial neoplasia (CIN) 2/3, and adenocarcinoma in situ (AIS) in clinical trials

High efficacy among persons without evidence of prior infection with HPV vaccine types

No evidence of efficacy against disease caused by HPV types with which participants were already infected at the time of vaccination

Prior infection with one HPV vaccine type did not diminish efficacy of vaccine against the other HPV vaccine types

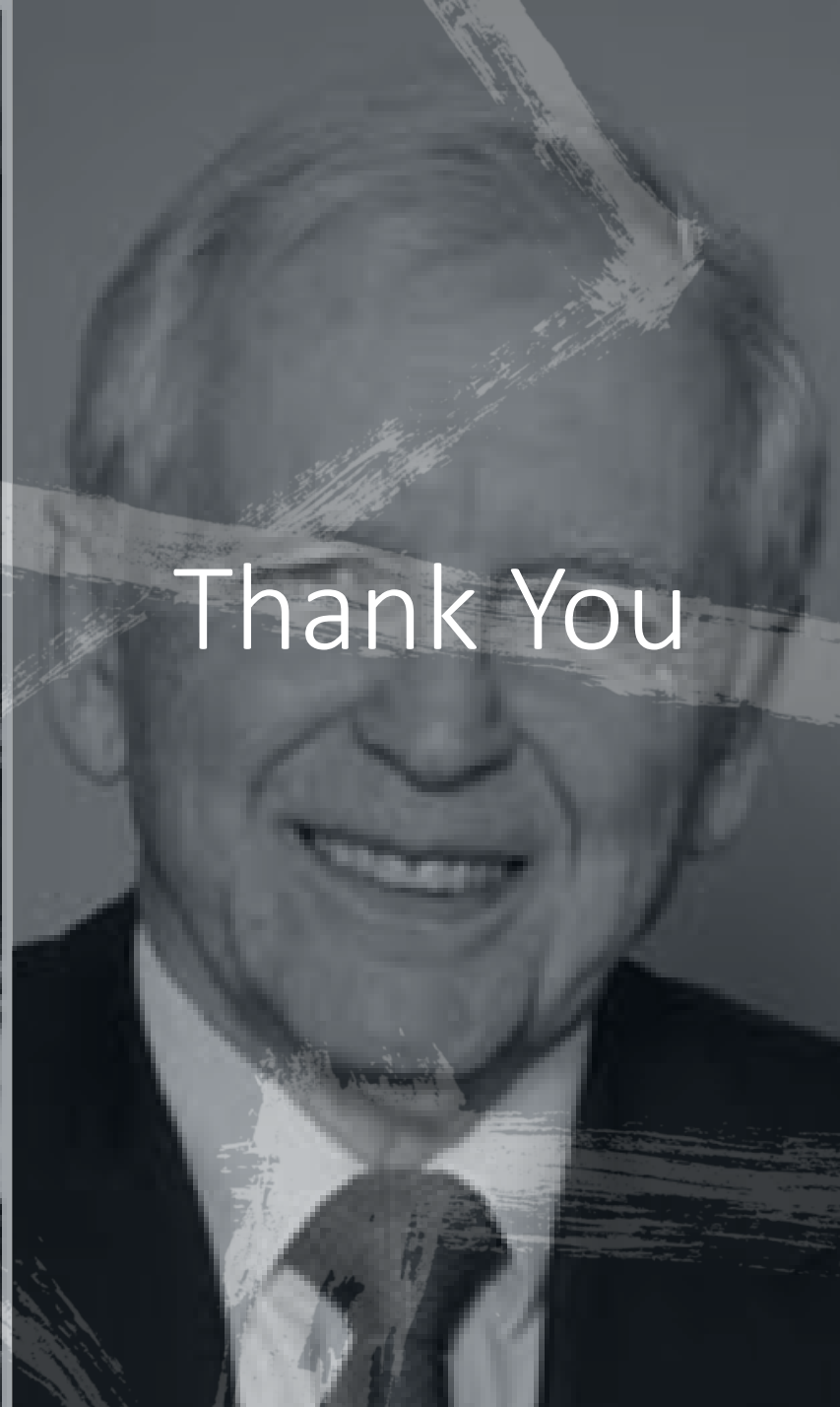
HPV  
Vaccination  
is Cancer  
Prevention



For additional information, visit:  
[www.cdc.gov/HPV](http://www.cdc.gov/HPV)

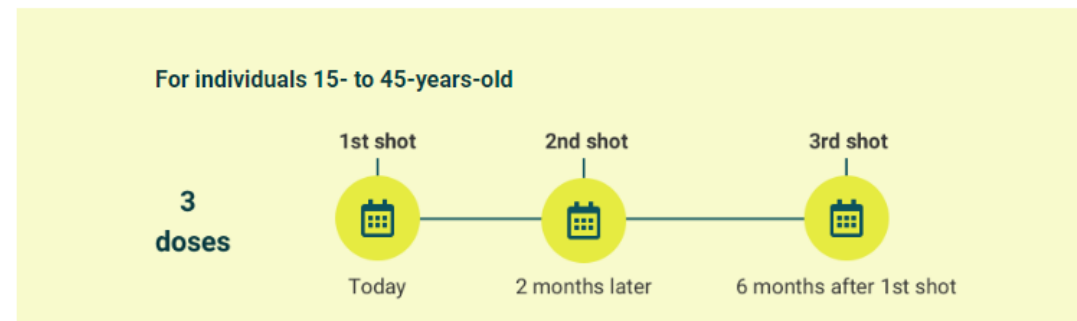
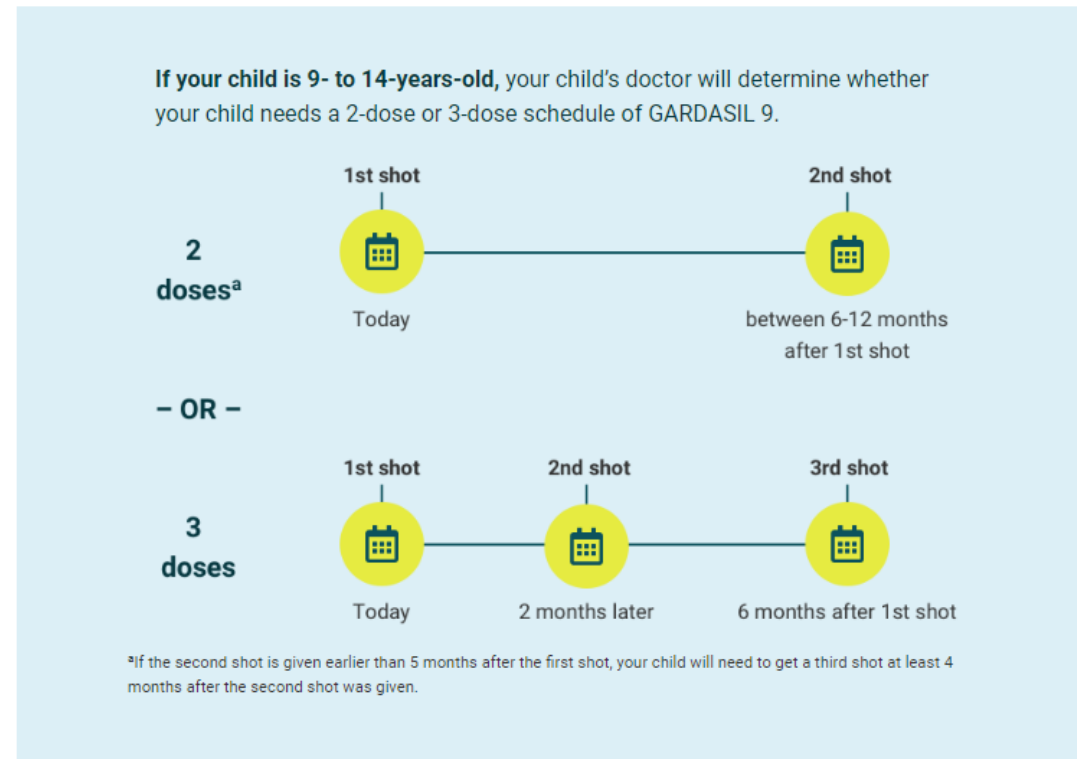


**HPV VACCINE**  
IS CANCER PREVENTION



## Make sure your child completes their recommended vaccine schedule.

The number of recommended doses is based on age when the first dose is given.



# Does it Work?

## Ten-Year Follow-up of 9-Valent Human Papillomavirus Vaccine: Immunogenicity, Effectiveness, and Safety

Jaime Restrepo, MD,<sup>a</sup> Teobaldo Herrera, MD,<sup>b</sup> Rudiwilai Samakoses, MD,<sup>c</sup> Julio C. Reina, MD,<sup>d</sup> Punnee Pitsuttithum, MBBS, DTM&H,<sup>e</sup> Angels Ulled, MD,<sup>f</sup> Linda-Gail Bekker, MBChB, DTMH, DCH,<sup>g</sup> Edson D. Moreira Jr, MD,<sup>h</sup> Sven-Eric Olsson, MD,<sup>i</sup> Stan L. Block, MD,<sup>j</sup> Luciano S. Hammes, MD, PhD,<sup>k</sup> Fabio Laginha, MD,<sup>l</sup> Alex Ferenczy, MD,<sup>m</sup> Robert Kurman, MD,<sup>n</sup> Brigitte M. Ronnett, MD,<sup>o</sup> Mark Stoler, MD,<sup>p</sup> Oliver Bautista, PhD,<sup>q</sup> Nancy E. Gallagher, BS,<sup>r</sup> Gino Salituro, PhD,<sup>s</sup> Min Ye, MS,<sup>t</sup> Alain Luxembourg, MD, PhD<sup>u</sup>

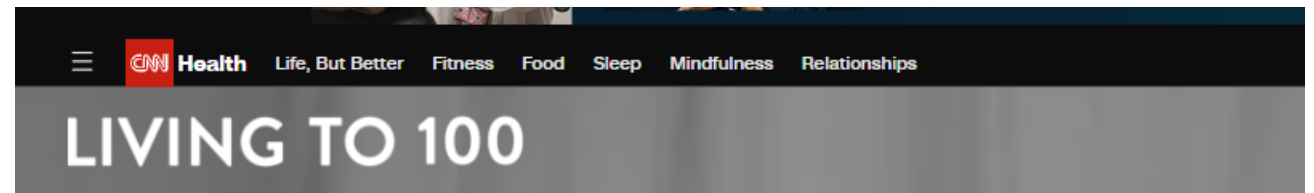
**BACKGROUND AND OBJECTIVES:** The 9-valent human papillomavirus (9vHPV) vaccine Phase III immunogenicity study in 9- to 15-year-old boys and girls was extended to assess immunogenicity and effectiveness through 10 years after the last vaccine dose (NCT00943722).

**METHODS:** Boys ( $n = 301$ ) and girls ( $n = 971$ ) who received three 9vHPV vaccine doses in the base study (day 1, months 2 and 6) enrolled in the extension. Serum was collected through month 126 for antibody assessments by competitive Luminex immunoassay and immunoglobulin G-Luminex immunoassay. For effectiveness analysis starting at age 16 years, genital swabs were collected (to assess HPV DNA by polymerase chain reaction) and external genital examinations conducted every 6 months. Primary analyses were conducted in per-protocol populations.

**RESULTS:** Geometric mean antibody titers peaked around month 7, decreased sharply between months 7 and 12, then gradually through month 126. Seropositivity rates remained  $\geq 81\%$  by competitive Luminex immunoassay and  $\geq 95\%$  by immunoglobulin G-Luminex immunoassay at month 126 for each 9vHPV vaccine type. After up to 11.0 (median 10.0) years of follow-up postdose 3, there were no cases of HPV6/11/16/18/31/33/45/52/58-related high-grade intraepithelial neoplasia or condyloma in males or females. Incidence rates of HPV6/11/16/18/31/33/45/52/58-related 6-month persistent infection in males and females were low (54.6 and 52.4 per 10000 person-years, respectively) and within ranges expected in vaccinated cohorts, based on previous human papillomavirus vaccine efficacy trials.

**CONCLUSIONS:** The 9vHPV vaccine demonstrated sustained immunogenicity and effectiveness through ~10 years post 3 doses of 9vHPV vaccination of boys and girls aged 9 to 15 years.

[abstract](#)



## Australia set to 'eliminate' cervical cancer by 2028

By Nina Avramova, CNN

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