# 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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## Acknowledgments

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# Preventing Cervical Cancer in the 21st Century




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# The Epidemiology of Cervical Cancer


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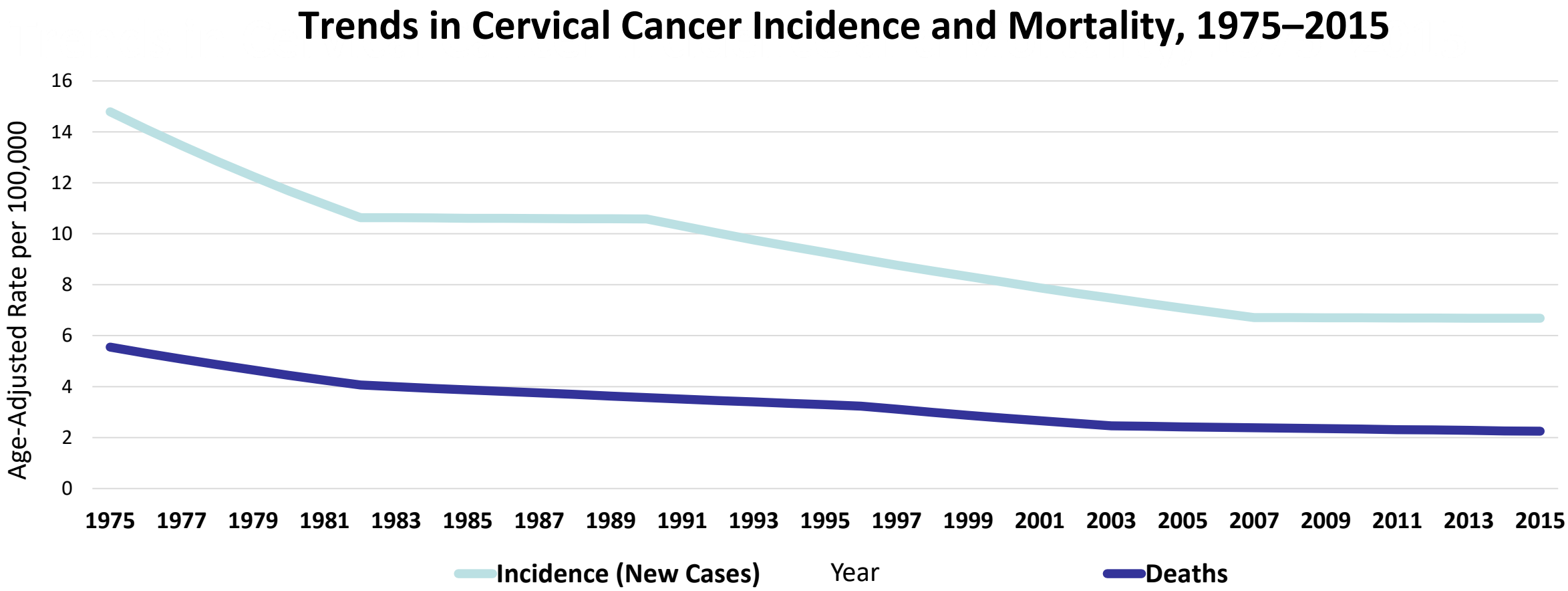
# Cervical Cancer Burden

| | | 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

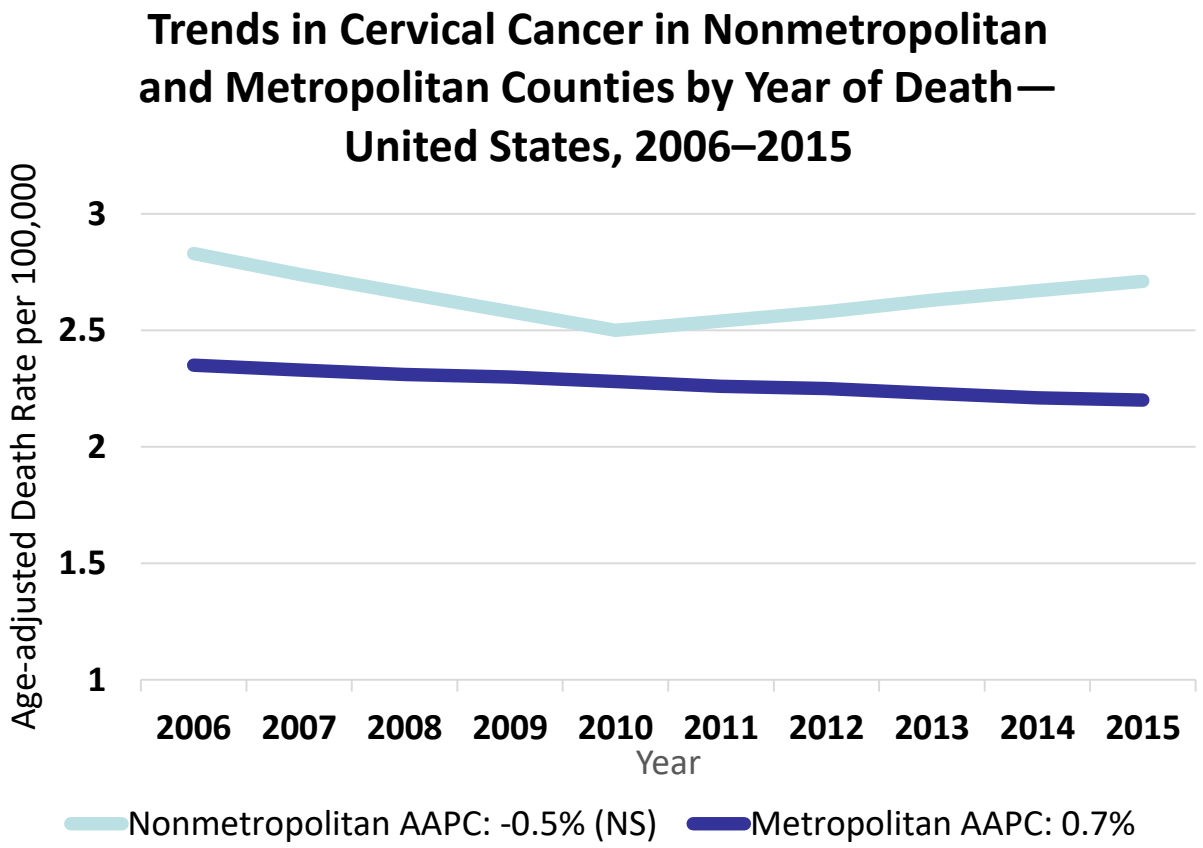



National Cancer Institute, Surveillance, Epidemiology, and End Results program: seer.cancer.gov/statfacts/html/cervix.html

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 screening or not screened in past 5 years

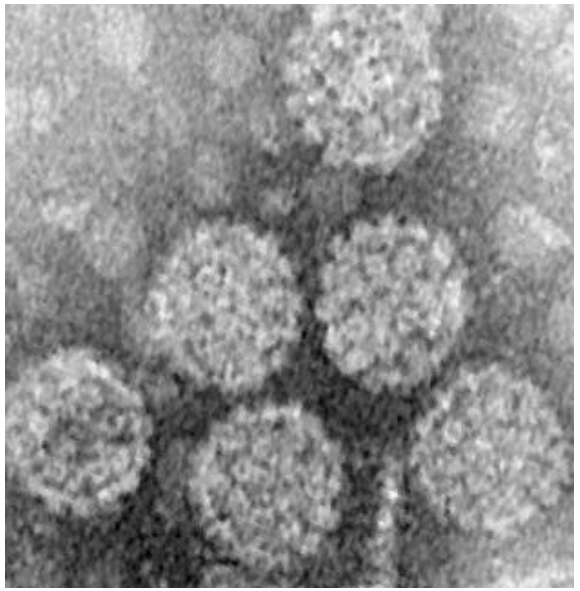



AAPC: Average annual percent change
NS: Non-significant

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

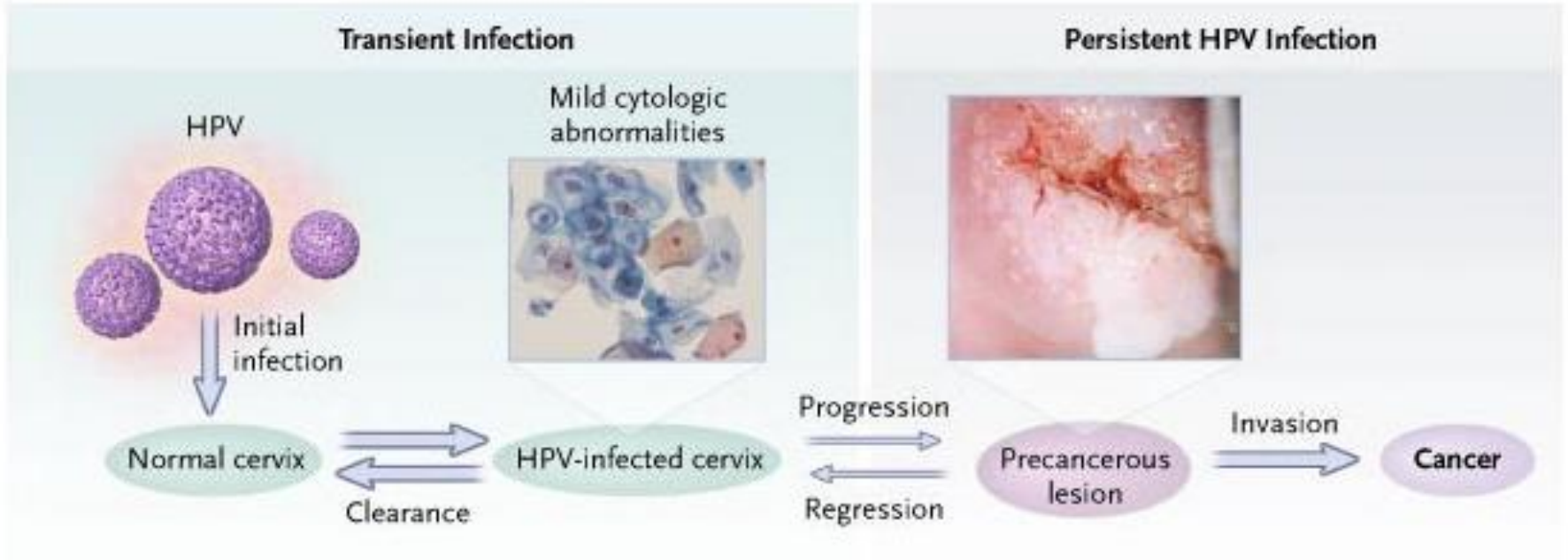
- **HPV infection is very prevalent in the population**
  - Almost all sexually active persons will acquire HPV
  - In the United States, approximately 79 million infected and 14 million new infections per year
- **Genital HPV is first acquired soon after onset of sexual activity**
  - 40% infected within 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

Satterwhite CL, Torrone E, Meites E, et al. *Sex Transm Dis* 2013 Mar;40(3):18793

Winer RL, Lee SK, Hughes JP, et al. *Am J Epidemiol* 2003;157:218–26

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

## HPV: Natural History of Cervical Infection

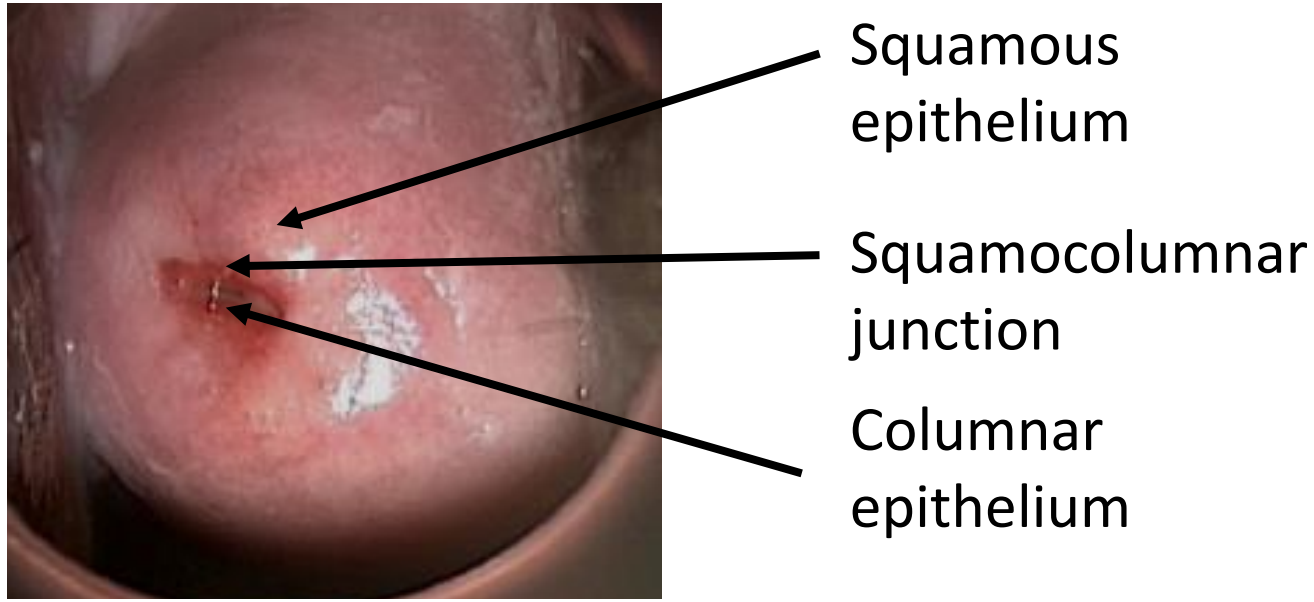



**Peak incidence of precancers in late 20s and peak incidence of cancers in early 40s**

Wright TC & Schiffman *N Engl J Med* 2003 Feb 6;348(6):489–90

# 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




Normal Cervix

# Cervical Cancer Screening

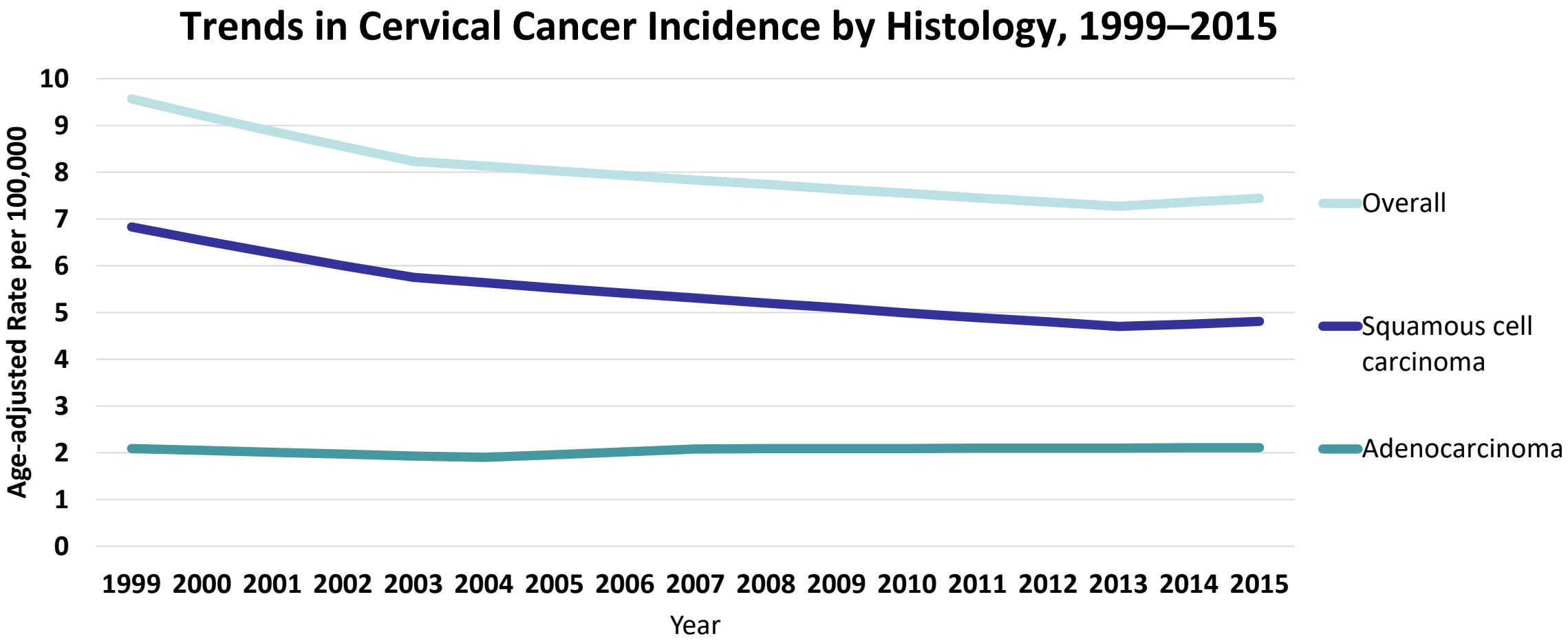
## Pap (Papanicolaou) Test

- 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

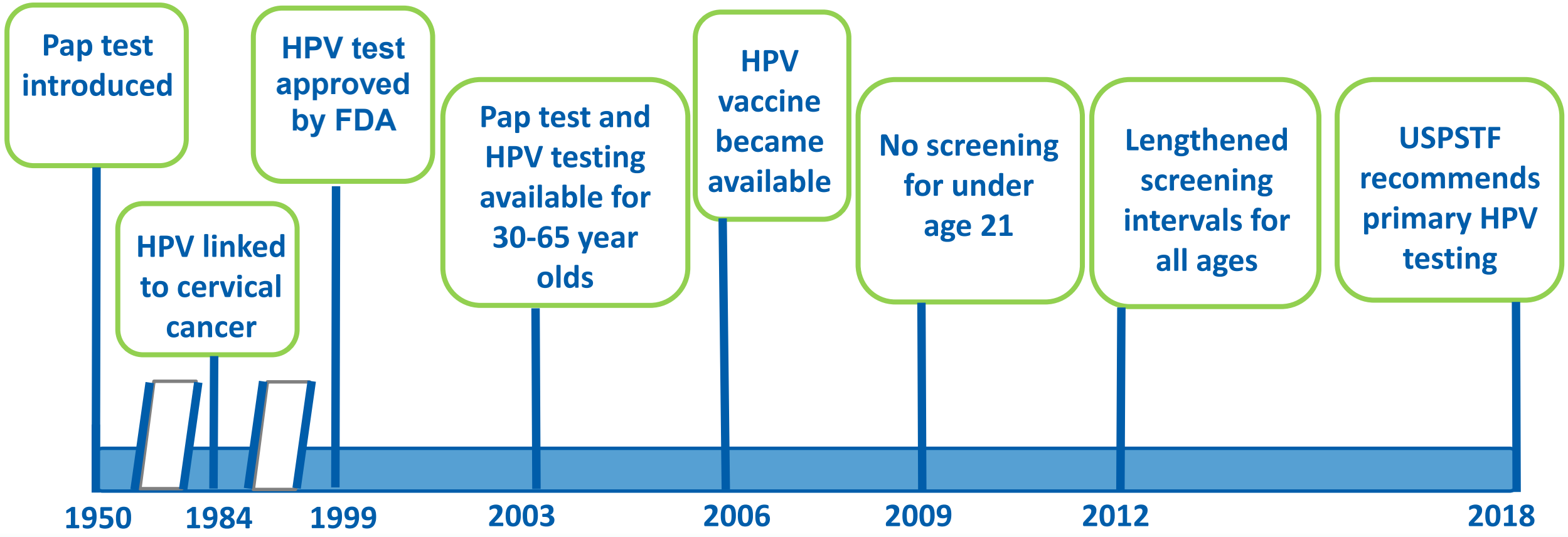
# Overall Rates Have Dropped But Adenocarcinoma Rates Remain Unchanged




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

# 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)<br>2) Pap alone every 3 years | 1) Co-testing every 5 years<br>2) Pap alone every 3 years<br>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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# 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

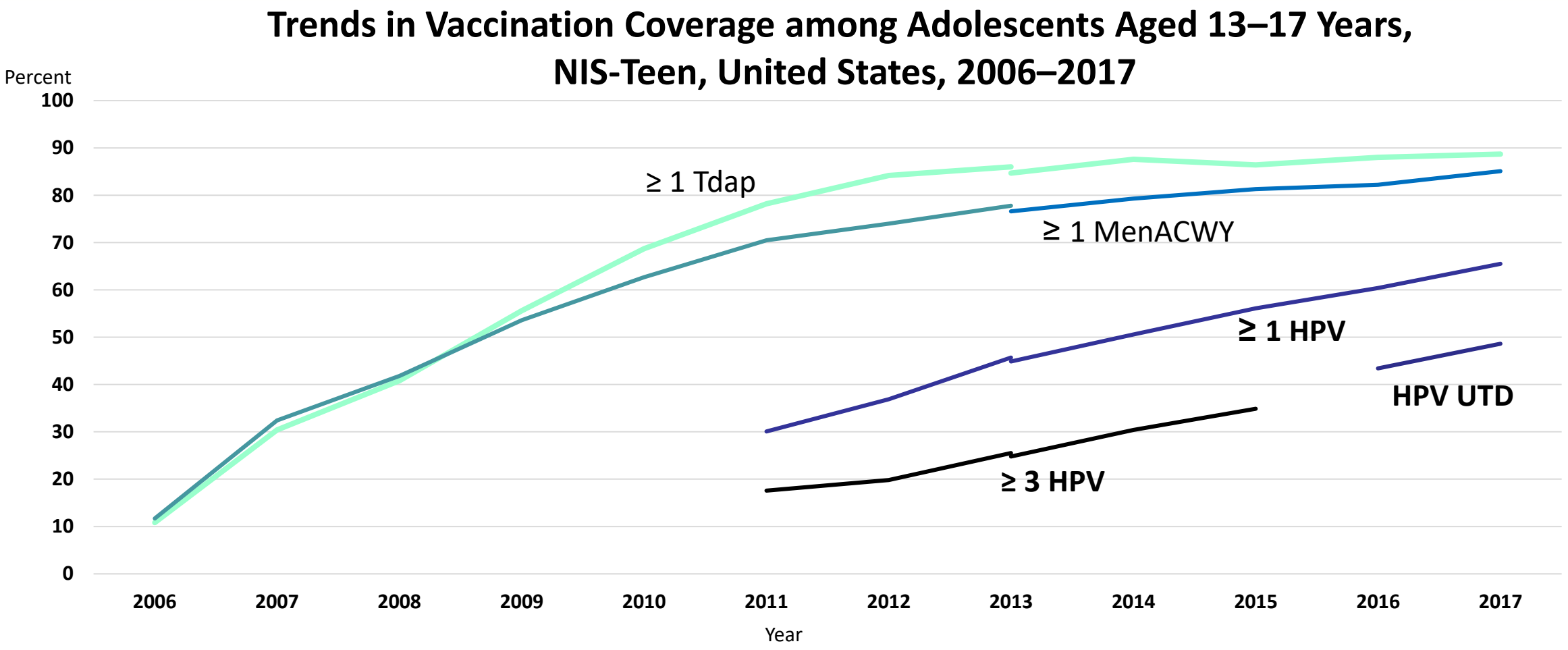
**2011** HPV vaccine recommended as three-dose series for boys at 11–12 years of age, with catch-p through 21 years of age

**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.

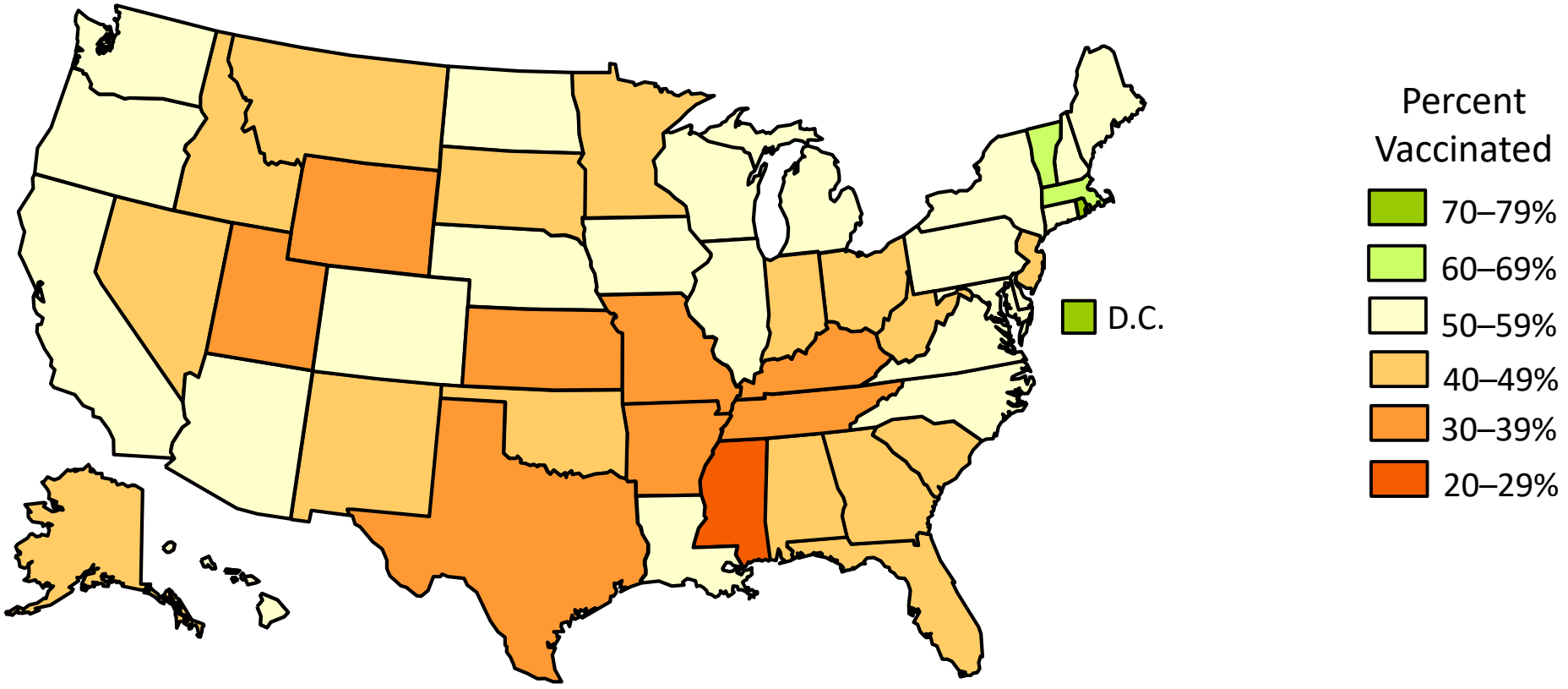
# HPV Vaccination Rates Lag Behind Other Vaccines Recommended at Ages 11–12 Years




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 an appropriate interval between the first and second dose.

# HPV Vaccination Rates Vary Widely Across the U.S.

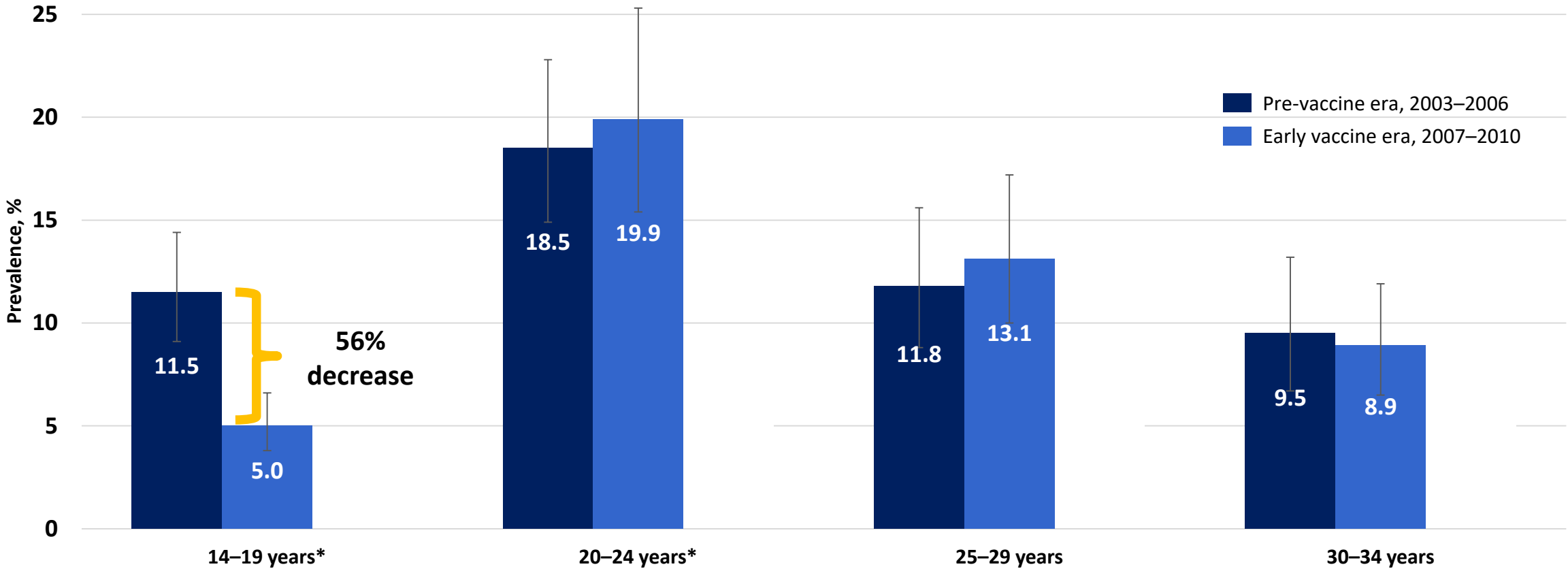
Vaccination Coverage Among Adolescents Aged 13–17 Years By State, United States, 2017




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

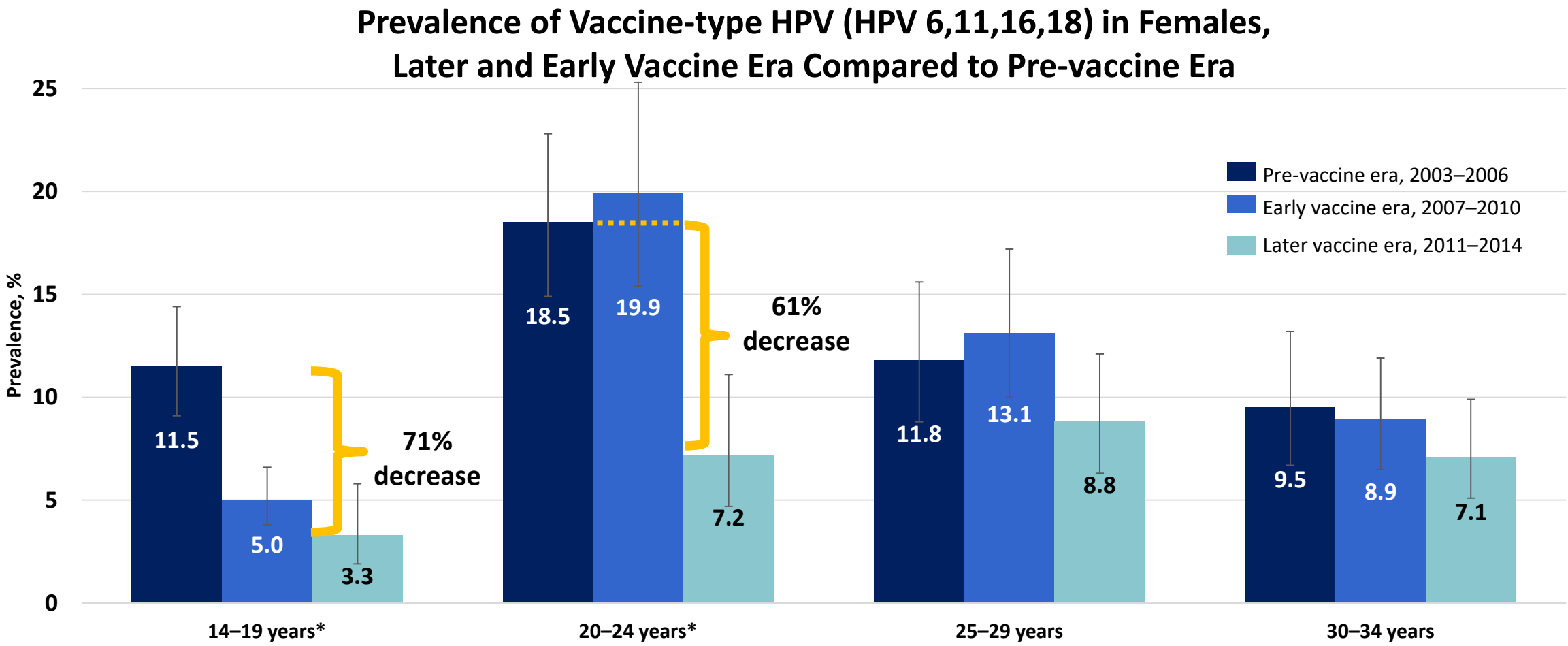
# Prevalence of HPV Drops After Vaccine Introduction

## 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

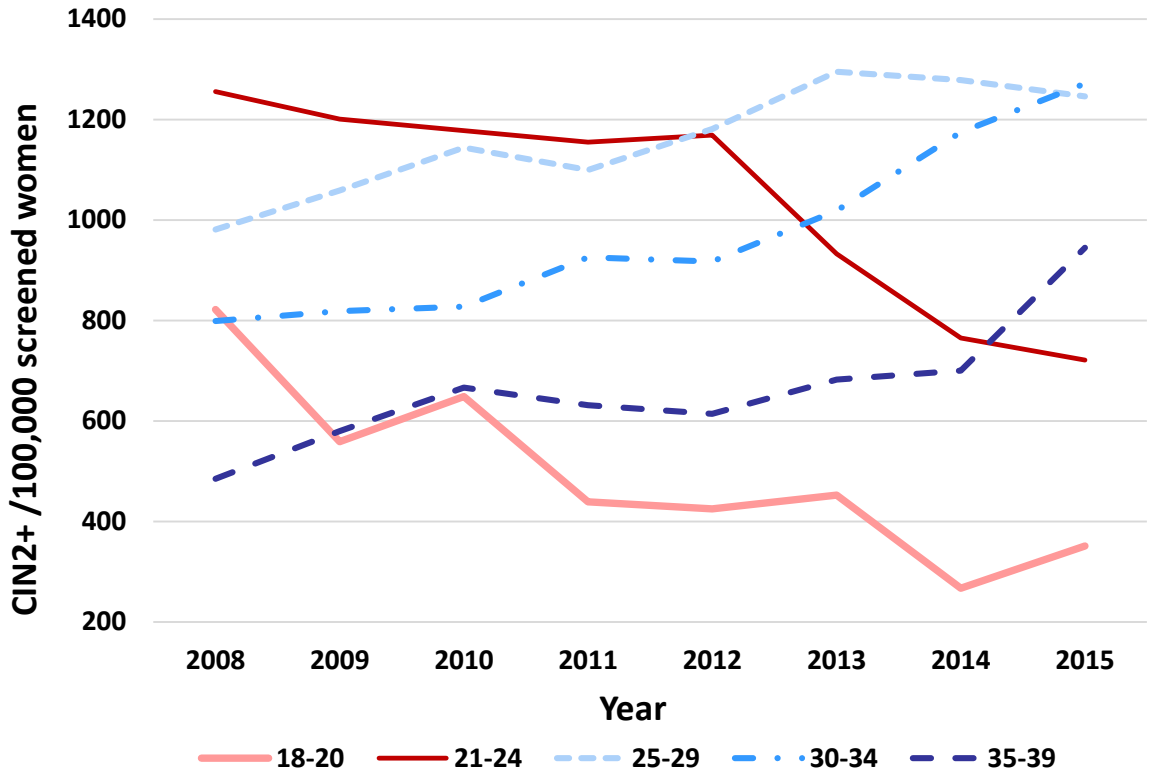

NHANES: National Health and Nutrition Examination Survey

# 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% |

NIS-Teen: National Immunization Survey-Teen

# Strong Provider Recommendations Increases HPV Vaccination Rates

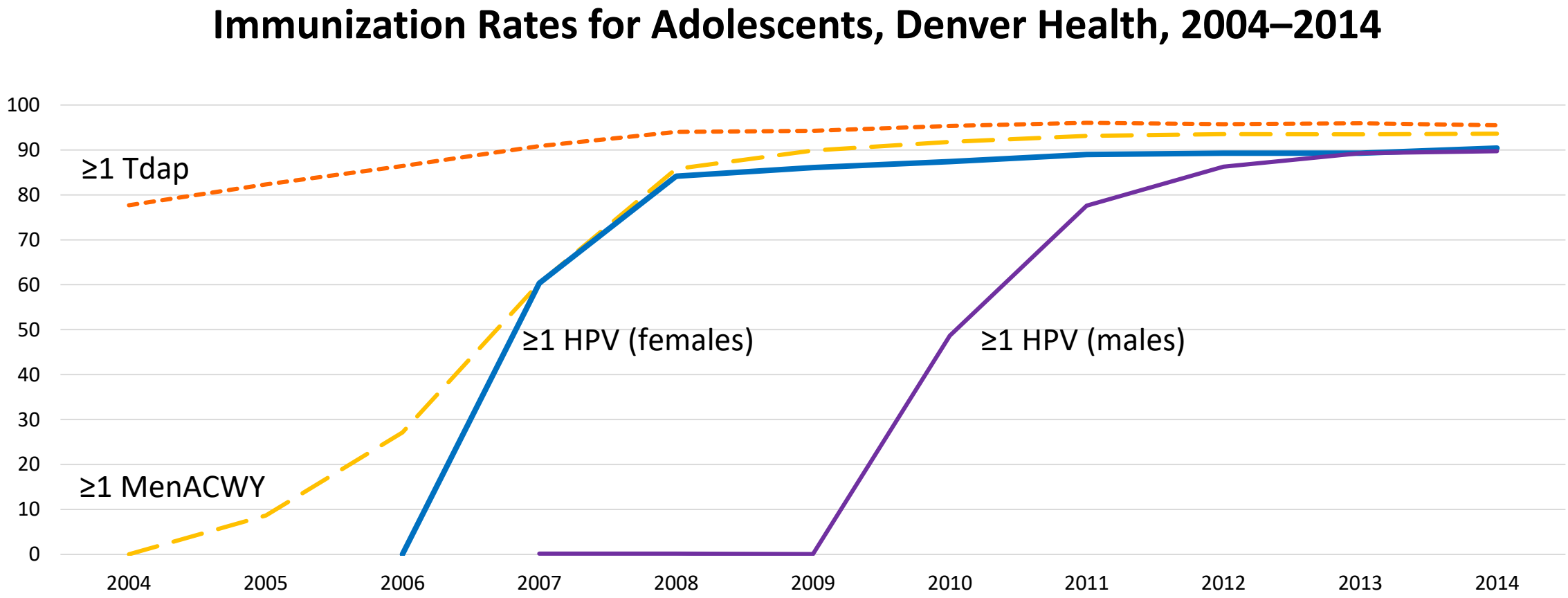
*"Now that Sophia is 11, she is due for vaccinations today to help protect her from meningitis, HPV cancers, and pertussis."*

# 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**

EHR: Electronic health record

# Immunization Rates Over 90% Are Achievable for Adolescents




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**

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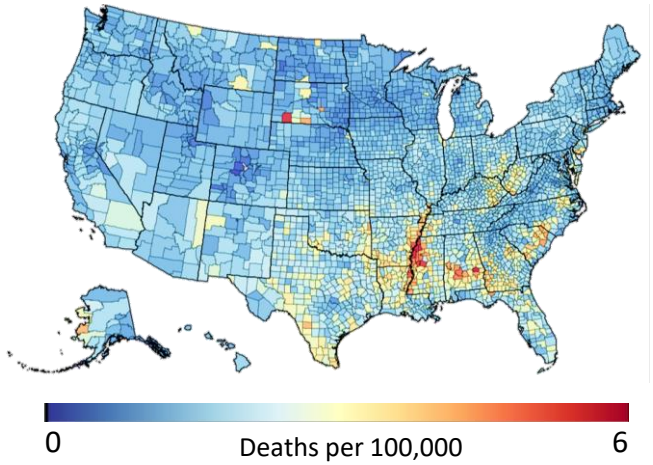
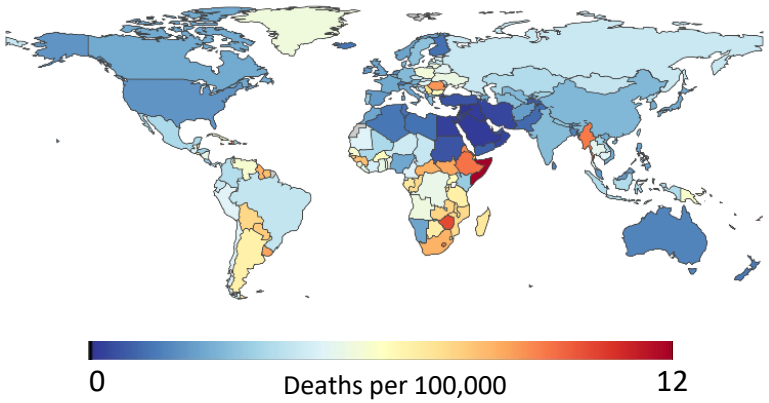
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health



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

# National Cancer Institute Moonshot: Accelerated Control of Cervical Cancer

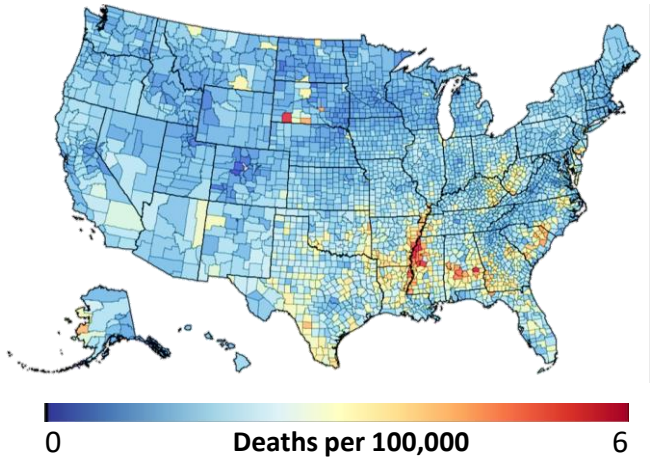


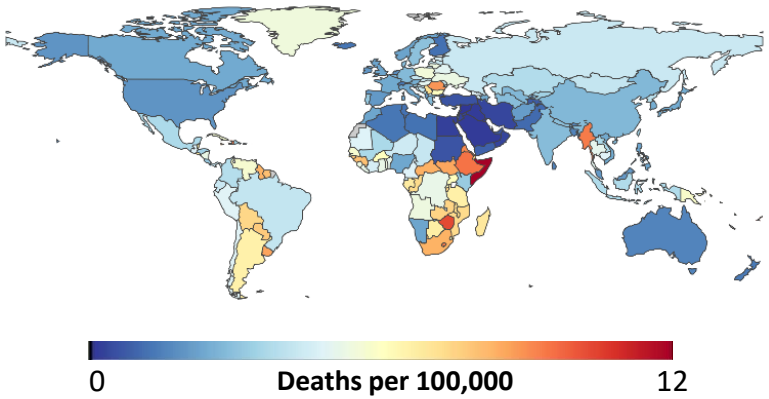




## High-resource settings

| Challenges and Inefficiencies | Goals and Solutions |
|---|---|
| Screening is not distributed equally | More efficient screening and triage strategies |
| Inefficient screening tools | Extend screening intervals |
| Overtreatment | Reduce overtreatment |
| Many choices lead to confusion among providers and women | Risk-based screening and management |

# NCI Moonshot: Accelerated Control of Cervical Cancer



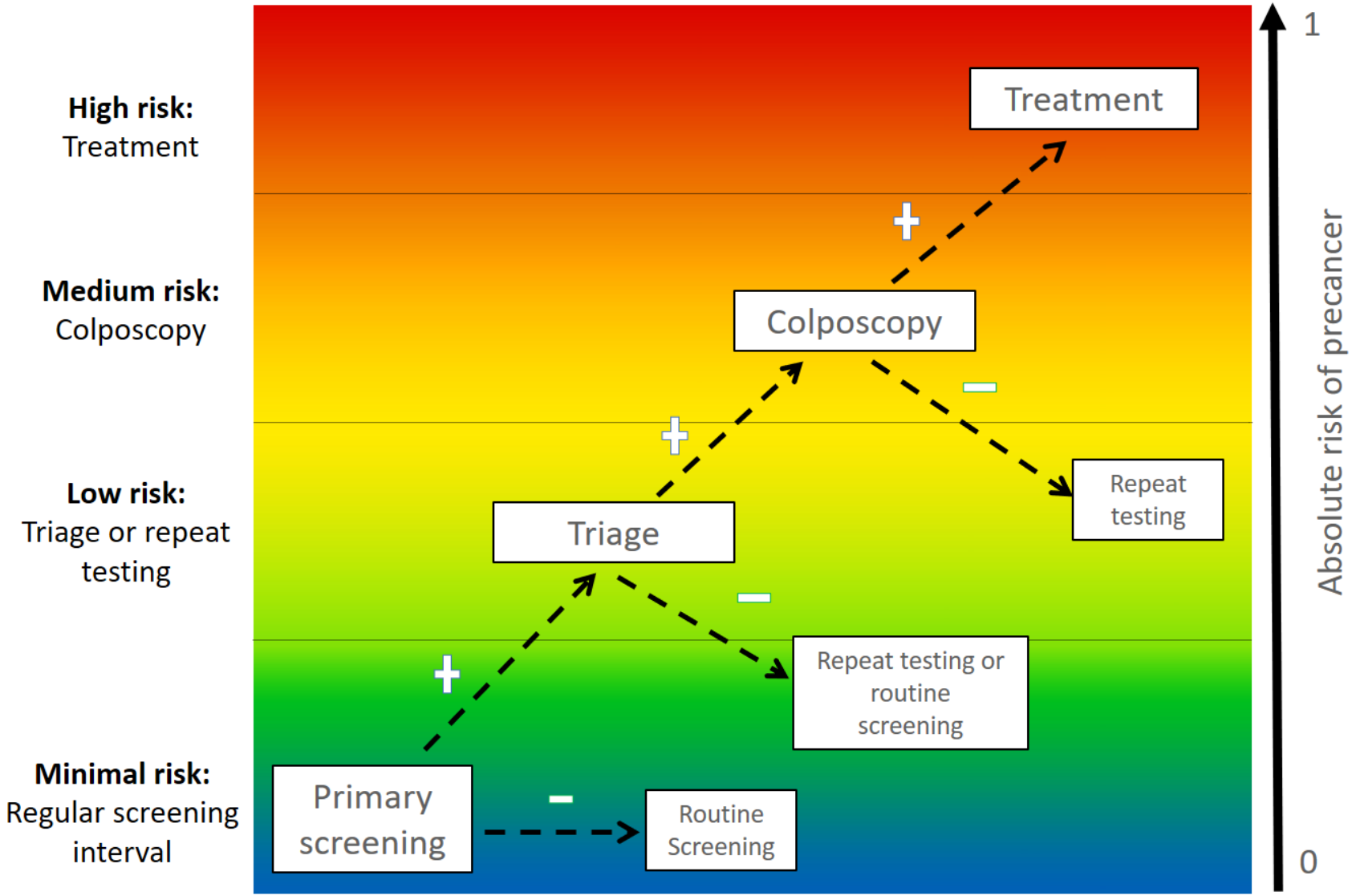




## Low-resource settings

| Challenges and Inefficiencies | Goals and Solutions |
|---|---|
| No sustainable multi-visit screening programs | Increase coverage through single-visit, "screen and treat" programs |
| Limited treatment capacity | Reduce unnecessary referral to treatment |
| Hardly any vaccination | Integrate vaccination and screening |

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

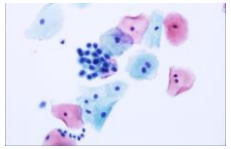
# Risk-based Screening and Management Guidelines

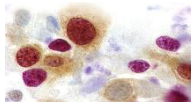




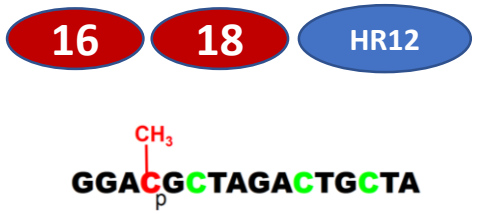

Wentzensen N, Schiffman M, Palmer T, et al. *J Clin Virol* 2016 Mar;76 Suppl 1:S49–S55

# Novel Screening and Triage Technologies






Cytology




Molecular


Visual

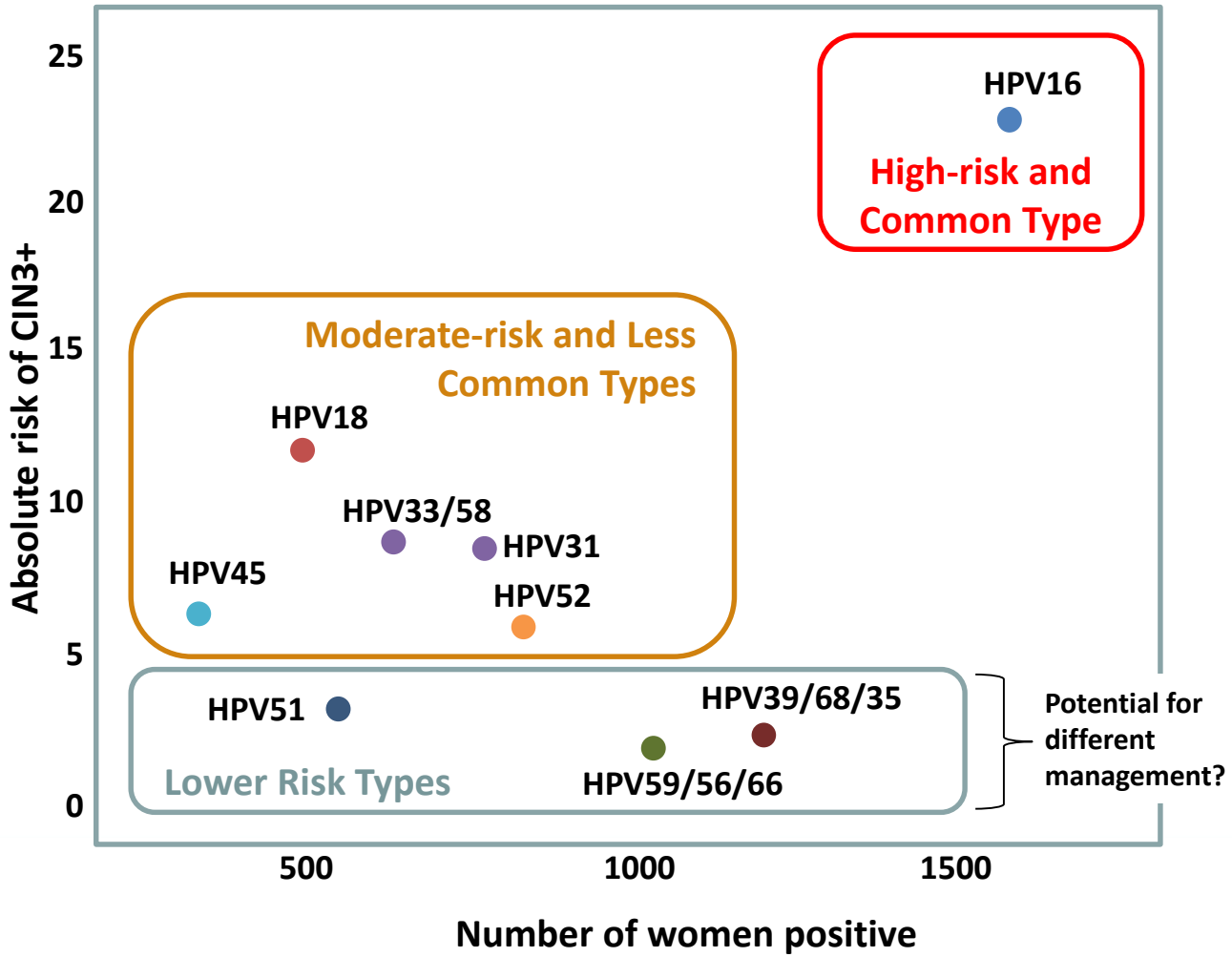
| Technology | Resource Setting | Key References |
|---|---|---|
| **Automated cytology** | High/ middle | Schiffman et al. Int J Cancer 2017<br>Yu et al. JNCI 2018 |
| **p16/Ki67 Dual stain (Automation)** | High/ middle | Wentzensen et al. JNCI 2015<br>Clarke et al. JAMA Oncology 2018 |
| **HPV testing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

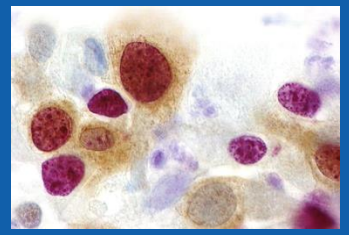
**Type restriction in low-resource settings**

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



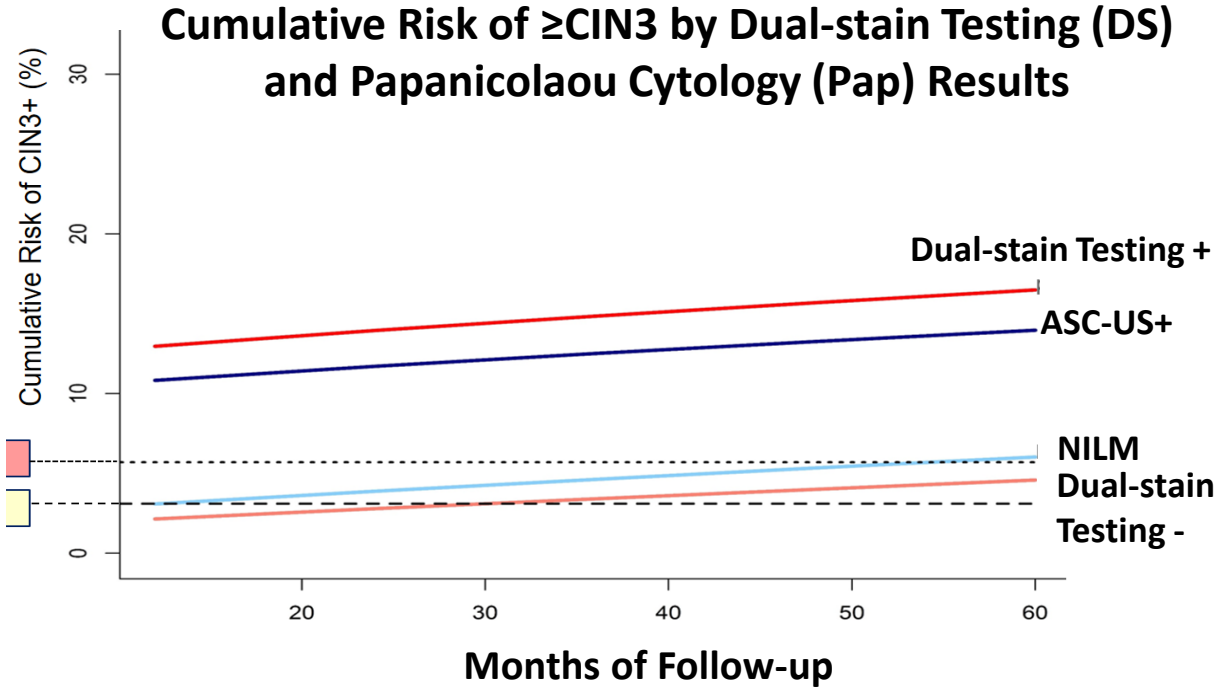



Adapted from Schiffman M, Hyun N, Raine-Bennett TR, et al. *Int J Cancer* 2016 Dec 1;139(11):2606–15



# 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**



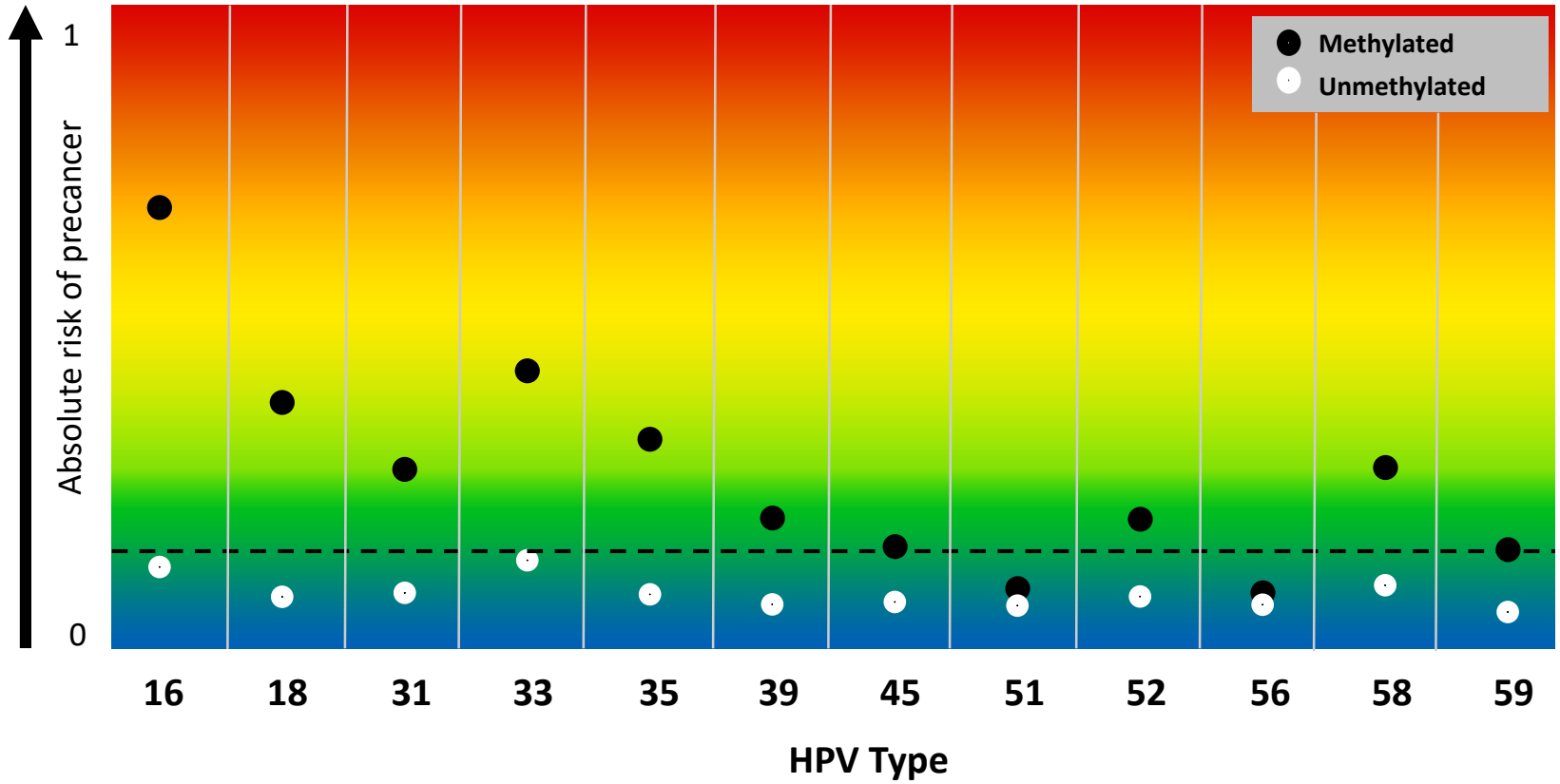

CIN3: Severely abnormal cells ASC-US+: Atypical squamous cells of undetermined significance NILM: Negative for intraepithelial lesion or malignancy

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**

Case (CIN2+)

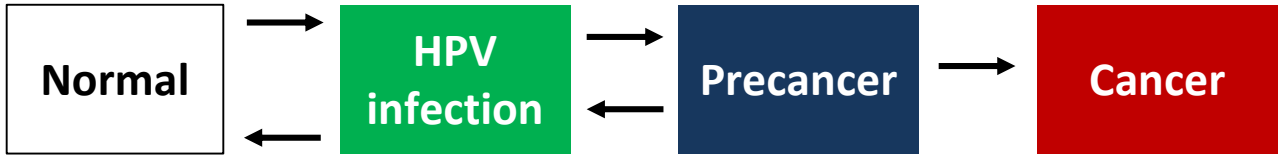
Control (<CIN2)

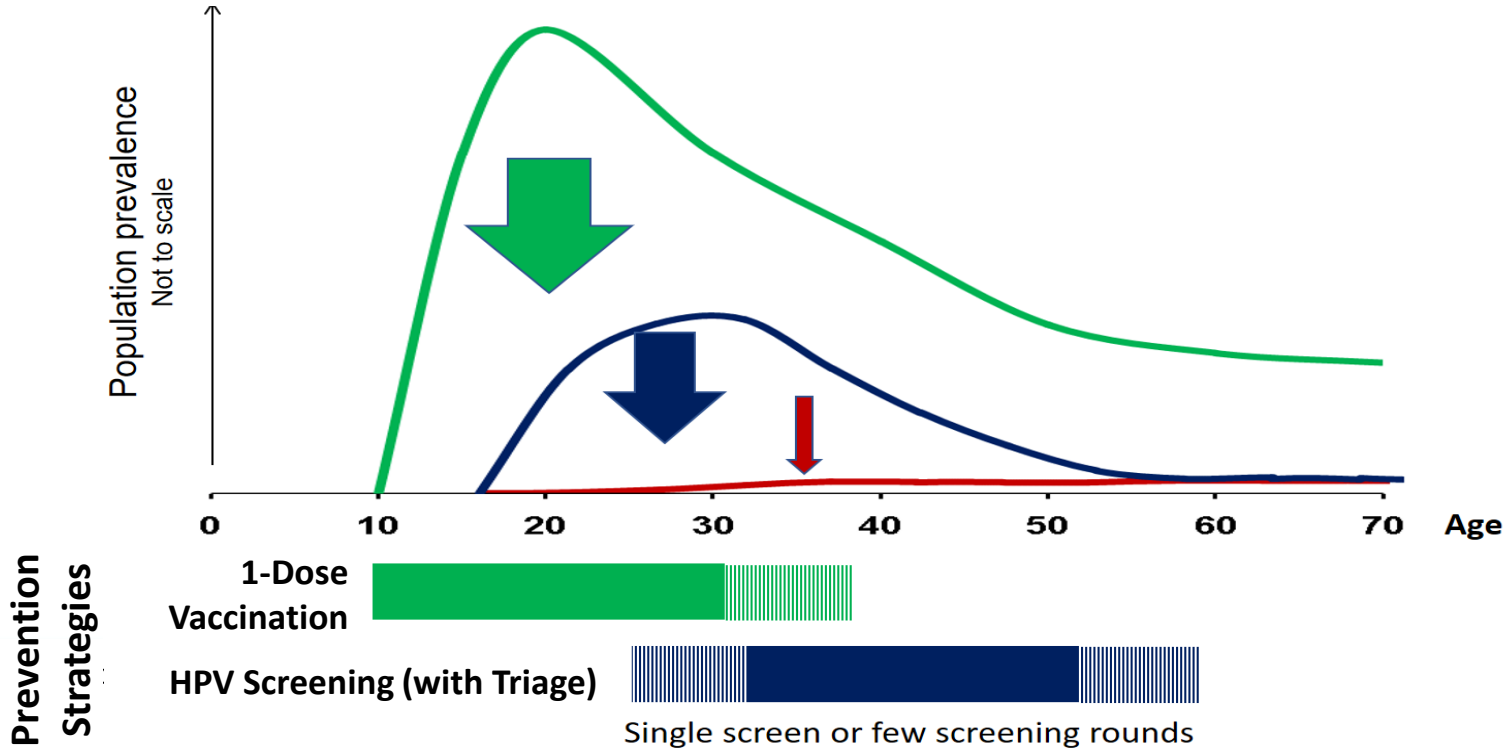
**AVE ALGORITHM**

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**



Wentzensen N & Schiffman M *Lancet Public Health* 2018 Jan;3(1):e6–e7

# Cervical Cancer Prevention in Border Communities


**Francisco A. R. Garcia, MD, MPH**

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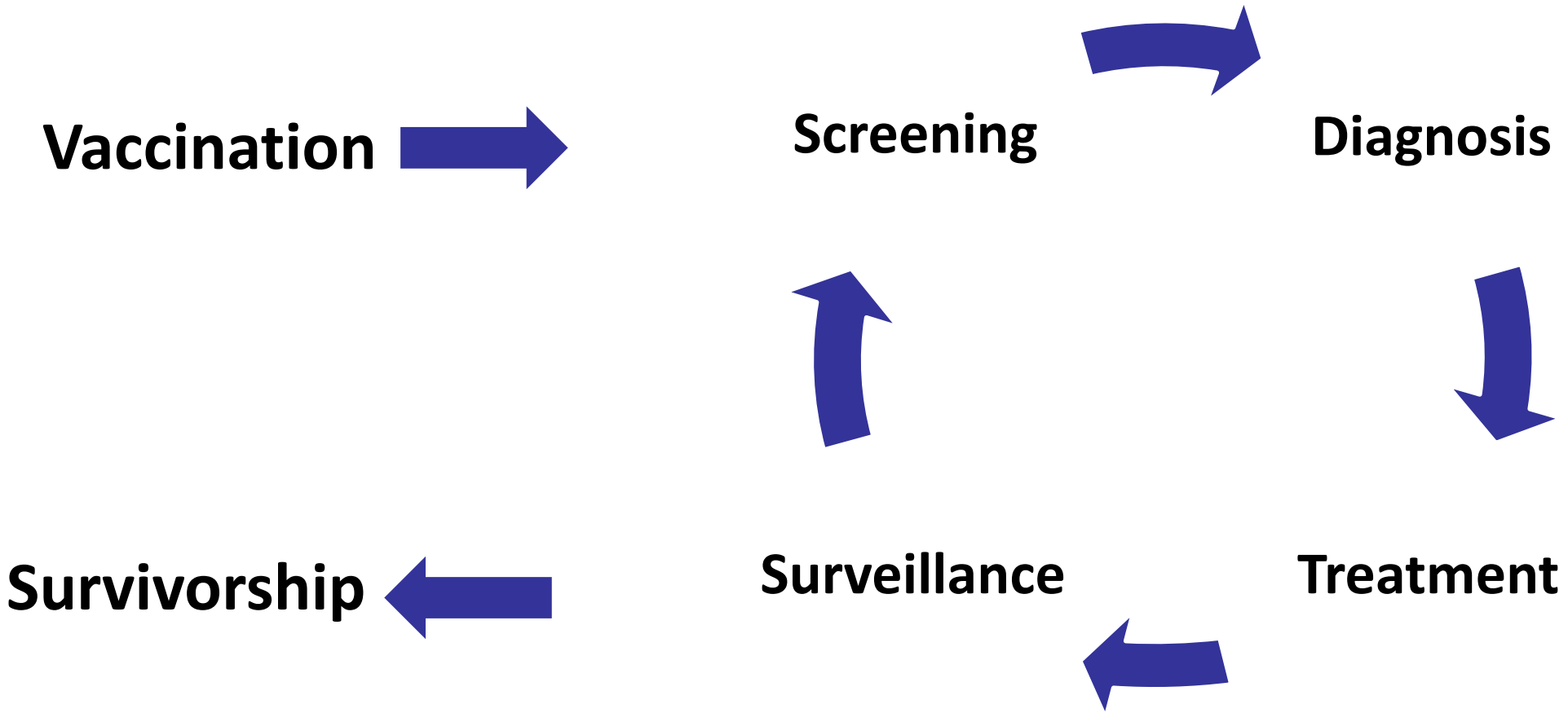
*Chief Medical Officer, Pima County*

*Professor Emeritus of Public Health*, University of Arizona

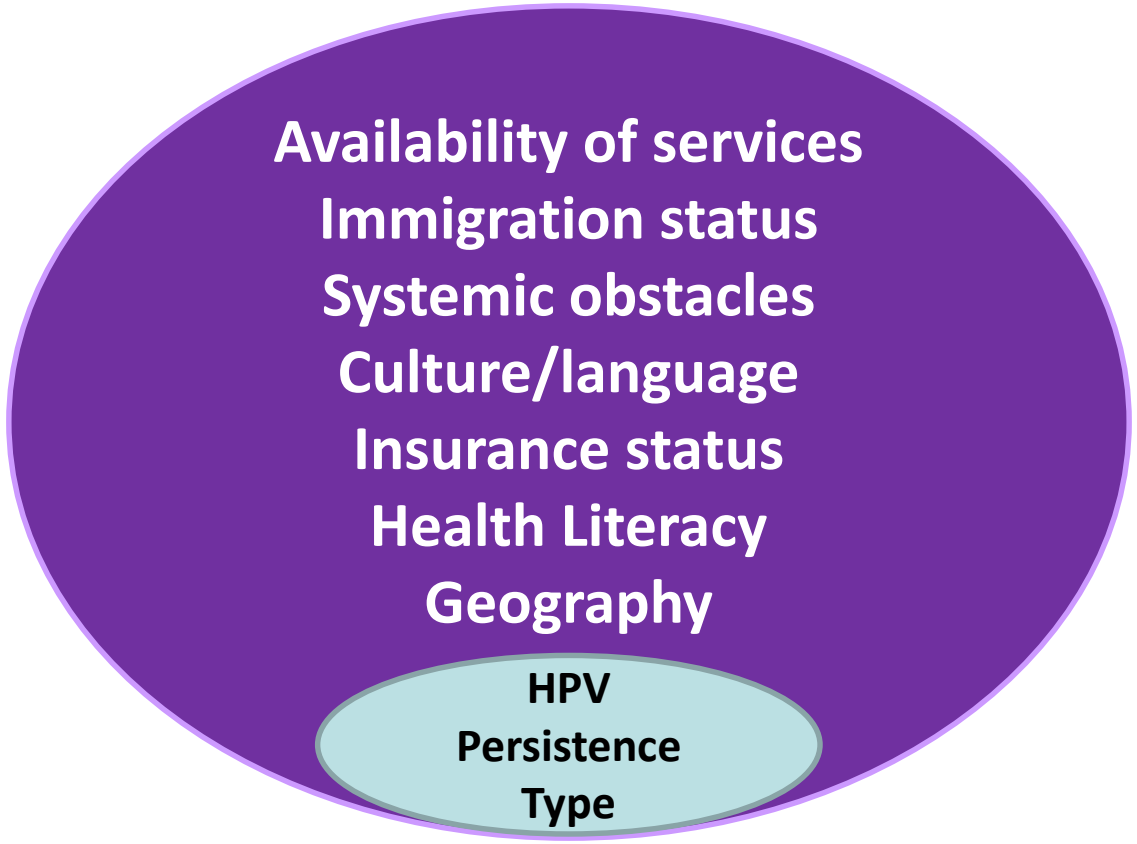


U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

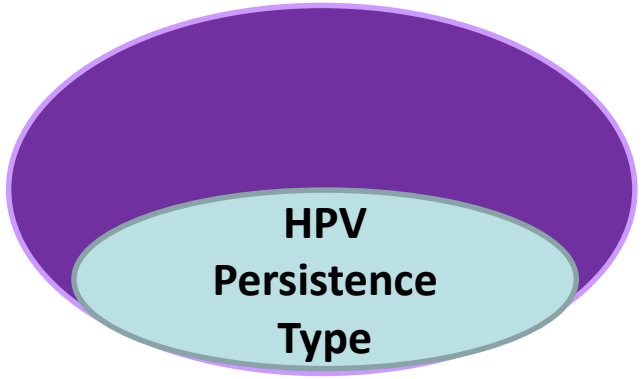
# Comprehensive Cervical Cancer Prevention in Vulnerable Communities



# 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

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

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## 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**

UA: University of Arizona

Moore-Monroy M, Wilkinson-Lee AM, Verdugo L, et al. *Health Promotion Practice* 2013 Mar;14(2):274–83

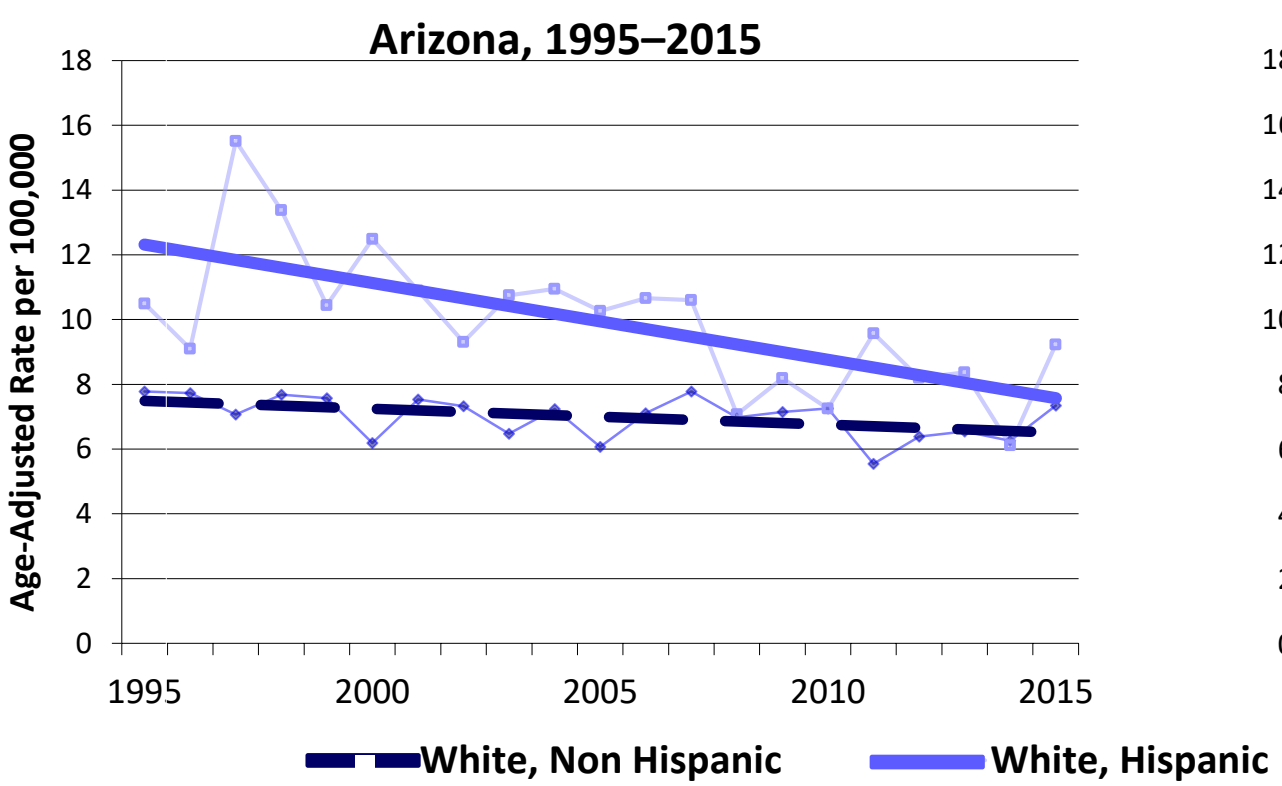
# CDC REACH Initiative: *Promotoras* Engaged in Preventing Cervical Cancer in Mexican-American Communities

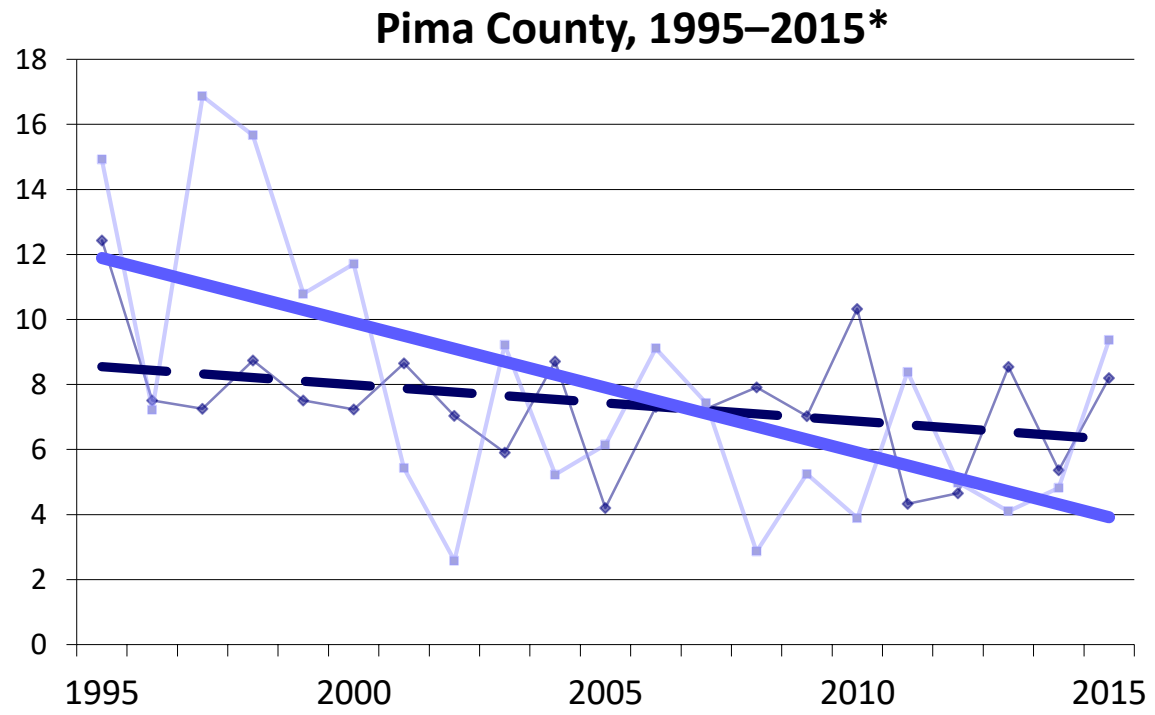
- During a 5-year funding period:
- Trained 300 community health workers (CHWs), called *promotoras*
- Over 100 *promotora* group presentations per year, reaching over 2,500 women
- 370 one-on-one client CHW encounters per year
- CHW case navigation (150 per year)
- Provider education CME & technical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



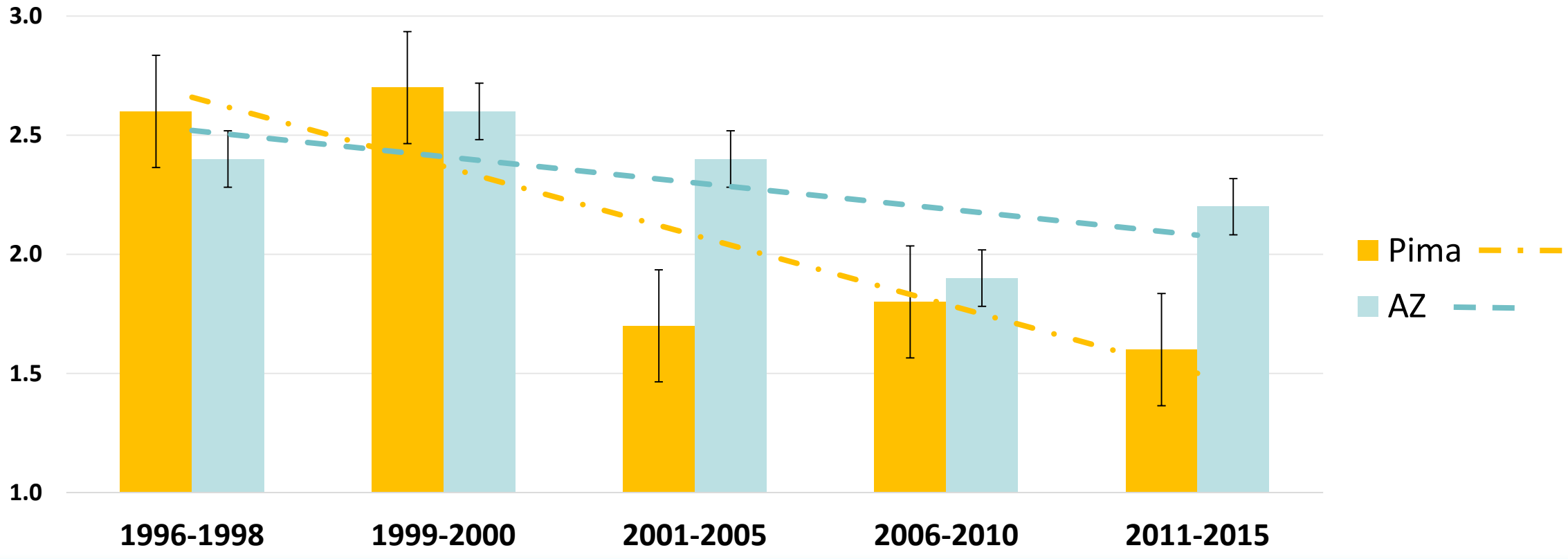




* Rates are based on fewer than 10 cases in most years. Interpret with caution.

Courtesy of the Arizona Department of Health Services

# Decreasing Rates of Cervical Cancer Mortality in Pima County

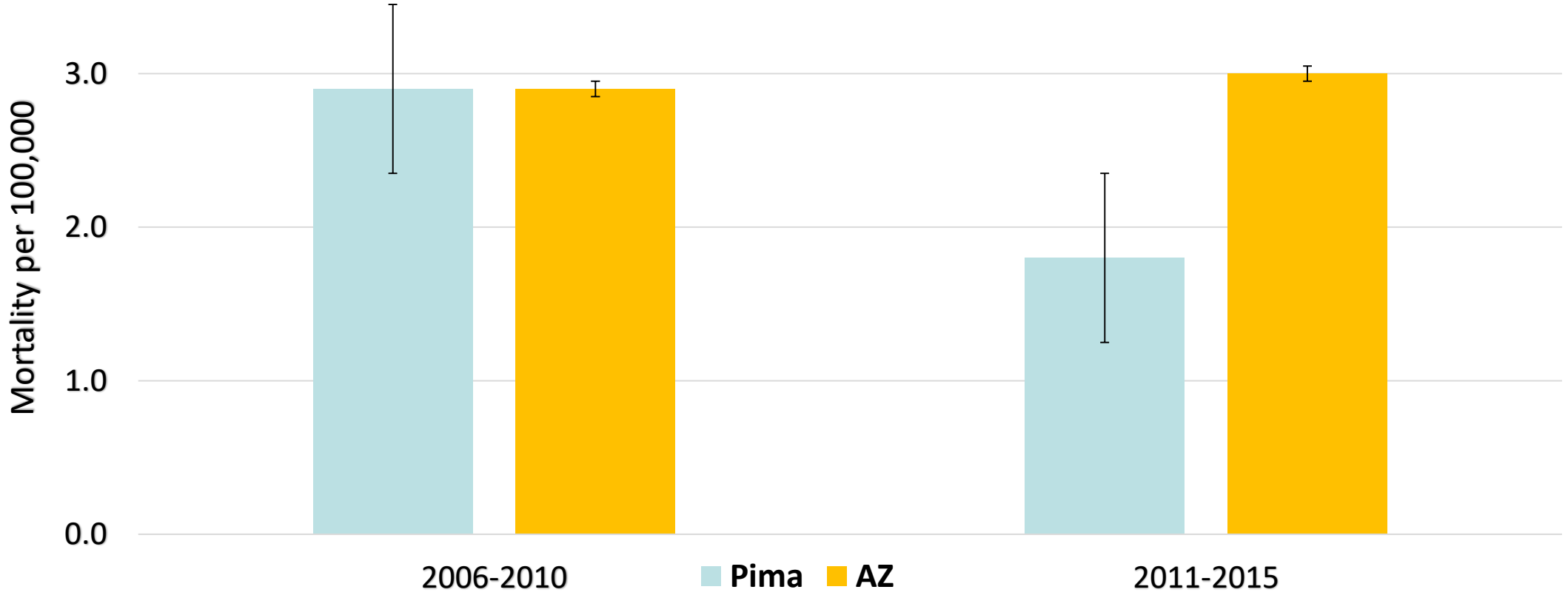
## Cervical Cancer Mortality Rate (per 100k) in Arizona and Pima County, 1996–2016




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 |

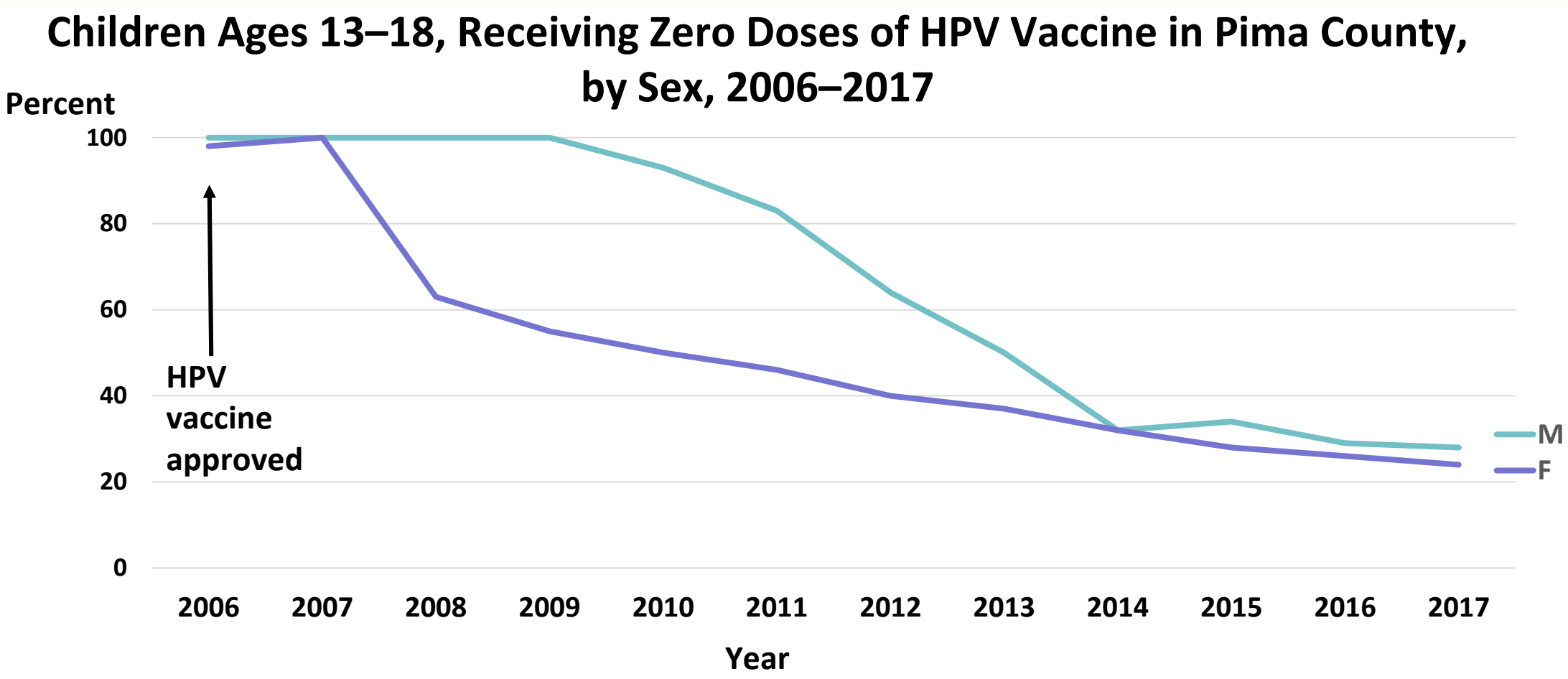
Nuño T, Castle PE, Harris R, et al. *J Womens Health*. 2011 May;20(5):685–93

# School Based Cancer Prevention Efforts

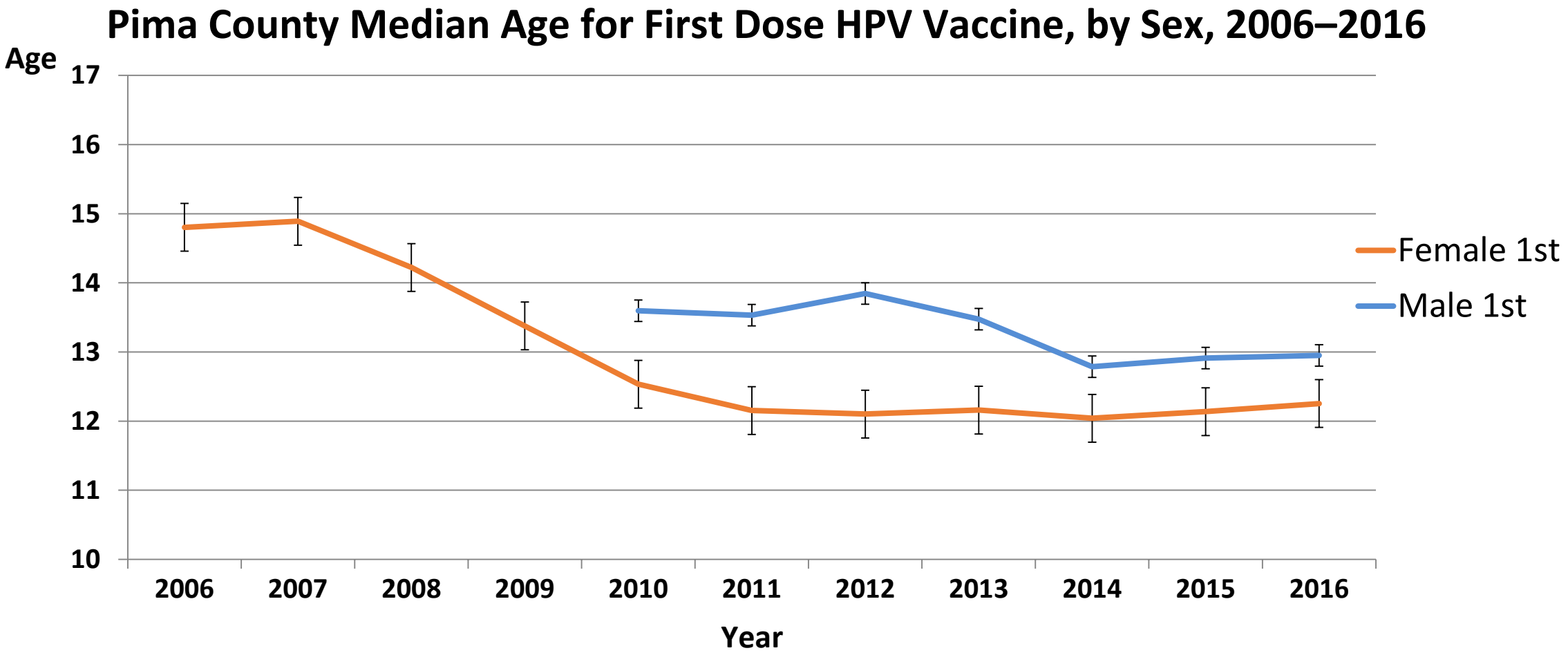
- **After-school girls' clubs & summer camps focused on health, education, and culture**
  - Tailored to urban and rural Hispanic girls
- **Classes for mothers on psychosocial topics and navigating educational systems to support daughters' academic success**
- **Opportunity for middle-school girl and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

Nuño VL, Gonzalez M, Loredo SM, et al. *J Low Genit Tract Dis* 2016 Apr;20(2):131–4

# HPV Non-vaccinated Children in Pima County Dropped



# First Dose HPV Vaccine is Reaching the Age-appropriate Children



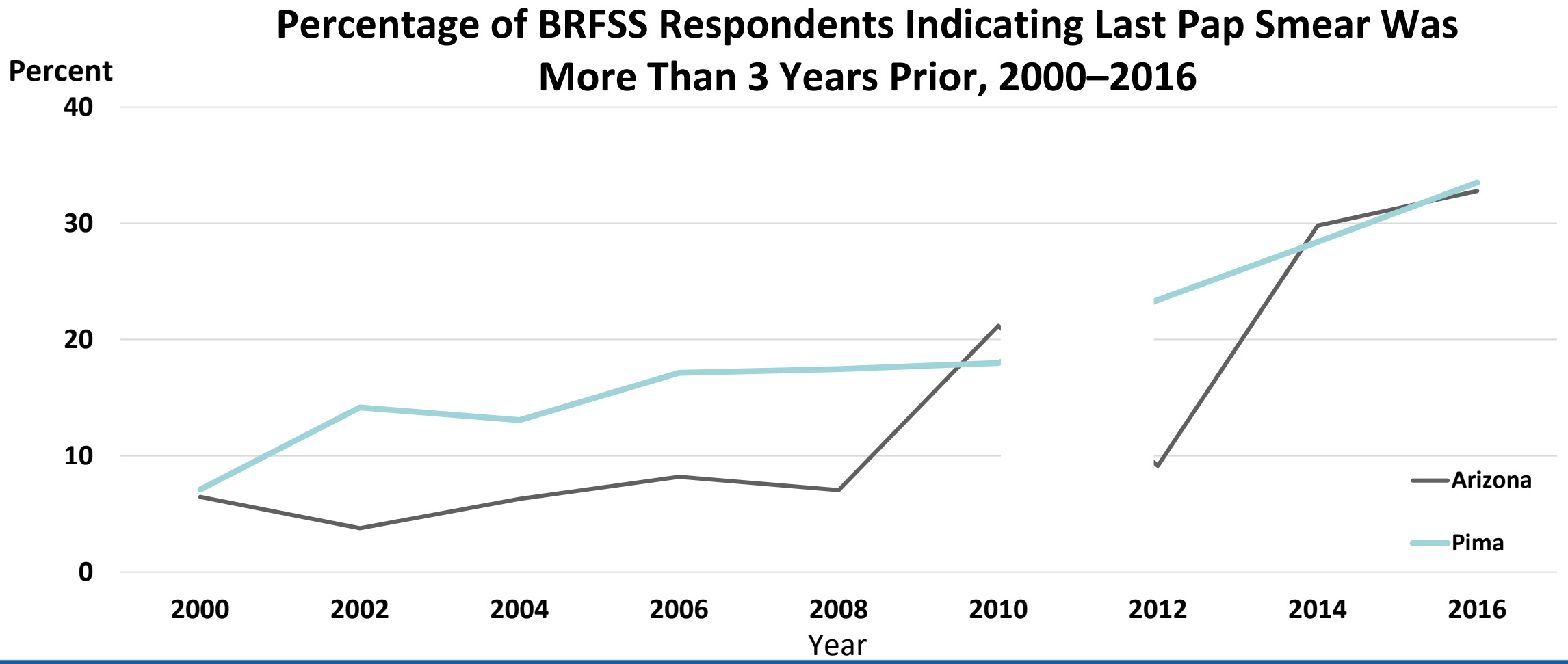
# Much Still to Be Done for Women At Increased Risk

## 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



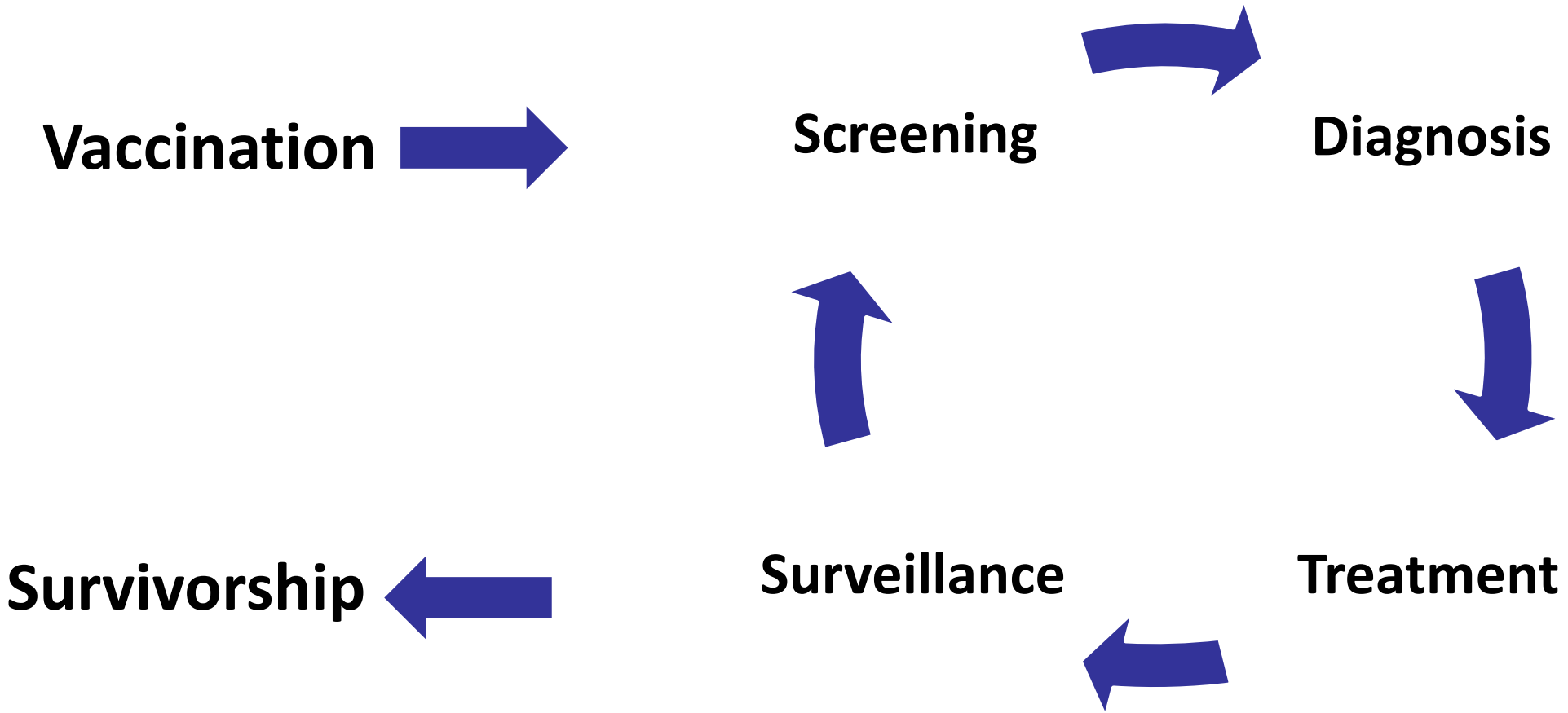

Courtesy of Arizona Department of Health Services

# 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**

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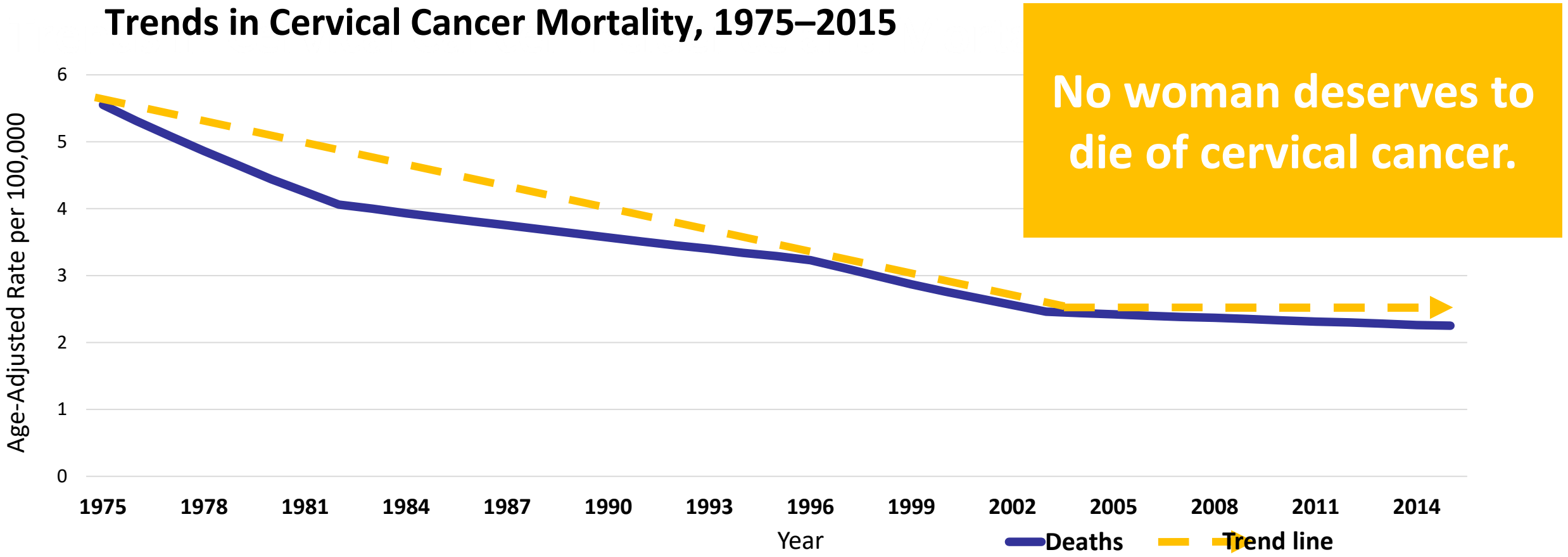
National Center for Chronic Disease Prevention and Health Promotion

Centers for Disease Control and Prevention



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

# Cervical Cancer is Still a Problem in the United States




**No woman deserves to die of cervical cancer.**

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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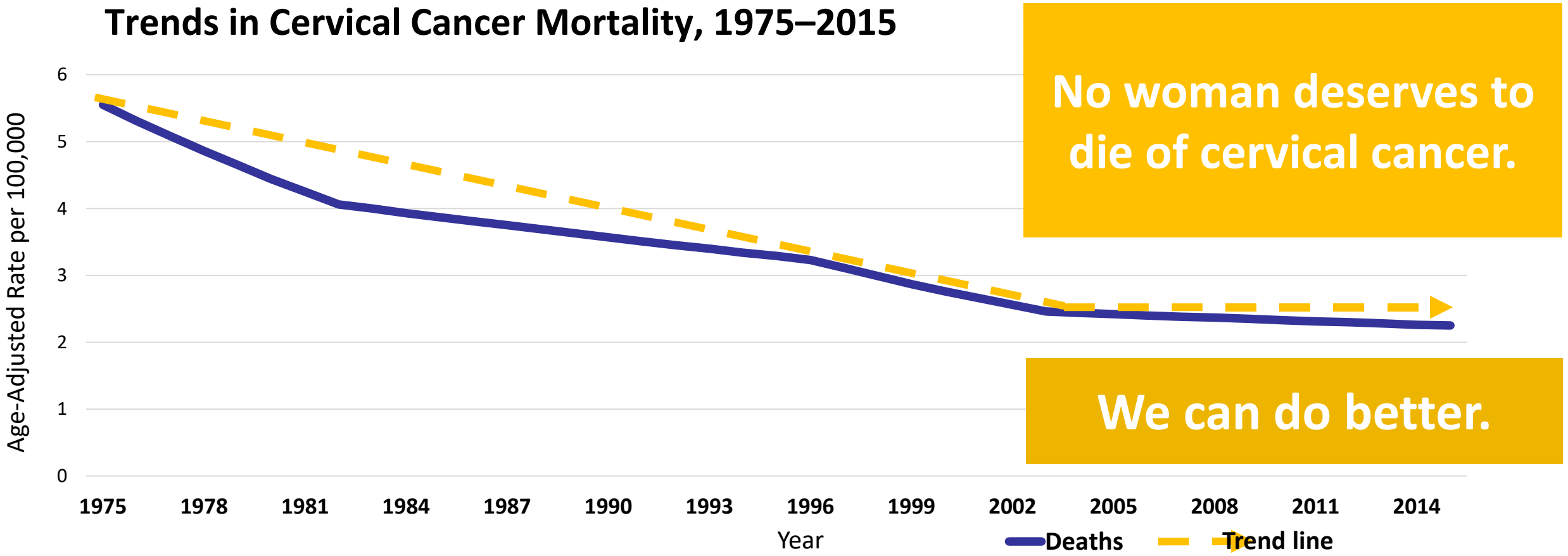


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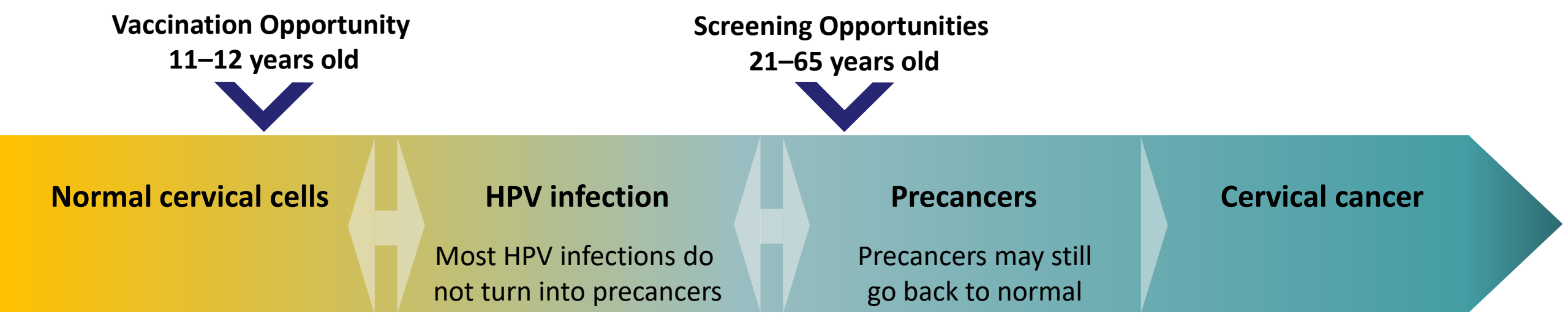
CDC, National Center for Health Statistics

# Two Proven Opportunities to Prevent Cervical Cancer




Saslow D, Solomon D, Lawson H.W, et al. *Am J Clin Pathol* 2012 Apr;137(4):516–42

# Call To Action For Healthcare Providers

**Everyone has a role in ending cervical cancer!**