

CDC PUBLIC HEALTH GRAND ROUNDS

Preventing Cervical Cancer in the 21st Century



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January 15, 2019



U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention

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CDC PUBLIC HEALTH GRAND ROUNDS

Preventing Cervical Cancer in the 21st Century



January 15, 2019



**U.S. Department of
Health and Human Services**
Centers for Disease
Control and Prevention

The Epidemiology of Cervical Cancer



Mona Saraiya, MD, MPH

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Cervical Cancer Burden

		Worldwide (2018 Estimated)	U.S. (2015 Actual)
Incidence	New Cases	More than 569,000	More than 12,000
	Rank Among Female Cancer Cases	4	13
Mortality	Deaths	More than 311,000	More than 4,000
	Rank Female Cancers Deaths	4	14

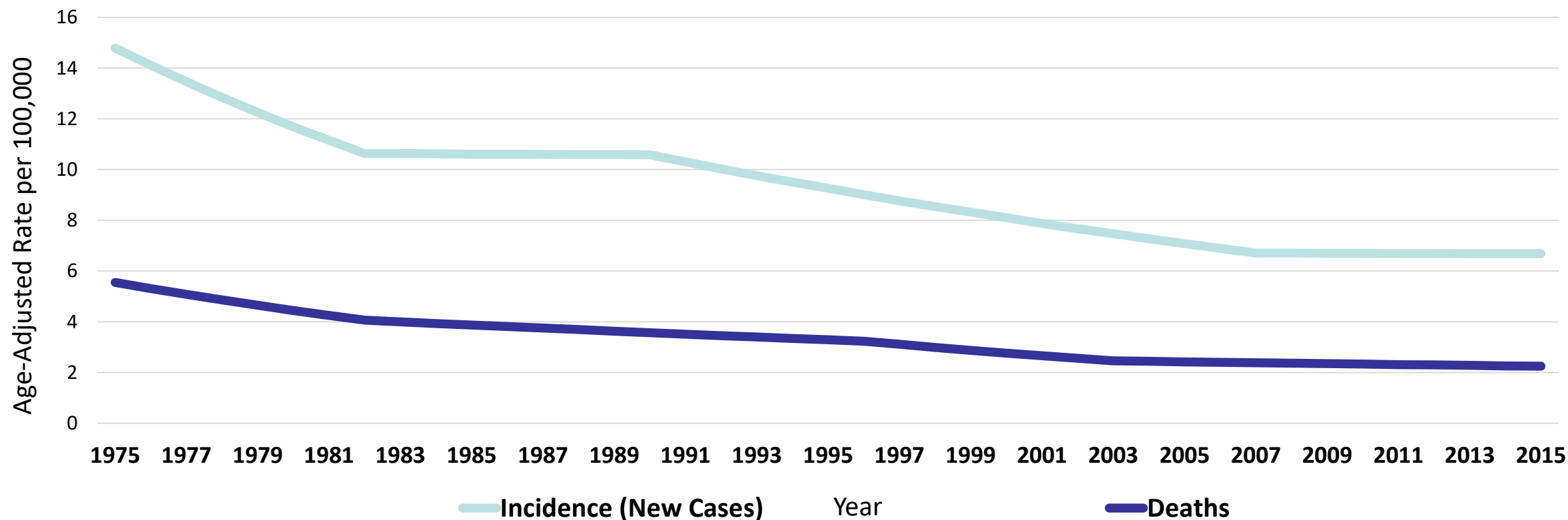
www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/global-cancer-facts-and-figures/global-cancer-facts-and-figures-4th-edition.pdf

gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf

Cronin KA, Lake AJ, & Scott S, et al. *Cancer* 2018 Jul 1;124(13):2785–2800

After Decades of Declining Rates, Incidence and Mortality Rates Have Levelled Off Since 2007

Trends in Cervical Cancer Incidence and Mortality, 1975–2015



National Cancer Institute, Surveillance, Epidemiology, and End Results program: seer.cancer.gov/statfacts/html/cervix.html

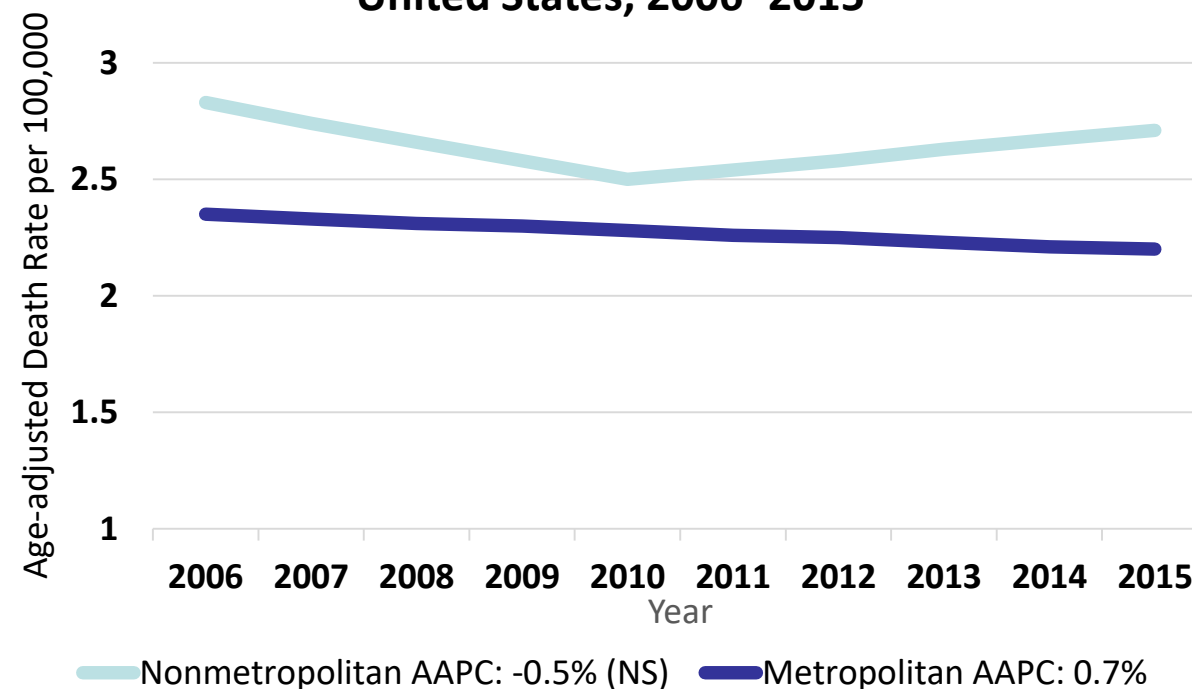
CDC, National Center for Health Statistics

Cervical Cancer Disparities in the United States

➤ Higher rates of cervical cancer in:

- Black and Hispanic women
- Women living in nonmetropolitan areas
- Women with lower socioeconomic status
- Women who have never been screened or not screened in past 5 years

Trends in Cervical Cancer in Nonmetropolitan and Metropolitan Counties by Year of Death—United States, 2006–2015



AAPC: Average annual percent change

NS: Non-significant

Henley SJ, Anderson RN, Thomas, CC, et al. *MMWR Surveill Summ* 2017; Jul 7;66(14):1–13

Human Papillomaviruses (HPV) Cause Many Types of Cancer

➤ **Double-stranded DNA virus**

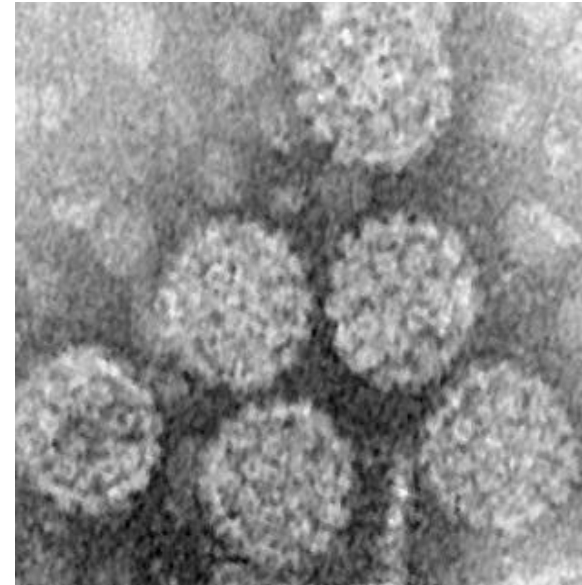
- More than 120 closely related viruses
 - ❑ Some types cause cancer, and others cause genital warts
 - ❑ Types numbered in order of discovery

➤ **HPV infection confined to epithelium**

- Begins in base of epithelium, cells proliferate and are not killed

➤ **Recombinant HPV vaccine in United States targets 9 types of HPV**

- 2 of these types cause 90% of genital warts
- 7 of these types cause 80% of cervical cancer

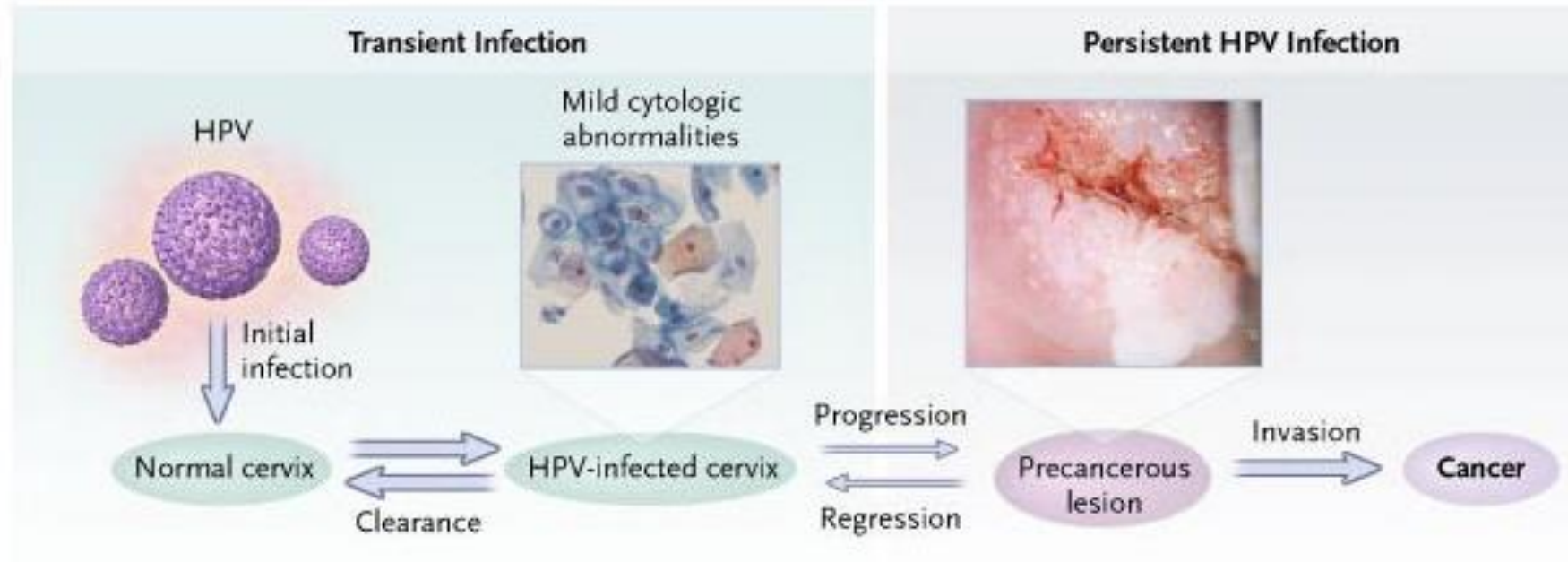


HPV Infection is Common

- **HPV infection is very prevalent in the population**
 - Almost all sexually active persons will acquire HPV
 - In the United States, approximately 79 million infected and 14 million new infections per year
- **Genital HPV is first acquired soon after onset of sexual activity**
 - 40% infected within 2 years
- **Infection is usually transient, asymptomatic**
 - 90% of infections clear within 2 years
- **Cancer is a rare outcome of HPV infection**
 - Requires persistent infection with high risk HPV types

Persistent Infection with High-risk Types Required for Progression to Precancer and Cancer

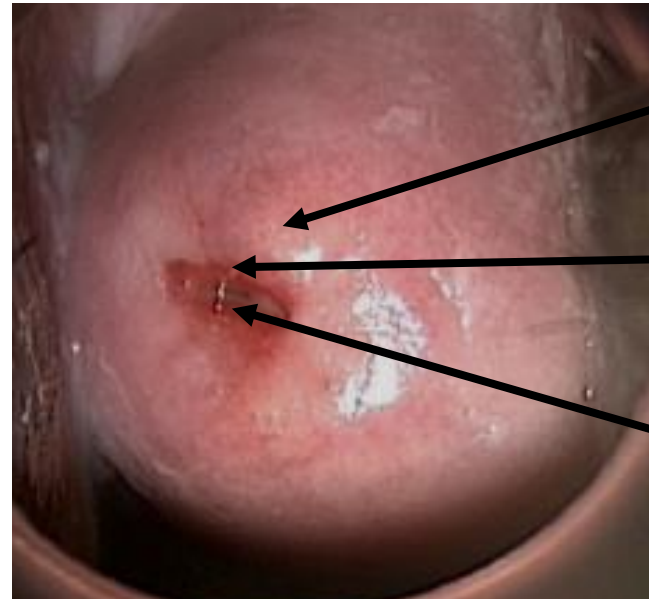
HPV: Natural History of Cervical Infection



Peak incidence of precancers in late 20s and peak incidence of cancers in early 40s

Cervical Carcinoma Histology

- **Squamous cell carcinoma (SCC) begins in squamous cells**
- **Adenocarcinoma begins in columnar (glandular) cells**
 - Harder to sample with a traditional Pap test due to location of cells



Squamous
epithelium

Squamocolumnar
junction

Columnar
epithelium

Normal Cervix

Cervical Cancer Screening

➤ Pap (Papanicolaou) Test

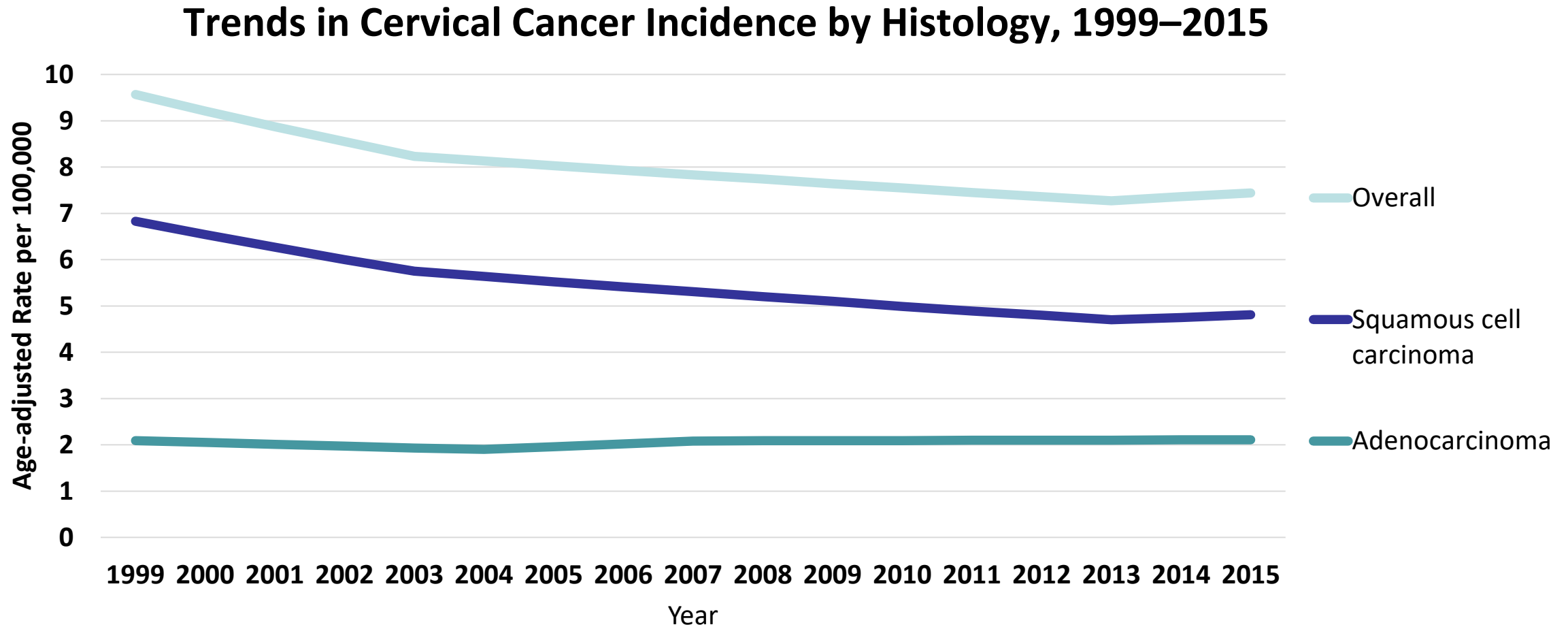
- Collects cells from the surface of the cervix and looks for abnormal cells
- Subjective test
- Lower sensitivity



➤ HPV Test

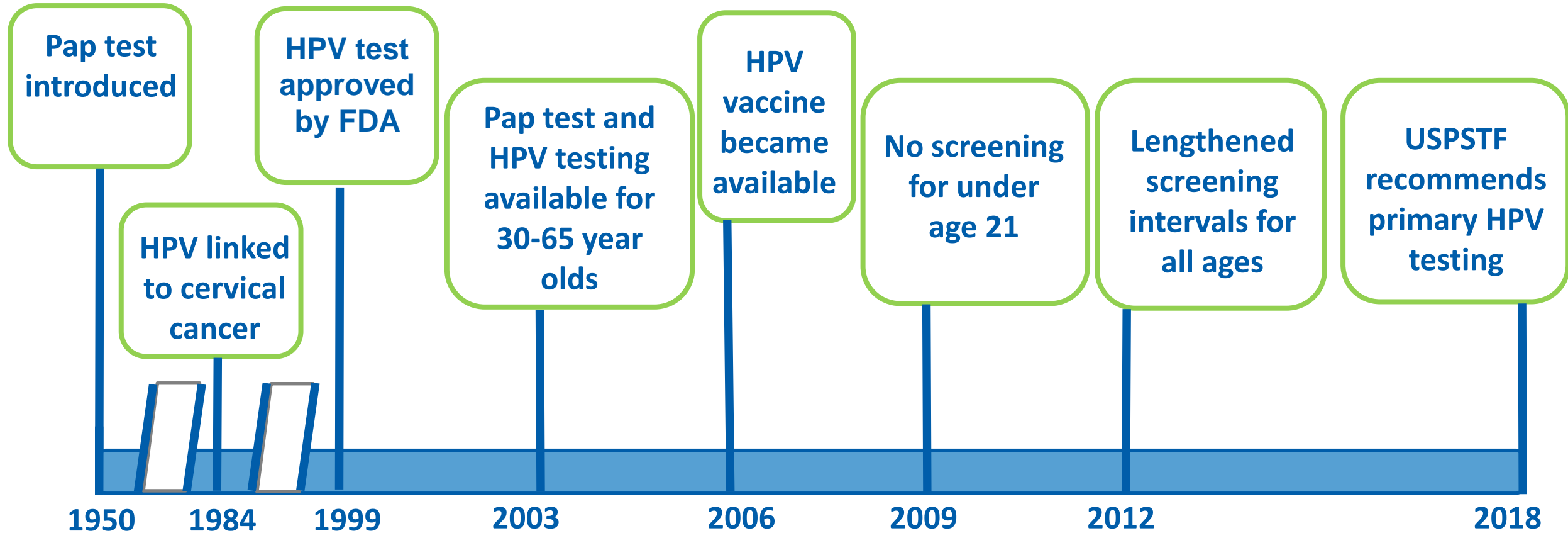
- Collects cells from the surface of the cervix and looks for presence of 14 types of cancer causing HPV
- Objective test
- Higher sensitivity
- 7 FDA-approved HPV tests
 - ❑ 2 approved for use alone
 - ❑ None approved for self-sampling

Overall Rates Have Dropped But Adenocarcinoma Rates Remain Unchanged



Our Understanding and Interventions Have Progressed

Major Events for Cervical Cancer Prevention in the United States



Cervical Cancer Screening Recommendations and Guidelines Are Based on Age

Cervical Cancer Screening Recommendations and Guidelines		
	ACS and ACOG, 2012	USPSTF, 2018
Screening Methods for Women Based on Age		
Ages 21-29 years	Pap every 3 years	Pap every 3 years
Ages 30-65 years	1) Co-testing (HPV and Pap) every 5 years (preferred) 2) Pap alone every 3 years	1) Co-testing every 5 years 2) Pap alone every 3 years 3) HPV alone every 5 years
Age to start	Age 21 years	Age 21 years
Screening among fully vaccinated	Same as for non-vaccinated	Same as for non-vaccinated

*All guidelines recommend that women who have been adequately screened can discontinue Pap at age 65.

ACS: American Cancer Society

USPSTF: US Preventive Services Task Force

ACOG: American College of Obstetricians and Gynecologists

Cervical Cancer Screening Recommendations and Guidelines Are Complicated



When choosing HPV screening methods, care providers and women will need to talk through their options based on their age, risk, and preferences.

We Should Use All Available Tools to Prevent Cervical Cancer

- **Cervical cancer has decreased in the United States in past century due to screening**
- **Significant disparities remain**
- **Screening technology has evolved**
- **Screening recommendations and guidelines are complicated**
- **HPV vaccination holds promise to decrease burden further**



HPV Vaccination in the United States: Current Status



Melinda Wharton, MD, MPH

Director, Immunization Services Division

National Center for Immunization and Respiratory Diseases

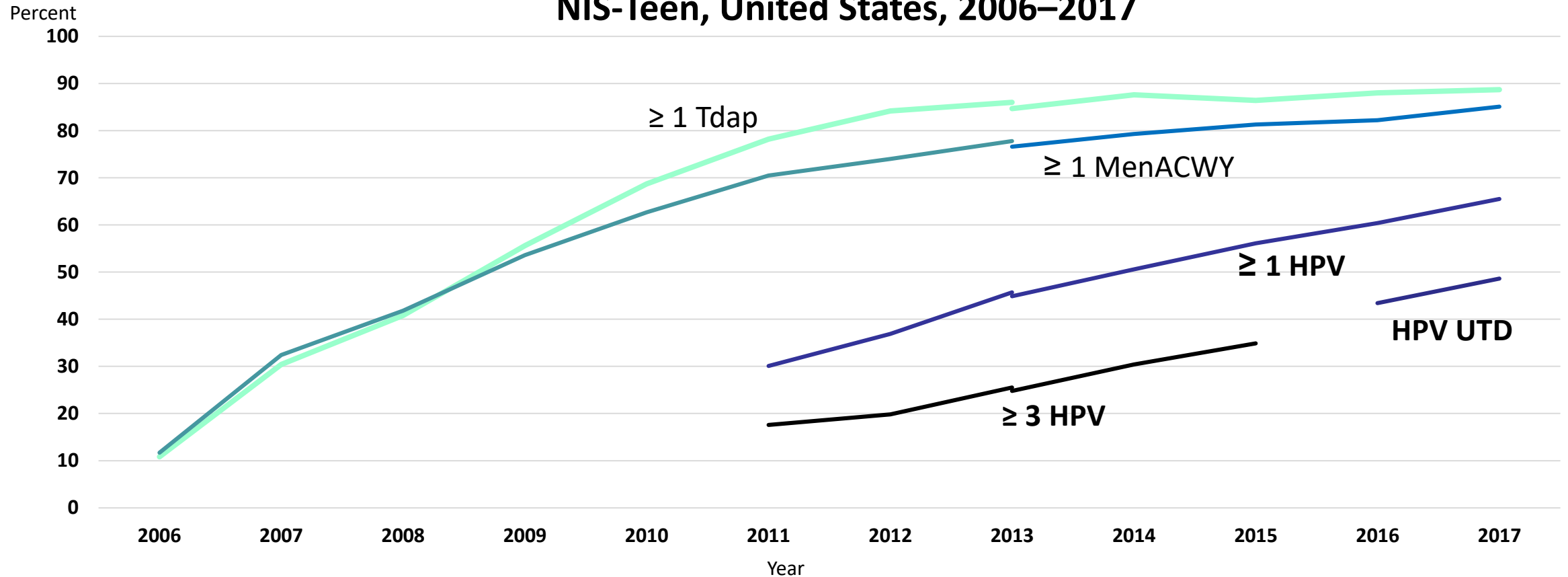
Centers for Disease Control and Prevention

HPV Vaccine Recommendations, United States, 2006–present

- 2006** HPV vaccine recommended as three dose series for girls at 11–12 years of age, with catch up for adolescents and young women through 26 years of age
 - 2011** HPV vaccine recommended as three-dose series for boys at 11–12 years of age, with catch-up through 21 years of age
 - 2015** 9-valent HPV vaccine replaced 4-valent HPV vaccine
 - 2016** For boys and girls who start series before 15th birthday, only two doses of HPV vaccine needed
- By late 2016, only 9-valent vaccine was marketed in U.S.

HPV Vaccination Rates Lag Behind Other Vaccines Recommended at Ages 11–12 Years

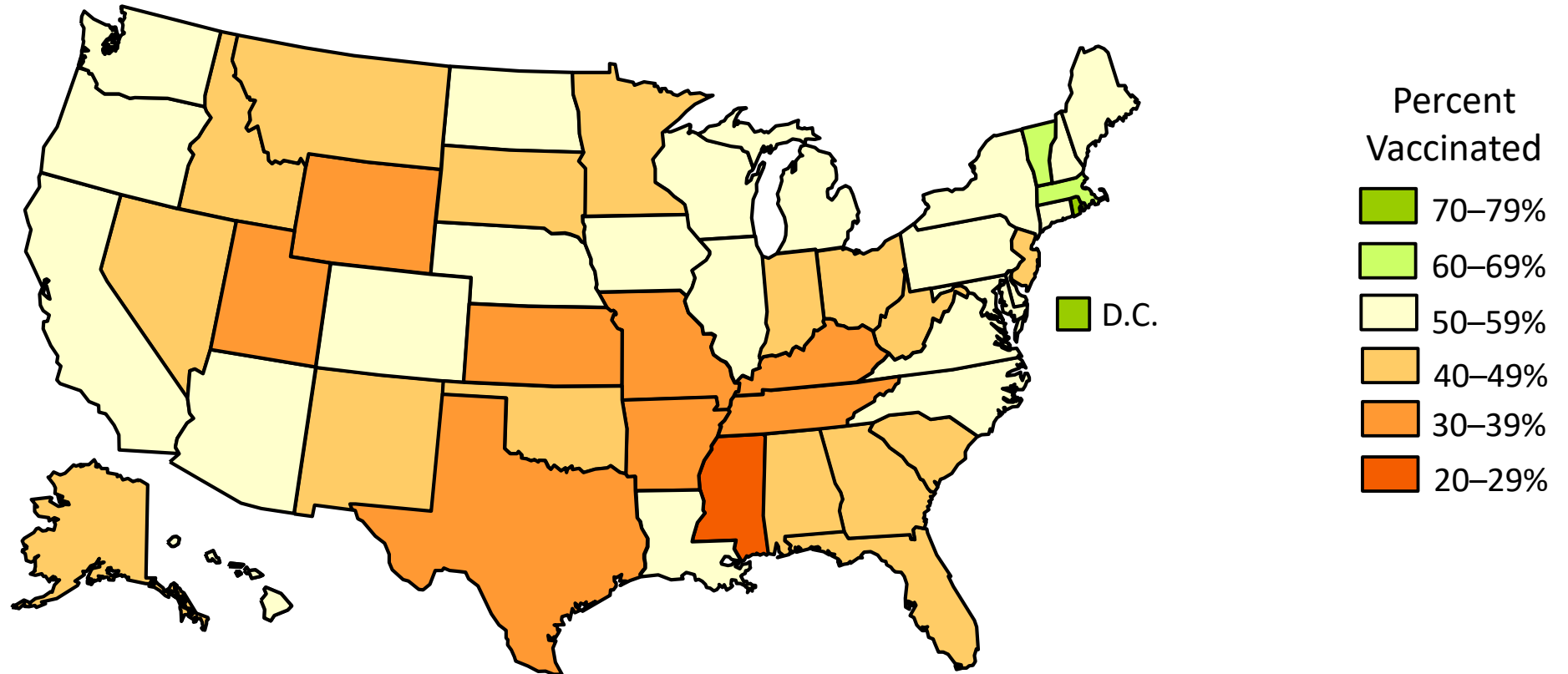
**Trends in Vaccination Coverage among Adolescents Aged 13–17 Years,
NIS-Teen, United States, 2006–2017**



HPV UTD: HPV up-to-date; includes those with ≥ 3 doses, and those with 2 doses when the first HPV vaccine dose was initiated before age 15 years with an appropriate interval between the first and second dose.

HPV Vaccination Rates Vary Widely Across the U.S.

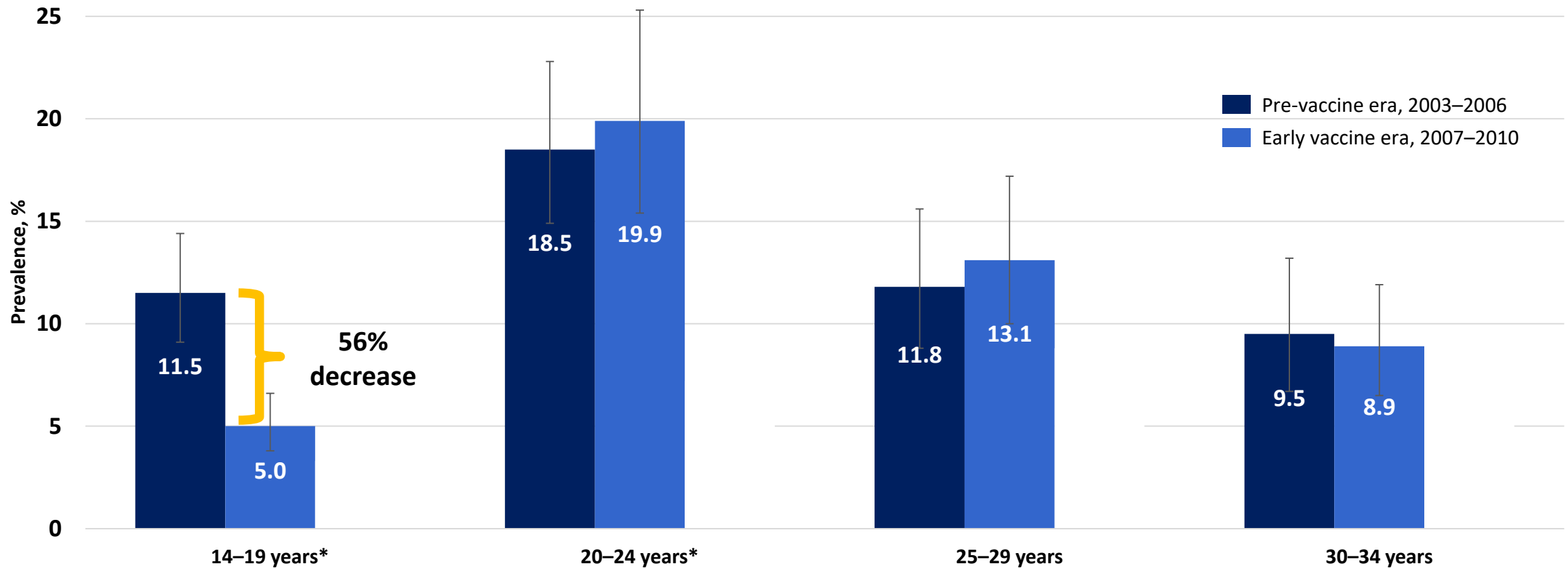
Vaccination Coverage Among Adolescents Aged 13–17 Years By State, United States, 2017



Walker TY, Elam-Evans LD, Yankey D, et al. *MMWR* 2018;67:909–917

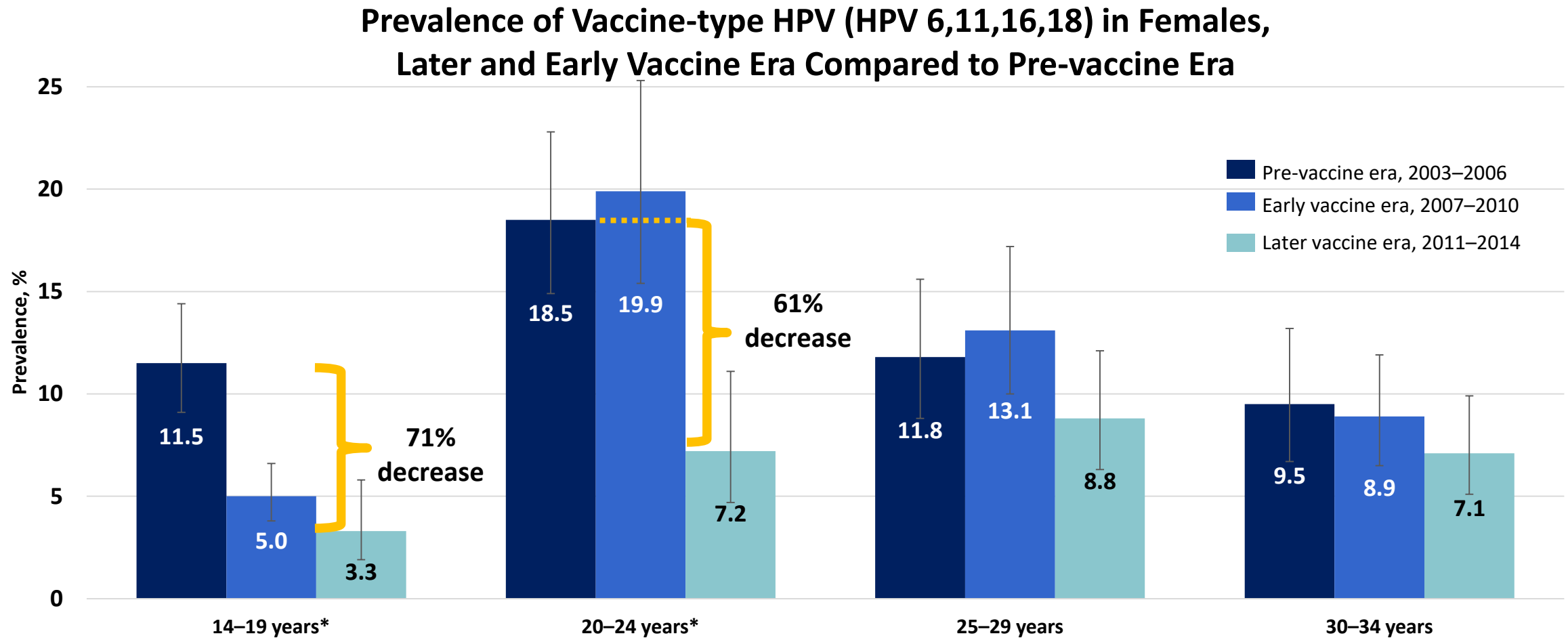
Prevalence of HPV Drops After Vaccine Introduction

Prevalence of Vaccine-type HPV (HPV 6,11,16,18) in Females, Early Vaccine Era Compared to Pre-vaccine Era



Markowitz LE, Hariri S, Lin C, et al. *J Infect Dis* 2013 Aug 1;208(3):385-93

Over Time Prevalence of HPV Drops Even Further



Markowitz LE, Hariri S, Lin C, et al. *J Infect Dis* 2013 Aug 1;208(3):385–93

Oliver SE, Unger ER, Lewis R, et al. *J Infect Dis* 2017 Sep 1;216(5):594–603

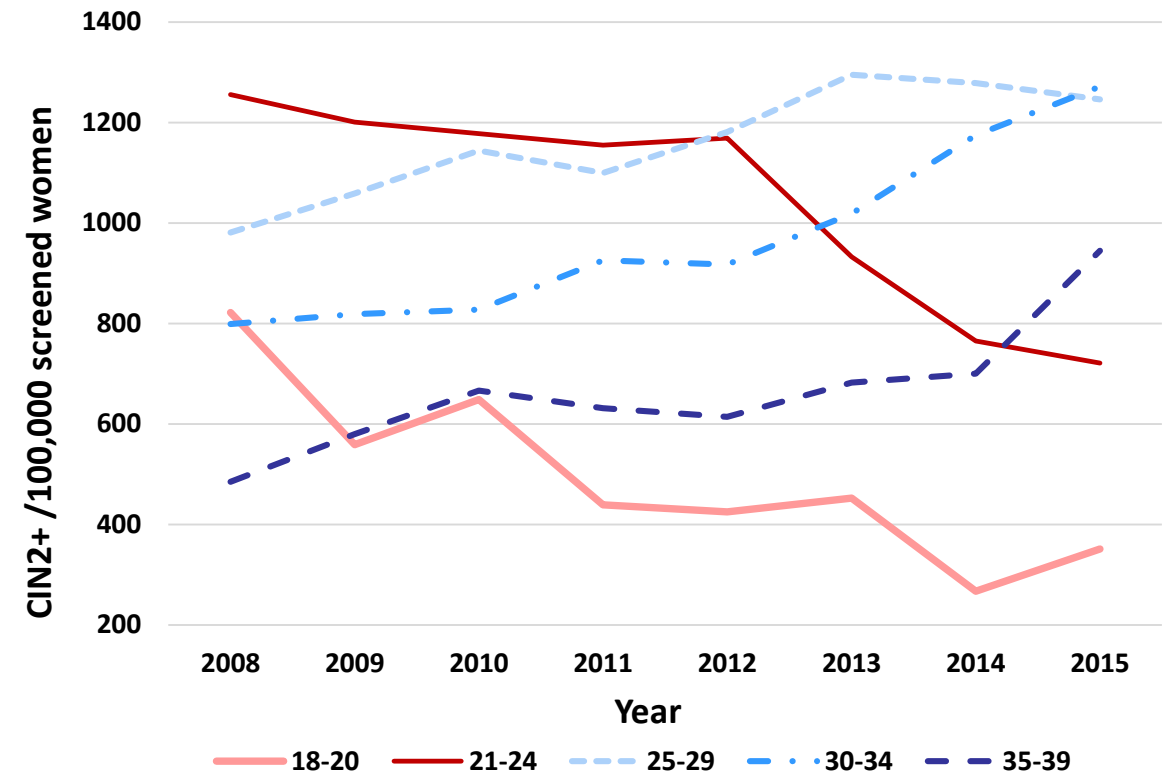
NHANES: National Health and Nutrition Examination Survey

Cervical Precancer Incidence Rates Have Decreased in Younger Women

➤ CIN2+ rates lower in younger women

- CIN2+ rates **decreased** significantly in estimated screened women ages 18–20 and 21–24 years
- CIN2+ rates **increased** in screened women ages 25–29, 30–34, and 35–39 years
- Could be attributable to:
 - Longer screening intervals and/or
 - Increased sensitivity of screening or diagnostic tests

Estimated Cervical Precancer Incidence Rates per 100,000 Screened Women, HPV IMPACT Project



CIN2+: Precancerous lesions called “cervical intraepithelial neoplasia, grade 2 or worse; or adenocarcinoma in situ”

Gargano JW, Park IU, Griffin MR, et al. *Clin Infect Dis*. 2018 Aug 23

Why Aren't Kids Being Vaccinated?

Improving HPV Vaccine Coverage

Parental Reasons Given for Not Vaccinating Adolescents with HPV Vaccine, Unvaccinated Adolescents* Aged 13–17 Years, NIS-Teen, United States, 2017

Parents of Girls		Parents of Boys	
Safety concerns/side effects	24%	Safety concerns/side effects	17%
Not needed/not necessary	14%	Not recommended	15%
Not recommended	8%	Not needed/not necessary	14%
Lack of knowledge	8%	Lack of Knowledge	9%
Not sexually active	7%	Not sexually active	8%

Strong Provider Recommendations Increases HPV Vaccination Rates



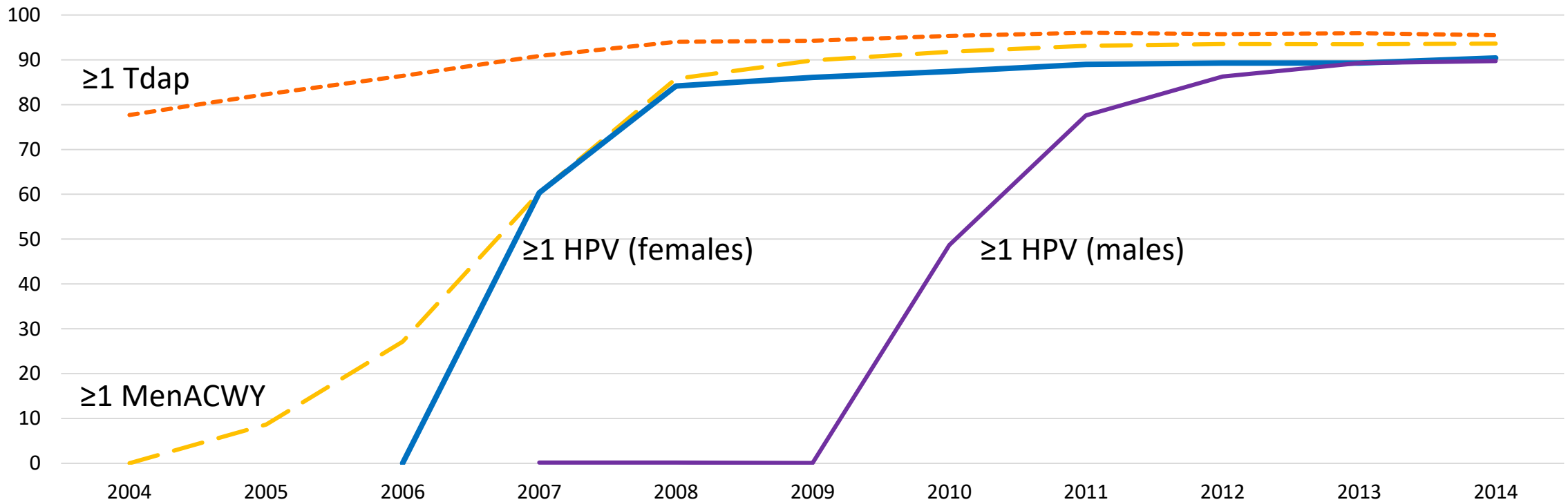
“Now that Sophia is 11, she is due for vaccinations today to help protect her from meningitis, HPV cancers, and pertussis.”

Comprehensive Quality Improvement Approaches Improve HPV Vaccine Coverage

- **Assess and offer feedback to providers about their vaccine coverage**
- **Engage all staff in the practice to support team-based efforts to improve HPV vaccine coverage**
- **Organize workflow to minimize burden on healthcare providers**
 - Use standing orders and allow immunization-only visits
 - Identify patients scheduled to be seen who are due HPV vaccine and prompt clinicians to recommend it at that visit
- **Establish reminder and recall systems**
- **Record all doses in EHR and state's immunization information system**

Immunization Rates Over 90% Are Achievable for Adolescents

Immunization Rates for Adolescents, Denver Health, 2004–2014



Modified from Farmar AM, Love-Osborne K, Chichester K, et al. *Pediatrics*. 2016 Nov;138(5)

Supporting Change: The Role of Partnerships and Coalitions

- **Working with national provider and quality improvement organizations**
 - HEDIS 2018 reflects current ACIP schedule
- **Convening national partners through the National HPV Vaccination Roundtable**
 - Sharing communication resources, best practices, and other tools and materials
- **Collaborating with cancer partners in national and state-level activities**
 - Comprehensive Cancer Control National Partnership
 - NCI-designated cancer centers
 - State coalitions and roundtables
- **Engaging integrated healthcare delivery systems**

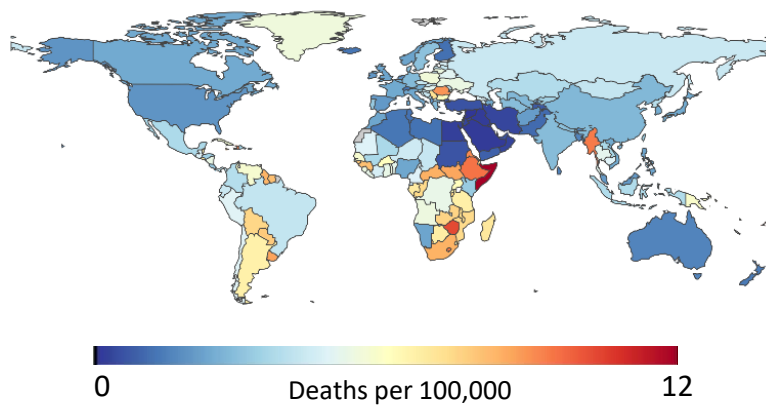
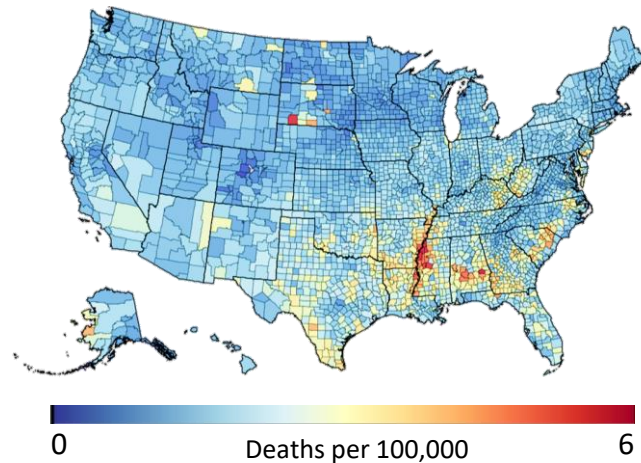
Novel Tools for Screening in High- and Low-Resource Settings



Nicolas Wentzensen, MD, PhD, MS

Deputy Chief and Senior Investigator, Clinical Genetics Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health

National Cancer Institute Moonshot: Accelerated Control of Cervical Cancer



High-resource settings

Challenges and Inefficiencies

Screening is not
distributed equally

Inefficient screening tools

Overtreatment

Many choices lead to confusion
among providers and women

Goals and Solutions

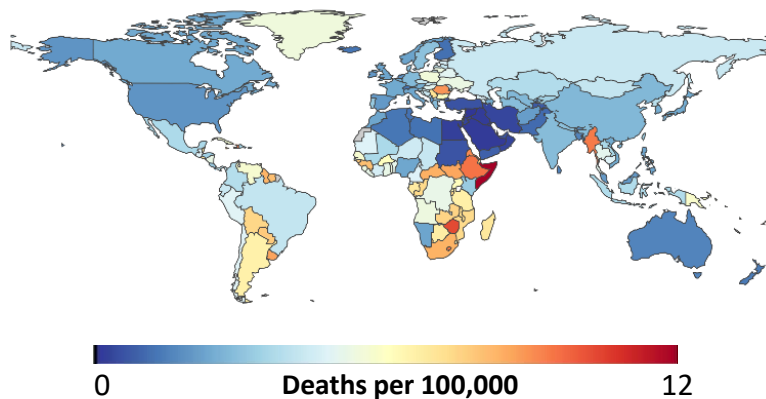
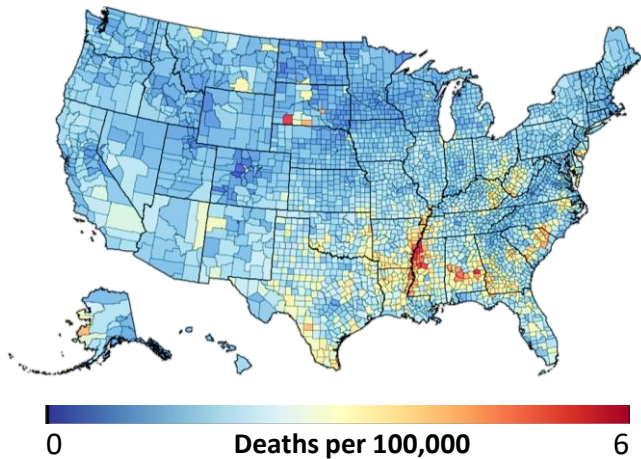
More efficient screening and
triage strategies

Extend screening intervals

Reduce overtreatment

Risk-based screening
and management

NCI Moonshot: Accelerated Control of Cervical Cancer



Low-resource settings

Challenges and Inefficiencies

No sustainable multi-visit screening programs

Limited treatment capacity

Hardly any vaccination

Goals and Solutions

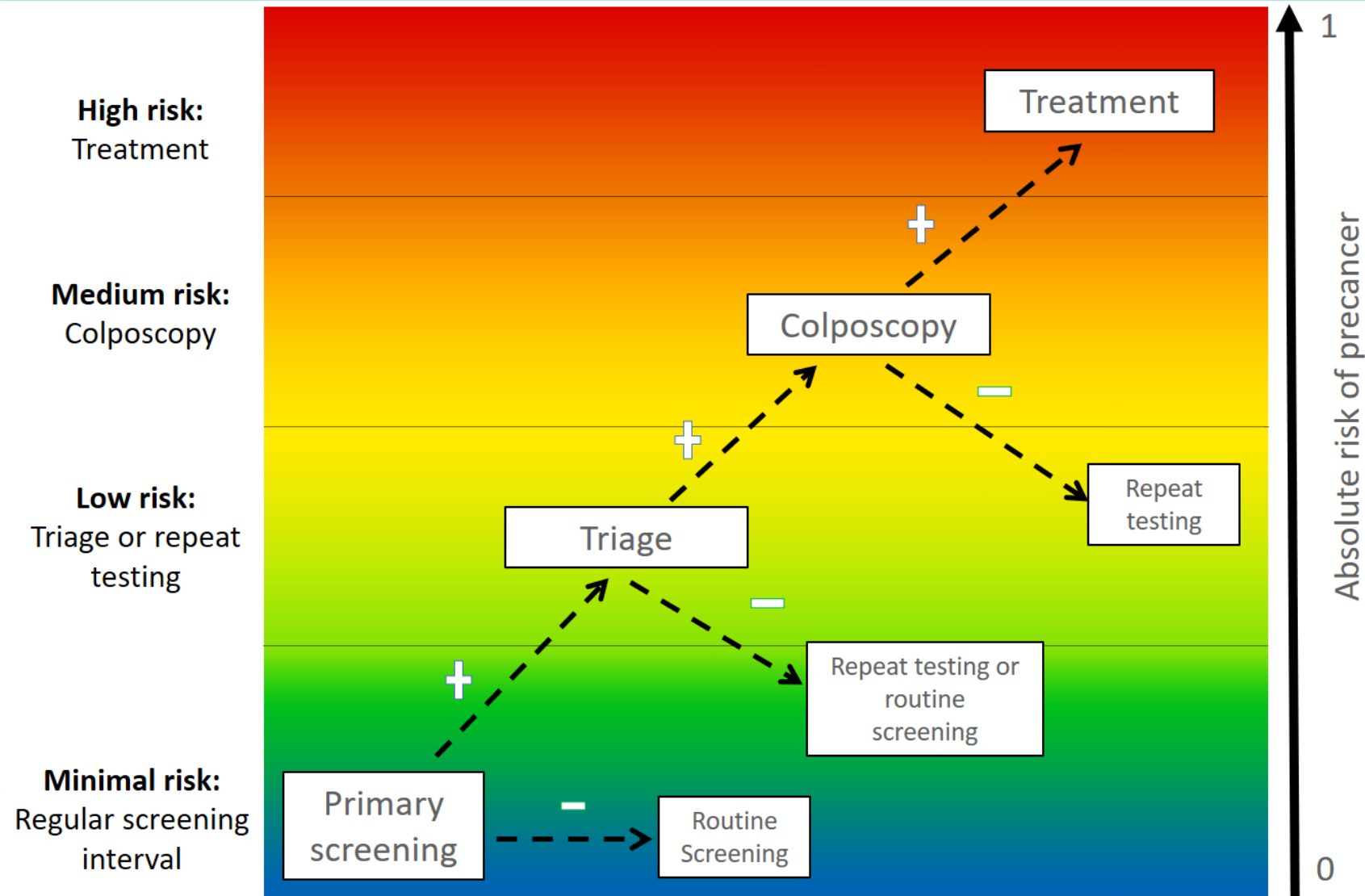
Increase coverage through single-visit, “screen and treat” programs

Reduce unnecessary referral to treatment


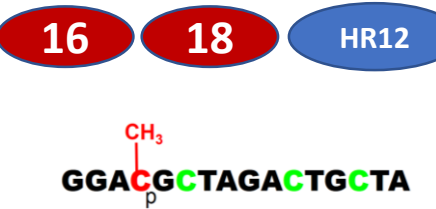

Integrate vaccination and screening

Low-resource settings exist in high-resource countries, e.g. US rural areas

Risk-based Screening and Management Guidelines



Novel Screening and Triage Technologies

		Technology	Resource Setting	Key References
 <p>Cytology</p>		Automated cytology	High/ middle	Schiffman et al. Int J Cancer 2017 Yu et al. JNCI 2018
		p16/Ki67 Dual stain (Automation)	High/ middle	Wentzensen et al. JNCI 2015 Clarke et al. JAMA Oncology 2018
 <p>Molecular</p>		HPV testing with extended genotyping; HPV protein	All	Schiffman et al. JNCI 2005 Schiffman et al. Int J Cancer 2016
		Viral methylation	All	Wentzensen et al. JNCI 2012, Clarke et al. Clin Cancer Res 2018
 <p>Visual</p>		Automated visual evaluation	Low	Schiffman et al. in press
		Risk-based colposcopy	High/ middle	Wentzensen et al. JCO 2015 Wentzensen et al. AJOG 2018

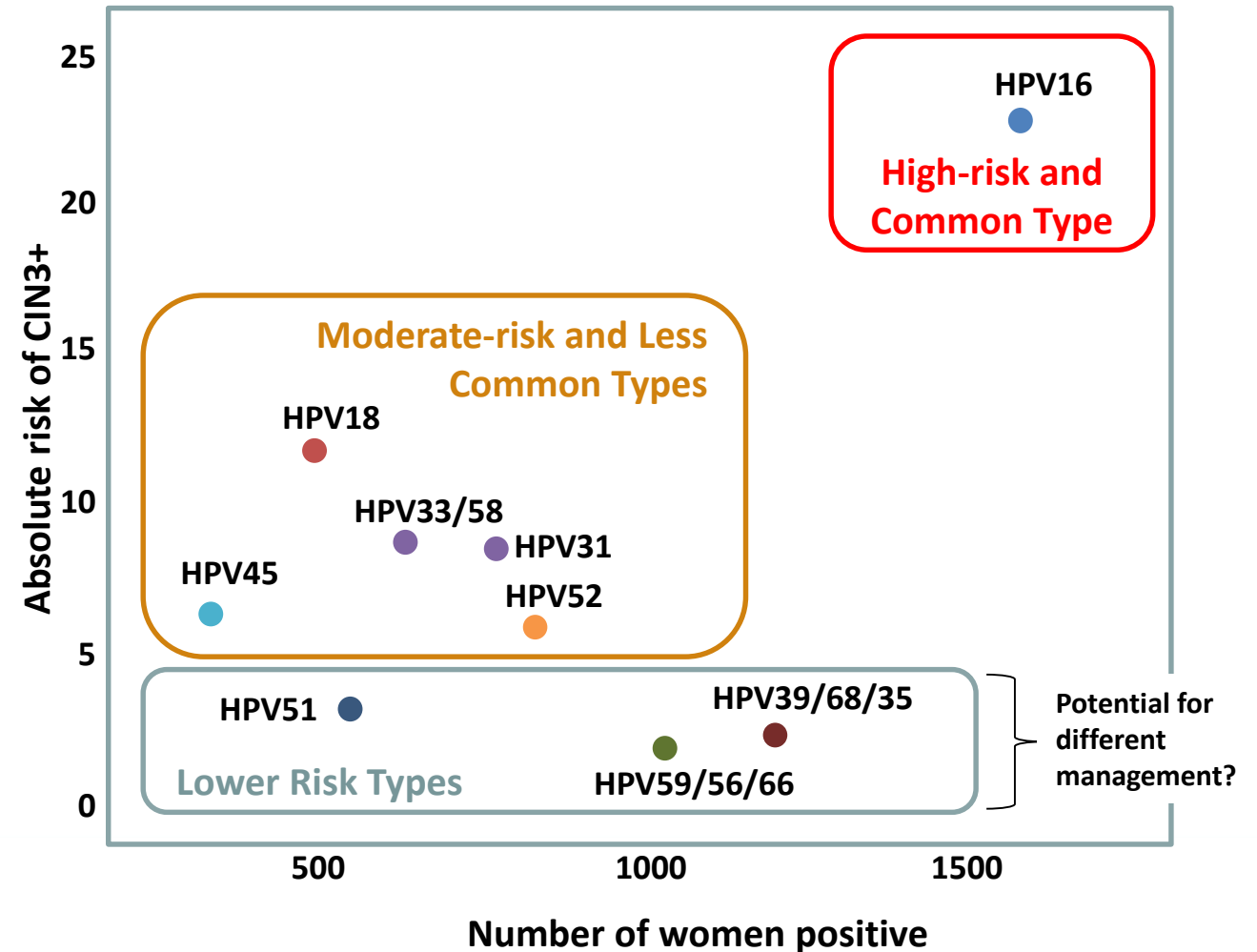
HPV Genotype

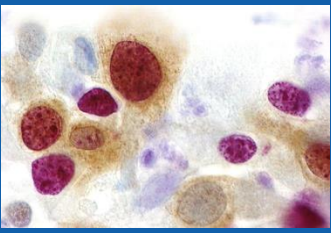
Implications for Screening and Management

- **Extended HPV genotyping gives information about:**
 - Individual risk
 - Insight into how common is each type of virus
- **HPV16 was both high-risk and common**
- **Other types with lower risk**
 - Consider different management?

Type restriction in low-resource settings

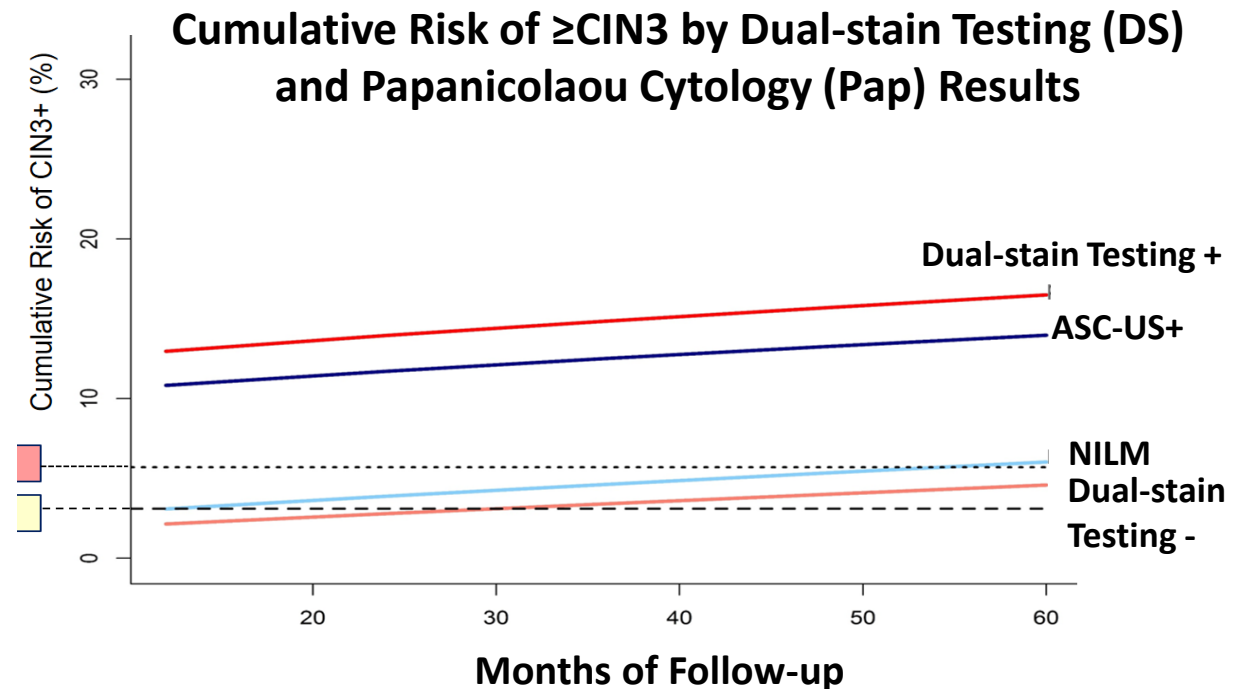
Risks of CIN3 by HPV Type Groups and Cytology, NCI/KPNC PaP cohort





p16/Ki-67 Dual Stain (DS) Is More Sensitive and Provides Insight Into Long-term Risk

- Dual stain has higher sensitivity with lower colposcopy referral compared to Pap cytology
- Dual stain provides long-term risk stratification
 - If results are negative, a woman can wait up to 3 years until next test
- Automated evaluation of DS slides improves accuracy



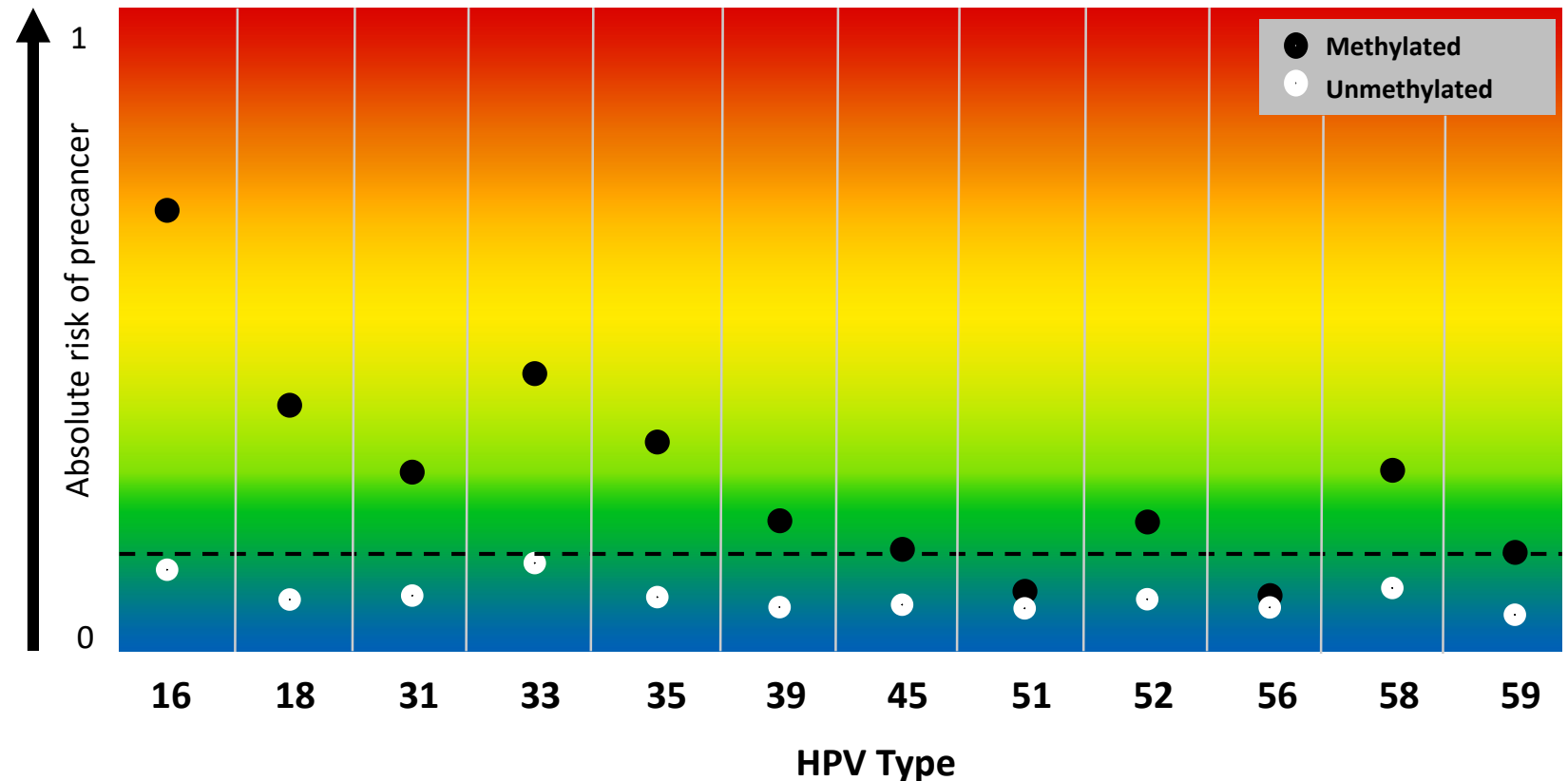
CIN3: Severely abnormal cells ASC-US+: Atypical squamous cells of undetermined significance NILM: Negative for intraepithelial lesion or malignancy

Wentzensen N, Fetterman B, Castle PE, et al. *J Natl Cancer Inst.* 2015 Sep 15;107(12):djv257

Clarke MA, Cheung LC, Castle PE, et al. *JAMA Oncology* 2018 Oct 11

Knowing Viral Methylation Adds to Understanding of Risk

- HPV methylation adds important risk stratification on top of genotype
- Development of integrated typing and methylation assay is underway
- Evaluation in self-collected specimens



Wentzensen N, Sun C, Ghosh A, et al. *J Natl Cancer Inst* 2012 Nov 21;104(22):1738–49

Clarke MA, Gradissimo A, Schiffman M, et al. *Clin Cancer Res* 2018 May 1;24(9):2194–2202

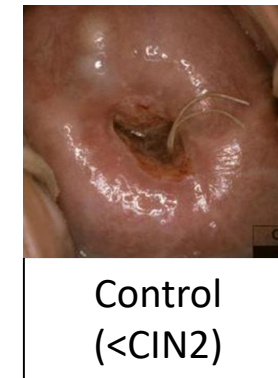
Implementing Efficient Screening Programs in Low-resource Settings

- **Screen and treat (e.g., single-visit strategies) are important**
- **Self-sampling can expand reach**
- **HPV testing is ideal for primary screening, but what to use for triage?**
- **Immediate treatment decision is desired**
- **Overtreatment should be reduced, immediate treatment with ablative technologies should be maximized**
- **Consider age range for screening, particularly if cancer treatment options are limited**

Machine-learning to Predict Precancer

Automated Visual Evaluation (AVE)

- Machine-learning-based algorithm to predict presence of cervical precancer
- Could expand “screen and treat” visits by aiding triage and diagnosis at time of visit
- Screening AUC 0.95
- Triage of HPV positive AUC 0.87



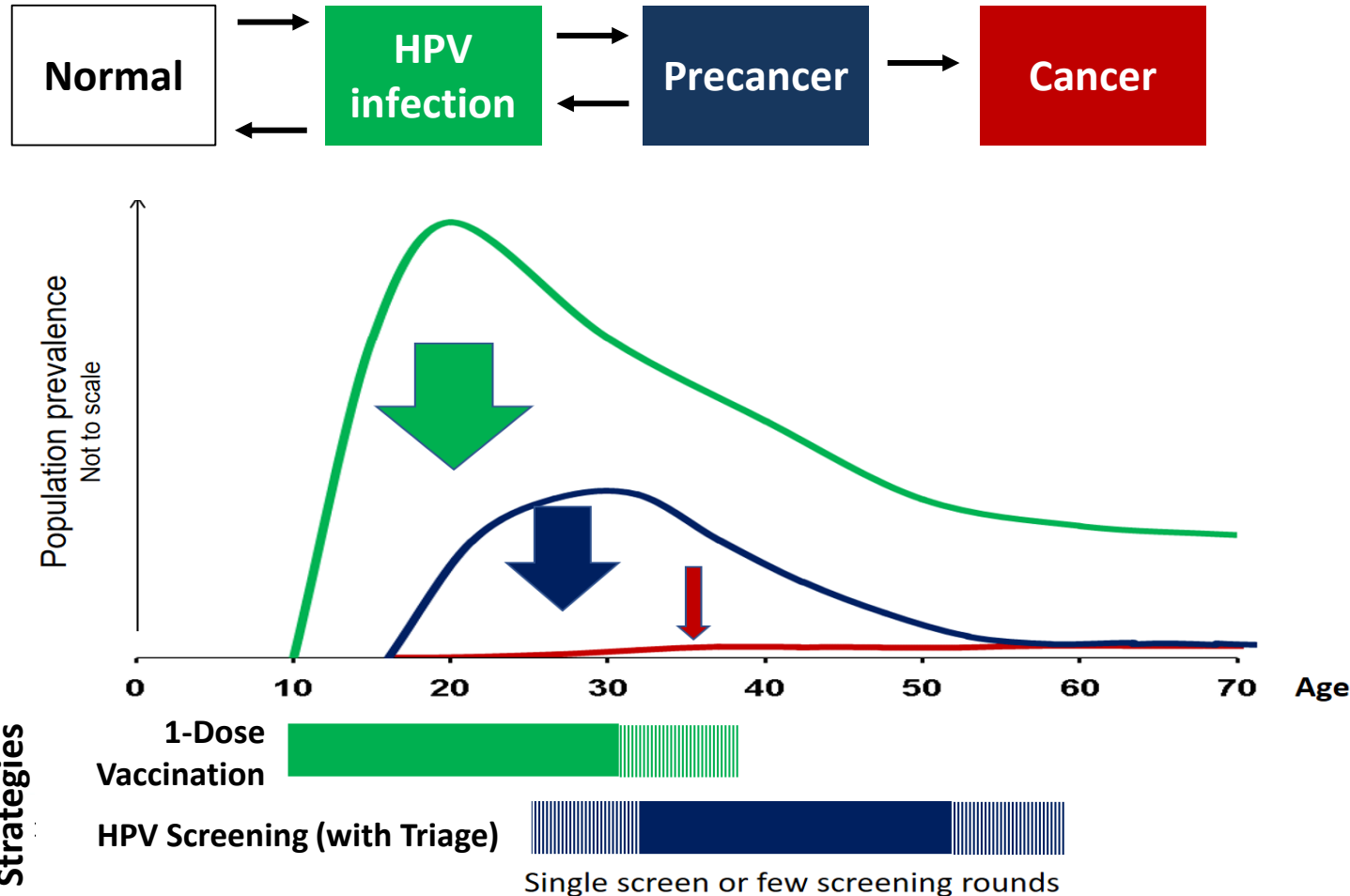
AVE
ALGORITHM



AUC: Area under the curve is a measurement of how well a test can distinguish between those with disease and those without disease. Values closer to 1 are better.

Combined Vaccination and Screening Program for Low-resource Settings

Progression of HPV Infection to Cervical Cancer Over Woman's Lifetime



Extended age range of vaccination reduces HPV population prevalence faster

HPV screen and treat reduces cancer prevalence faster

Cervical Cancer Prevention in Border Communities



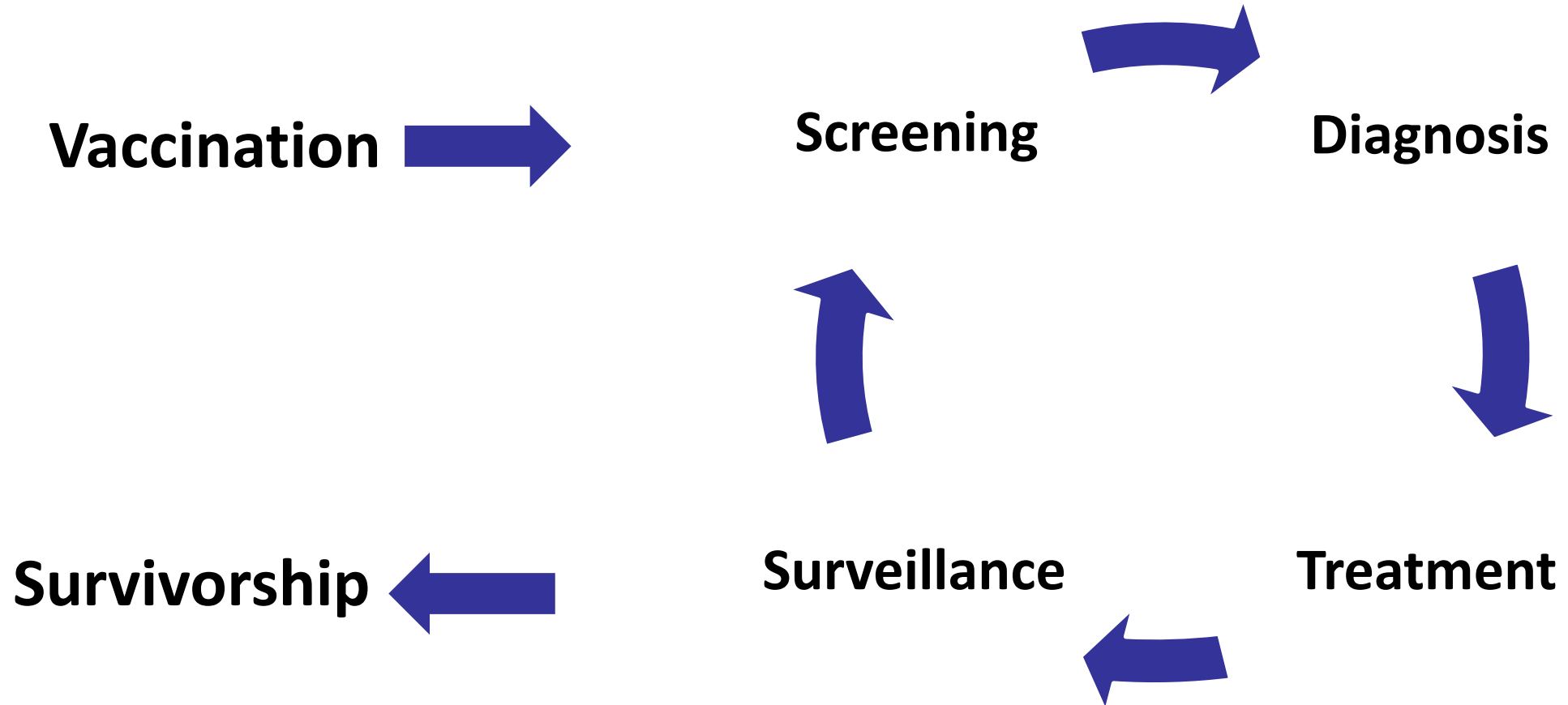
Francisco A. R. Garcia, MD, MPH

Assistant County Administrator, Pima County

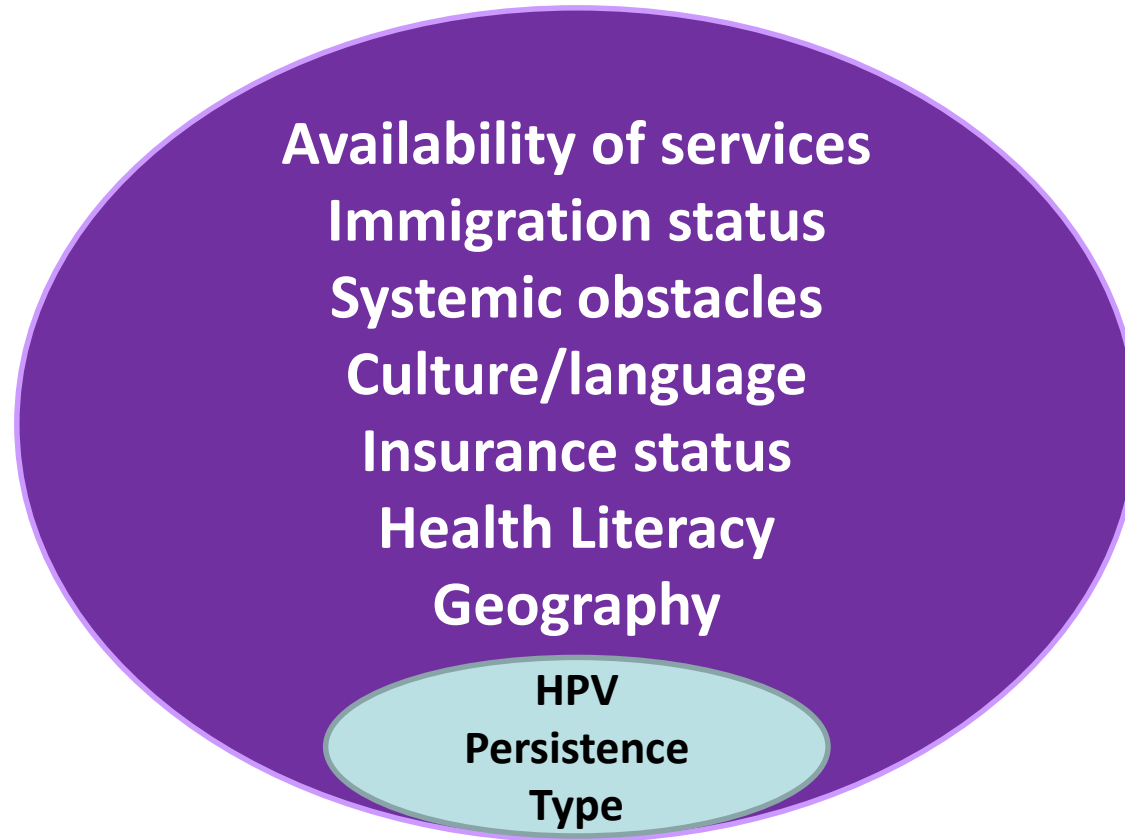
Chief Medical Officer, Pima County

Professor Emeritus of Public Health, University of Arizona

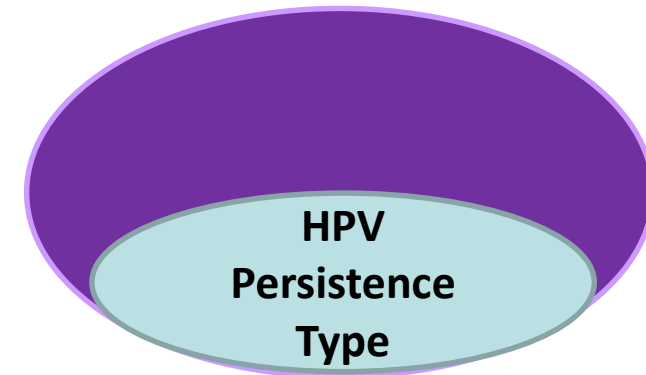
Comprehensive Cervical Cancer Prevention in Vulnerable Communities



Relative Role of Contextual and Host Factors



Vulnerable Population



Resilient Population

Barriers Cervical Cancer Prevention

Individual Factors

- Low HPV awareness
- Poor understanding of HPV/cancer link
- Cultural issues
- Poor screening uptake
- Compromised follow-up

Barriers Cervical Cancer Prevention

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Provider and Facilities Factors

- Training and education
- Resource and facilities
- Advance therapeutics (chemo/rad)
- Palliation

Barriers Cervical Cancer Prevention

Individual Factors

- Low HPV awareness
- Poor understanding of HPV/cancer link
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- Poor screening uptake
- Compromised follow-up

Provider and Facilities Factors

- Training and education
- Resource and facilities
- Advance therapeutics (chemo/rad)
- Palliation

Systemic Factors

- Access to healthcare
- Un-insurance
- Surveillance and tracking systems
- Immigration status

Pima County Cervical Cancer Prevention Coalition

- **Population:** Hispanic women with school aged children or grandchildren
- **Providers:** Federally Qualified Health Centers, Safety Net clinics, state, UA
- **Outcomes:** Age-appropriate screening; timely follow up; vaccination
- **Methodology:** Woman-centered, culturally tailored, linguistically accessible, set multi-modal community health worker interventions



Promotoras (e.g., community health workers) teaching at community site

CDC REACH Initiative: *Promotoras* Engaged in Preventing Cervical Cancer in Mexican-American Communities

- During a 5-year funding period:
- Trained 300 community health workers (CHWs), called *promotoras*
- Over 100 *promotora* group presentations per year, reaching over 2,500 women
- 370 one-on-one client CHW encounters per year
- CHW case navigation (150 per year)
- Provider education CME & technical assistance (17 presentations or consultations per year)

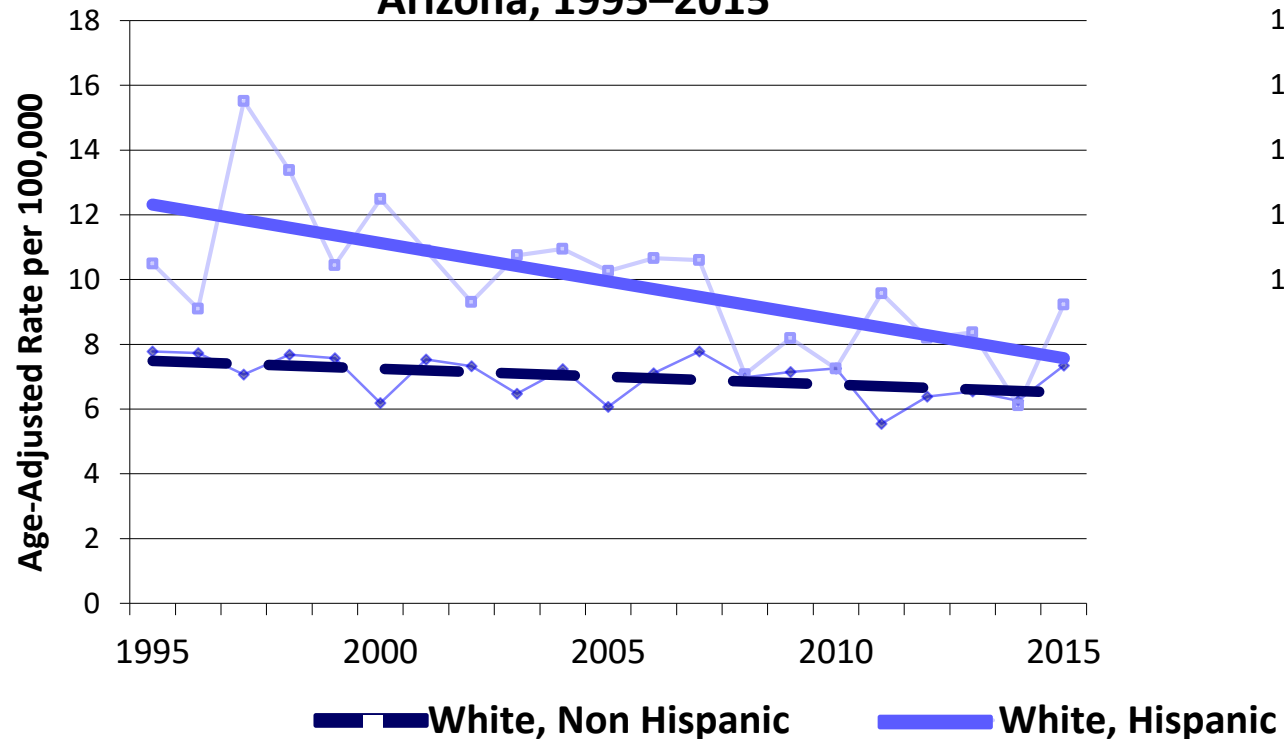


Promotoras during home visit

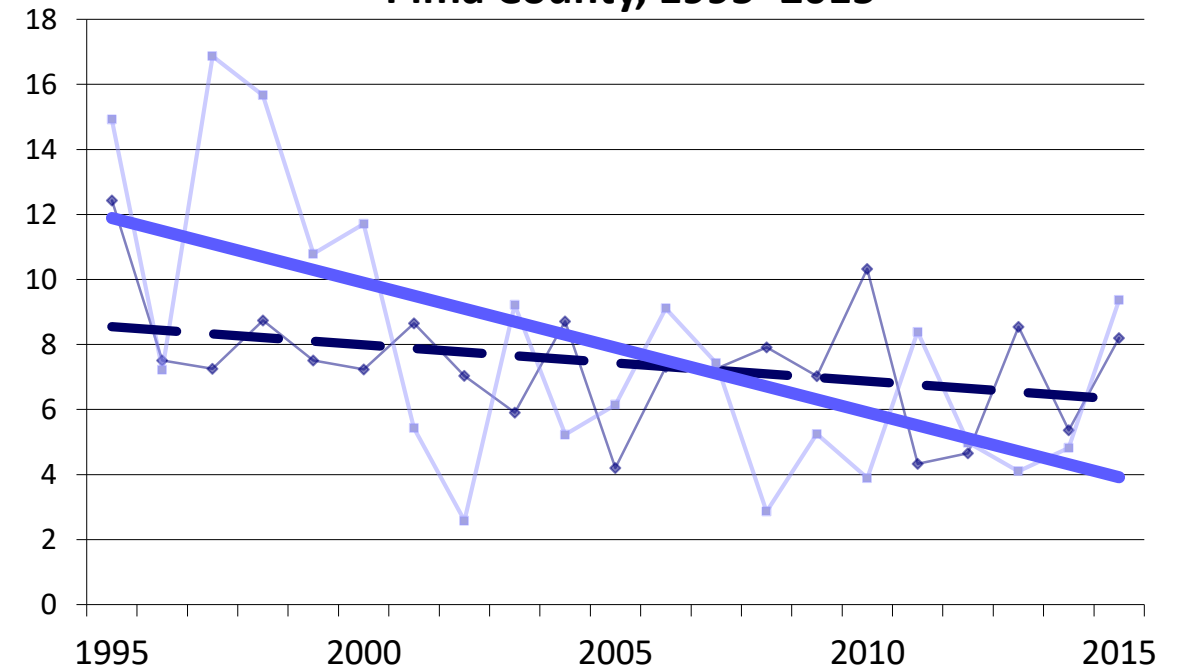
Incidence of Invasive Cervical Cancers Decline in Hispanics in Pima County

Invasive Cervical Cancer (Age-Adjusted) Incidence, 1995–2015

Arizona, 1995–2015



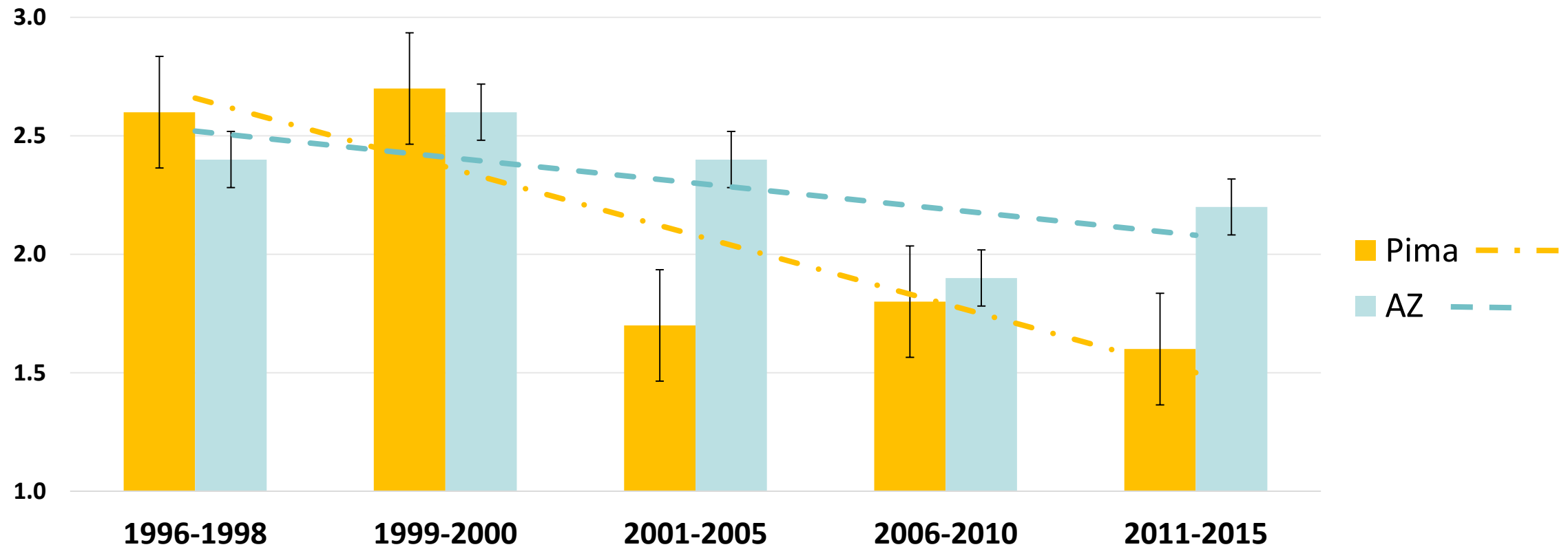
Pima County, 1995–2015*



* Rates are based on fewer than 10 cases in most years. Interpret with caution.

Decreasing Rates of Cervical Cancer Mortality in Pima County

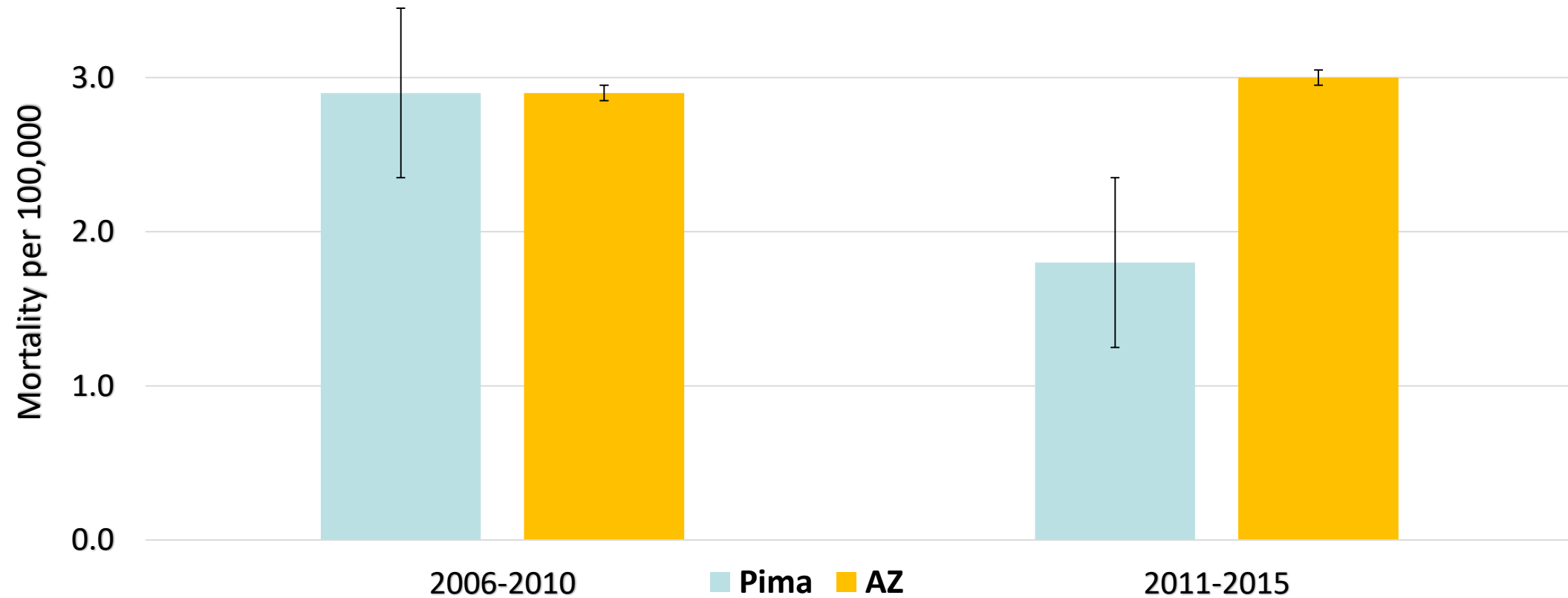
Cervical Cancer Mortality Rate (per 100k) in Arizona and Pima County, 1996–2016



Courtesy of the Arizona Department of Health Services

Rates of Cervical Cancer Mortality Declining in Pima County

Hispanic Cervical Cancer Mortality (per 100k) in Arizona and Pima County, 2006–2015



Courtesy of the Arizona Department of Health Services

Community Health Worker Interventions Improve Screening Adherence in Border Communities

Yuma Promotora Intervention, 3-year follow-up

	Number (%)	Odds Ratio
Usual Care (n=116)	87 (75%)	1.0
Intervention (n=104)	93 (89%)	2.8



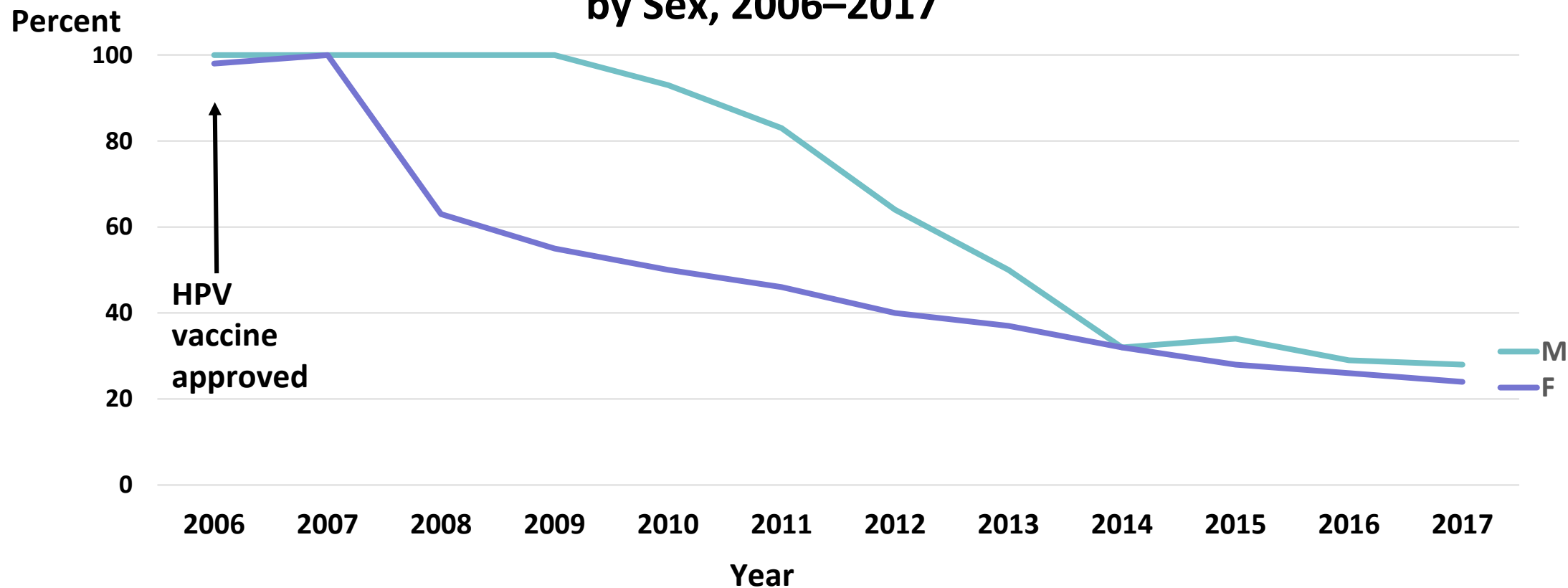
School Based Cancer Prevention Efforts

- **After-school girls' clubs & summer camps focused on health, education, and culture**
 - Tailored to urban and rural Hispanic girls
- **Classes for mothers on psychosocial topics and navigating educational systems to support daughters' academic success**
- **Opportunity for middle-school girl and moms to talk about sexuality, healthy development, STIs, vaccination, etc.**

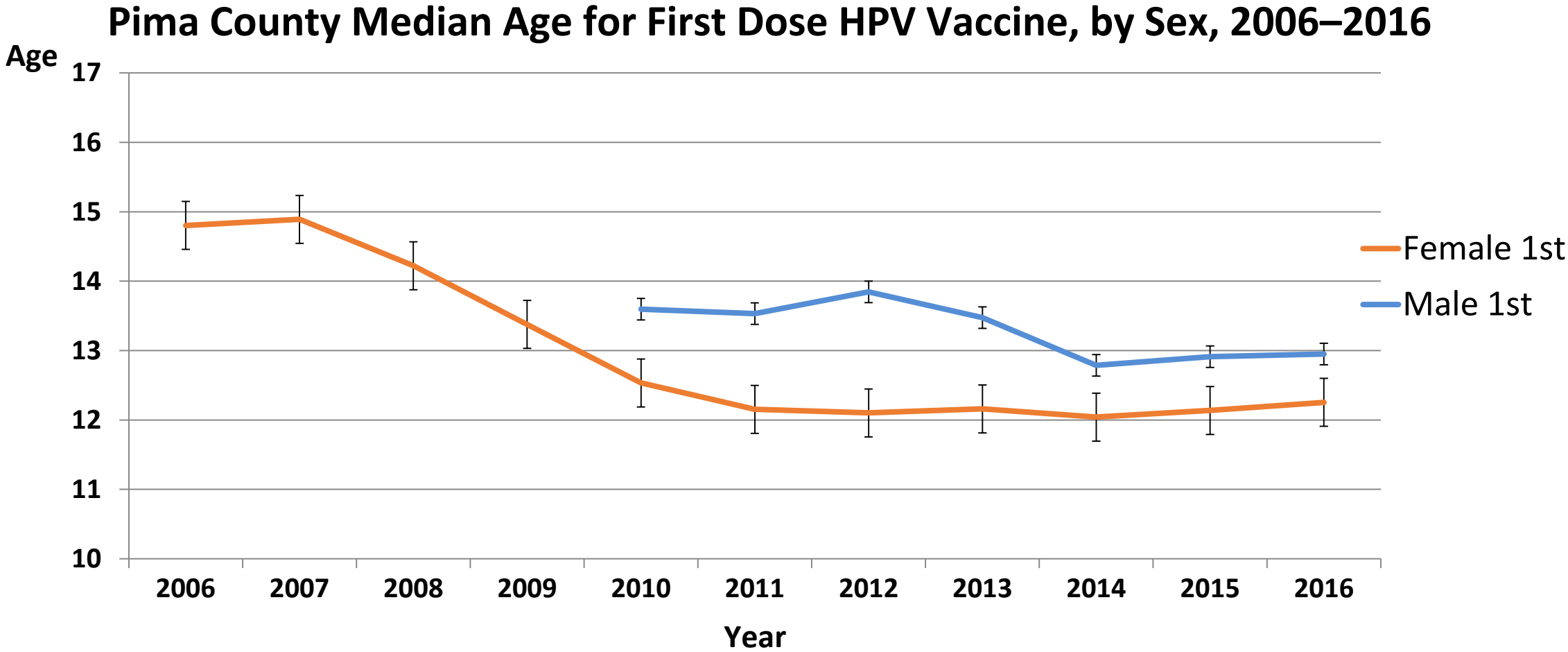


HPV Non-vaccinated Children in Pima County Dropped

Children Ages 13–18, Receiving Zero Doses of HPV Vaccine in Pima County, by Sex, 2006–2017



First Dose HPV Vaccine is Reaching the Age-appropriate Children



Much Still to Be Done for Women At Increased Risk

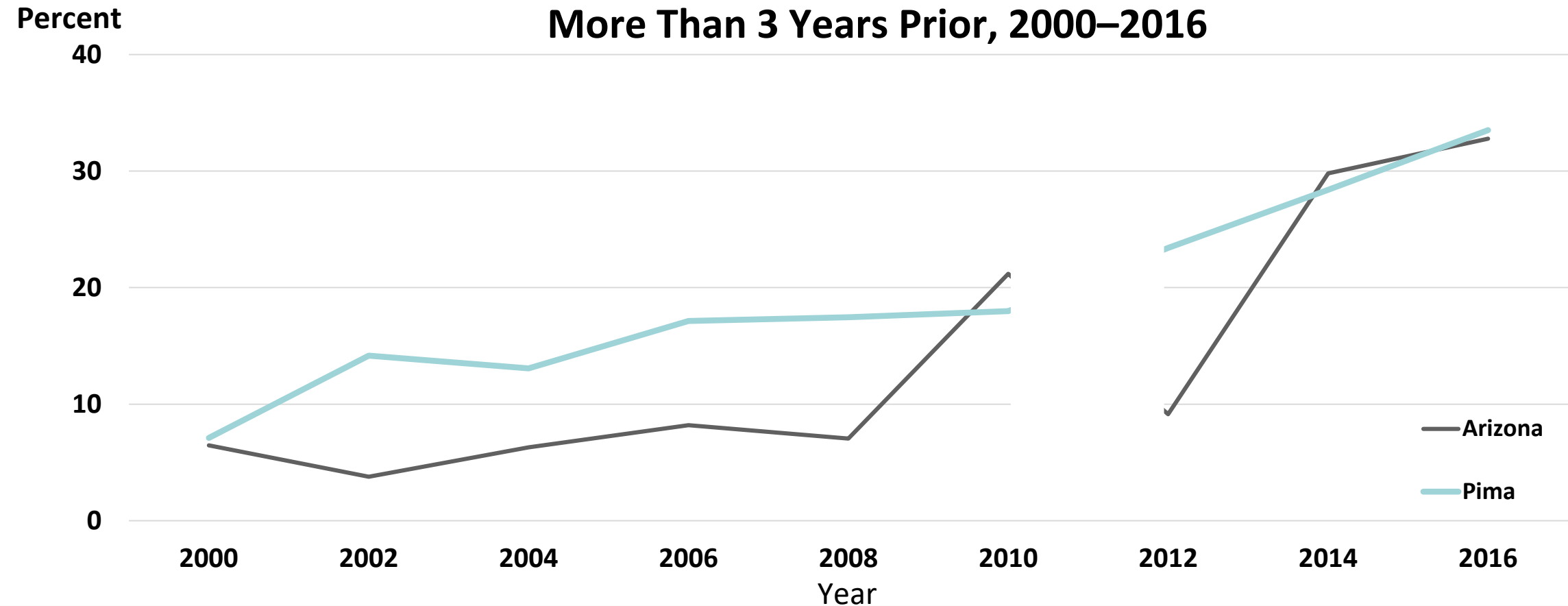
**Women 40 or Older Reporting Last Pap Screening More Than 5 Years Ago,
by Race/Ethnicity and Rural/Urban Domicile, in AZ and NM, 2006–2008**

Race/Ethnicity	Domicile	
	Urban	Rural
All	8%	13%
Hispanic	7%	9%
American Indian	5%	5%
White, Non-Hispanic	8%	16%

Adapted from: Nuño T, Gerald JK, Harris R, et al. *Cancer Causes Control*. 2012 Aug;23(8):1333–41

Longer Intervals Are Being Reported Between Screenings

Percentage of BRFSS Respondents Indicating Last Pap Smear Was More Than 3 Years Prior, 2000–2016



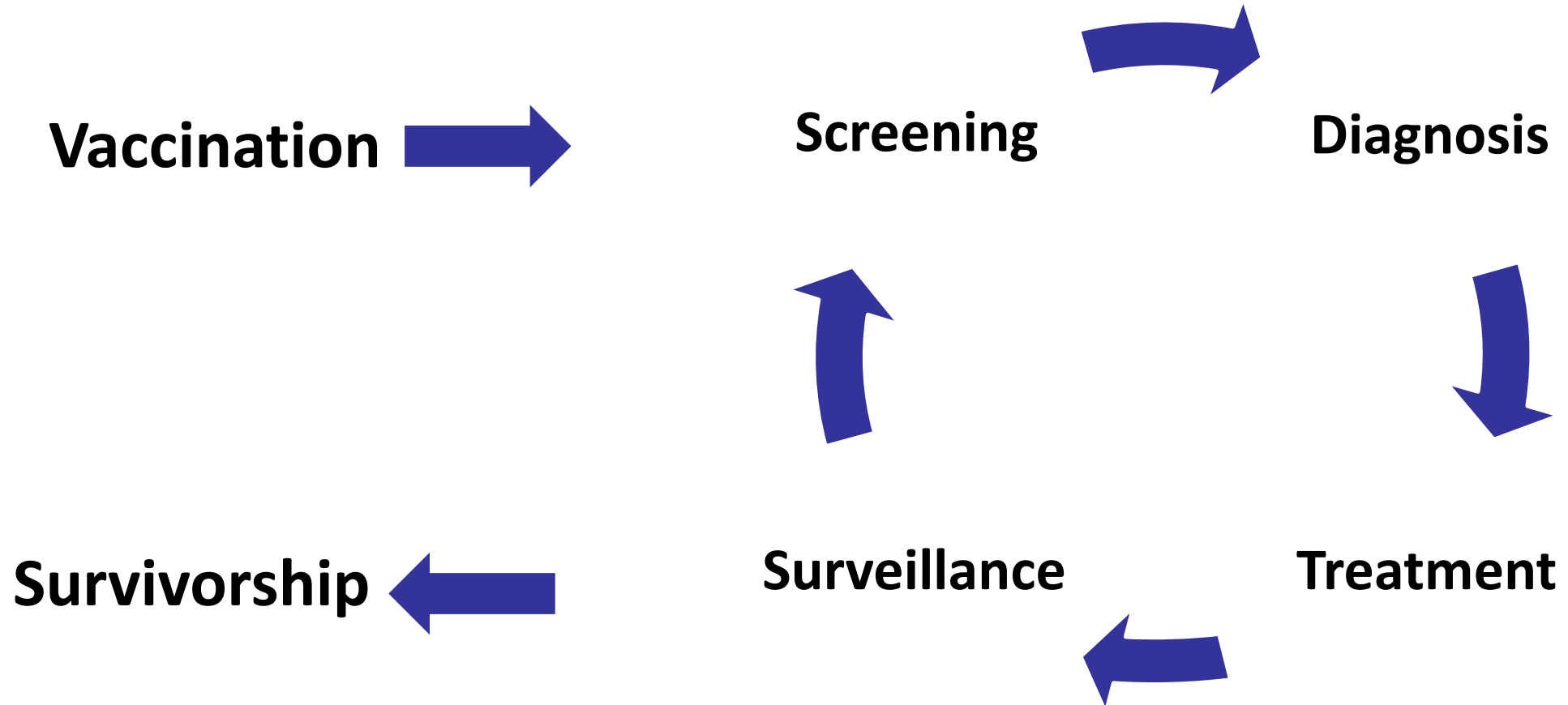
Courtesy of Arizona Department of Health Services

Comprehensive Cervical Cancer Prevention in Communities: Lessons Learned

- Listen to women, early, often, continuously
- Find the right partners
- It's all about access to health care—
vaccination, screening, follow up
- Cervical cancer should be
entirely preventable
- One cervical cancer death is
one too many



Comprehensive Cervical Cancer Prevention in Vulnerable Communities



Role of Healthcare Providers in Cervical Cancer Prevention: Now and in the Future



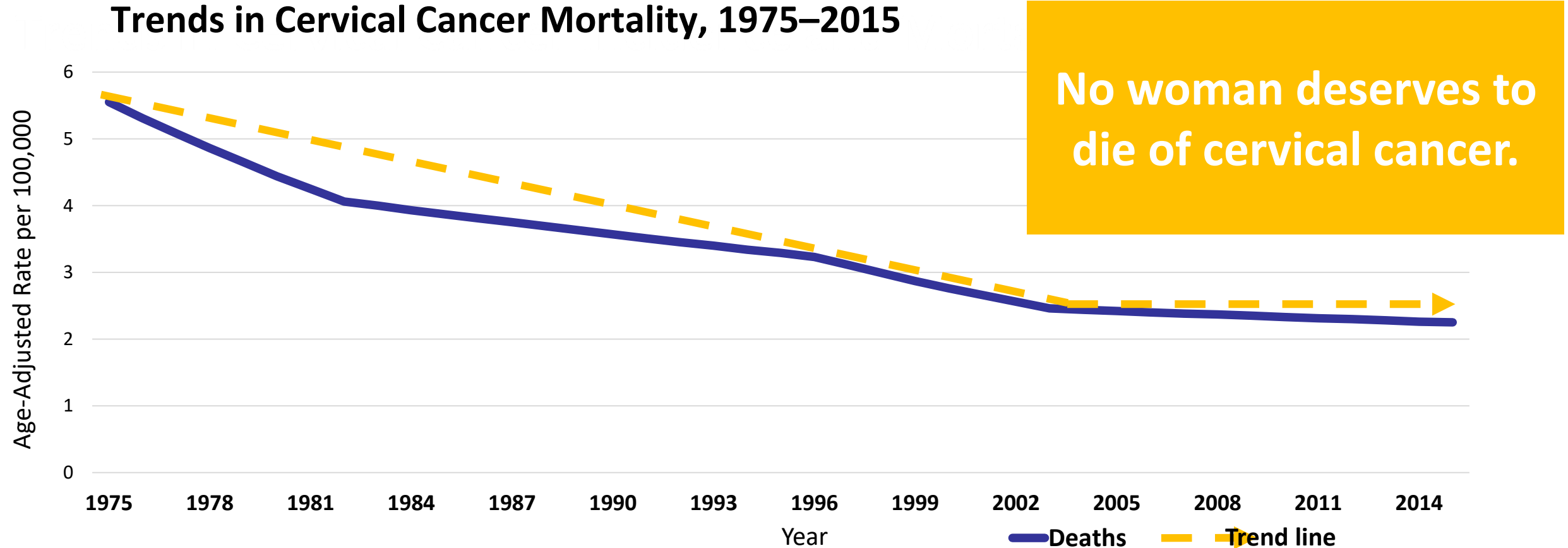
Lisa C. Richardson, MD, MPH

Director, Division of Cancer Prevention and Control

National Center for Chronic Disease Prevention and Health Promotion

Centers for Disease Control and Prevention

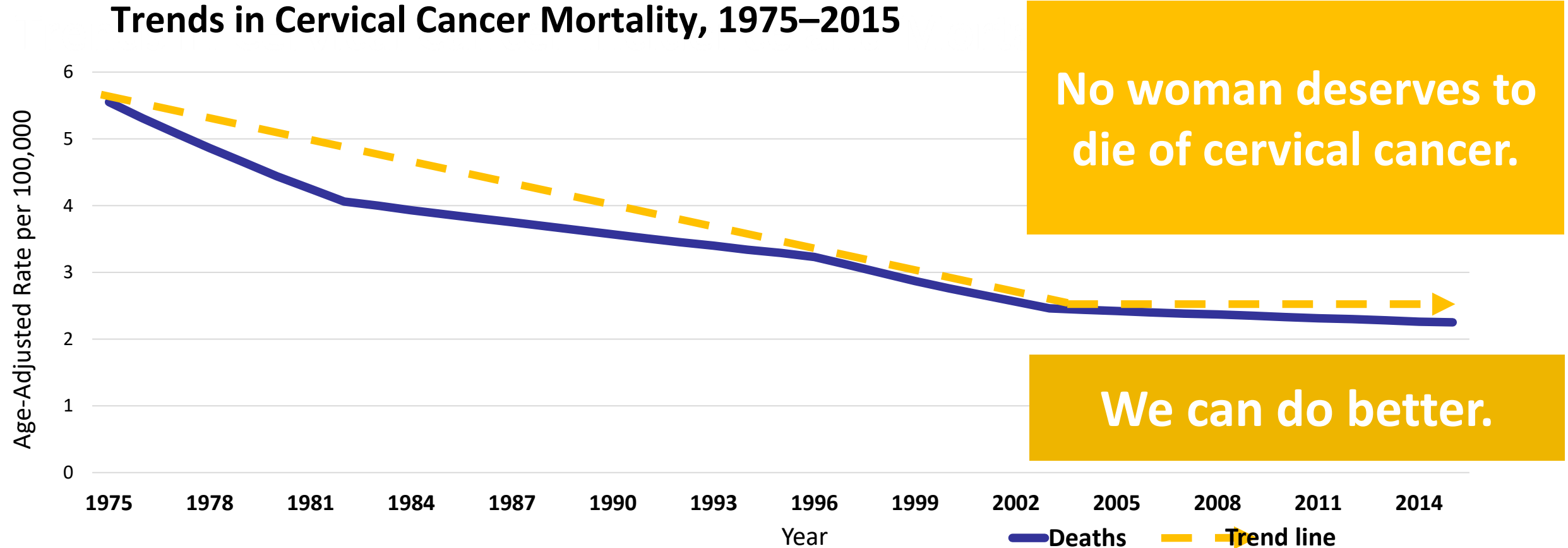
Cervical Cancer is Still a Problem in the United States



National Cancer Institute, Surveillance, Epidemiology, and End Results program: seer.cancer.gov/statfacts/html/cervix.html

CDC, National Center for Health Statistics

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CDC, National Center for Health Statistics

Two Proven Opportunities to Prevent Cervical Cancer

Vaccination Opportunity
11–12 years old



Screening Opportunities
21–65 years old



Normal cervical cells

HPV infection

Most HPV infections do
not turn into precancers

Precancers

Precancers may still
go back to normal

Cervical cancer

Call To Action For Healthcare Providers



Everyone has a role in ending cervical cancer!