The natural history and epidemiology of HPV and cervical cancer

Ellen Baker, MD, MPH
UT MD Anderson Cancer Center

Prevent Cancer Foundation Dialog for Action

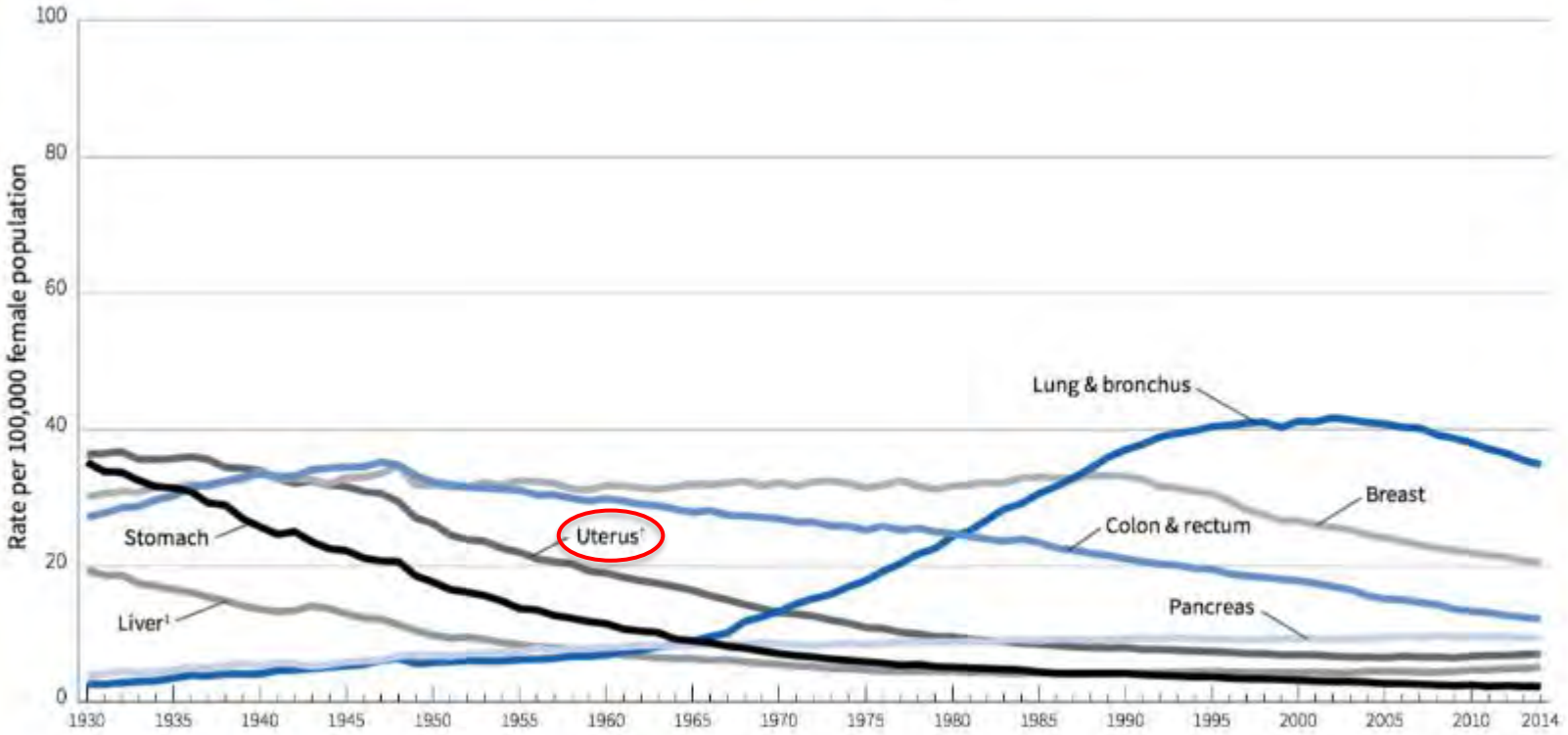
June 17, 2020

Virtually

With thanks to:
Philip Castle, PhD, MPH – Albert Einstein College of Medicine, NYC, USA
Kathleen Schmeler, MD – UT MD Anderson Cancer Center, Houston, USA

No financial relationships to disclose

Figure 2. Trends in Age-adjusted Cancer Death Rates* by Site, Females, US, 1930-2014

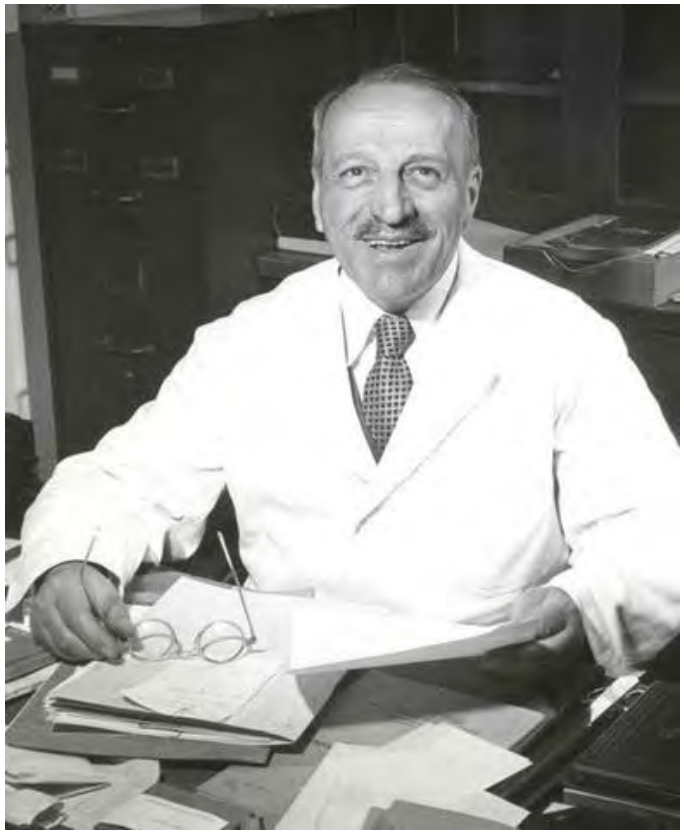


*Per 100,000, age adjusted to the 2000 US standard population. †Uterus refers to uterine cervix and uterine corpus combined. ‡The mortality rate for liver cancer is increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the liver, lung and bronchus, uterus, and colon and rectum are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2014, National Center for Health Statistics, Centers for Disease Control and Prevention.

George Papanicolaou (1883-1962)



Pap smear

- Sample cells from cervix & place on a glass slide/vial
- Detect pre-cancerous and cancerous cells
- First reported in 1928 but not widely used until 1941
- Decreased cervical cancer rates by 70% in the US

Population Effects of Pap Screening

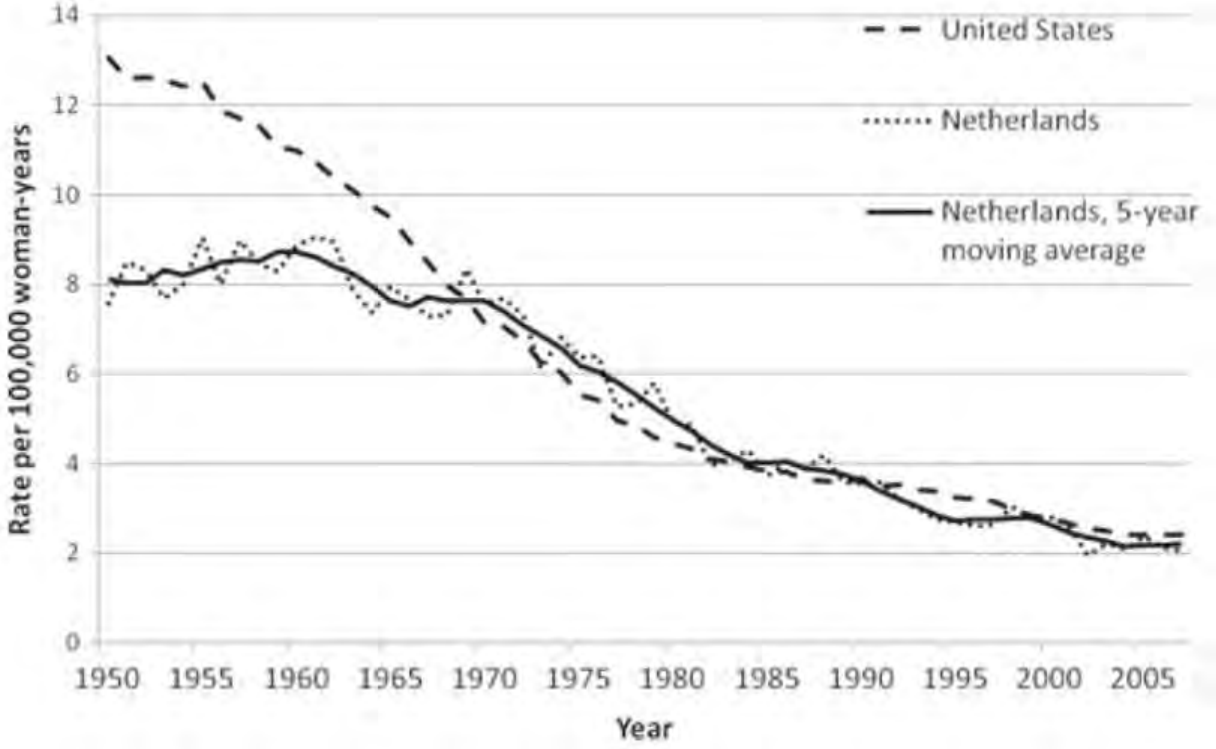
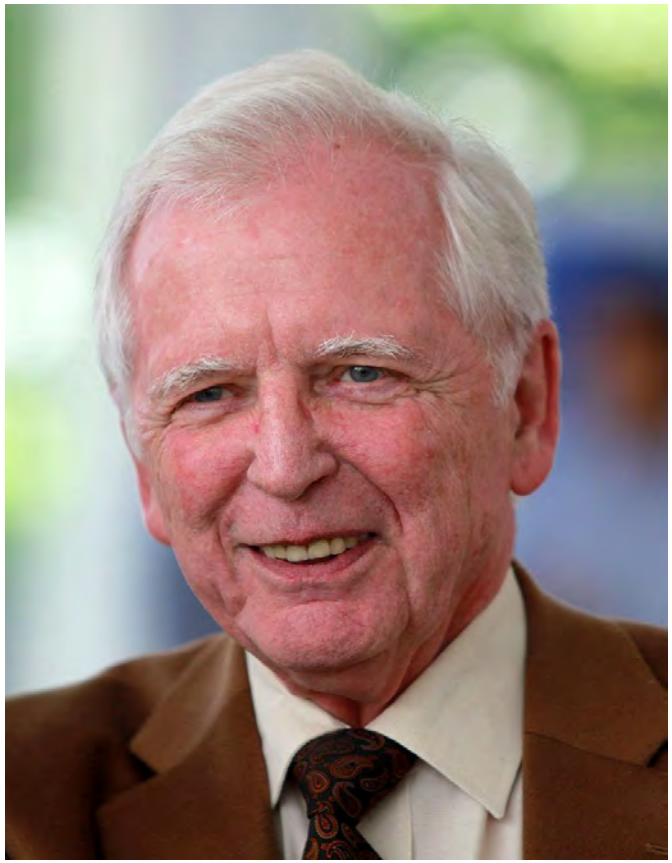


FIGURE 2. Cervical Cancer Mortality Rates in the United States and in the Netherlands, Age Standardized to the U.S. 2000 Population
Sources: United States: NCHS, see Altekruse et al. 2010. Netherlands: Statistics Netherlands (CBS) 2010a.

Dr. Harald zur Hausen
Nobel Prize, 2008



Known Etiology of Cervical Cancer:
Human Papillomavirus (HPV)

Primary Prevention:

- HPV Vaccination

Secondary Prevention:

- Screening with Pap test, HPV DNA test, VIA

Treatable Pre-Invasive Phase:

- Takes ~10 - 20y to progress from pre-invasive disease to cancer
- Ablation or Excision

Human papillomavirus (HPV)

Most common sexually transmitted disease

- Initial infection occurs as a teenager or young adult
- >80% of people will have HPV at some point in their life
- Global prevalence ~12%
  - 79 million Americans are currently infected
  - 14 million new infections/year in the US
  - <5% will have significant pre-cancerous lesions
  - <1% will develop invasive cervical cancer

https://www.cdc.gov/std/hpv/stdfact-hpv.htm
Li and Xu. Human Papillomavirus-related Cancers. Epidemiology and Molecular Biology 2017: 23-34.

Human papillomavirus

- >100 HPV genotypes
- At least 14 HPV genotypes are considered high risk
- HPV types 16 and 18 cause
  - 70% Cervical cancers
  - >70% Anal cancers in men & women
  - 70% of Oropharynx cancers in men & women
  - 50% Penile cancers
  - 50% Vaginal and vulvar cancers
- HPV types 6 and 11 cause
  - 90% of genital warts
  - Recurrent Respiratory Papillomatosis (RRP)

Castle and Maza. Prophylactic HPV vaccination: past, present, and future. Epidemiol Infect 2016: 449-468
de Sanjose et al., Lancet Onc, 2010
Li and Xu. Human Papillomavirus-related Cancers. Epidemiology and Molecular Biology 2017: 23-34.

HPV–Associated Cancers in the US 2012-2016

About 44,000 new cases of HPV-associated cancers occurred in the US each year

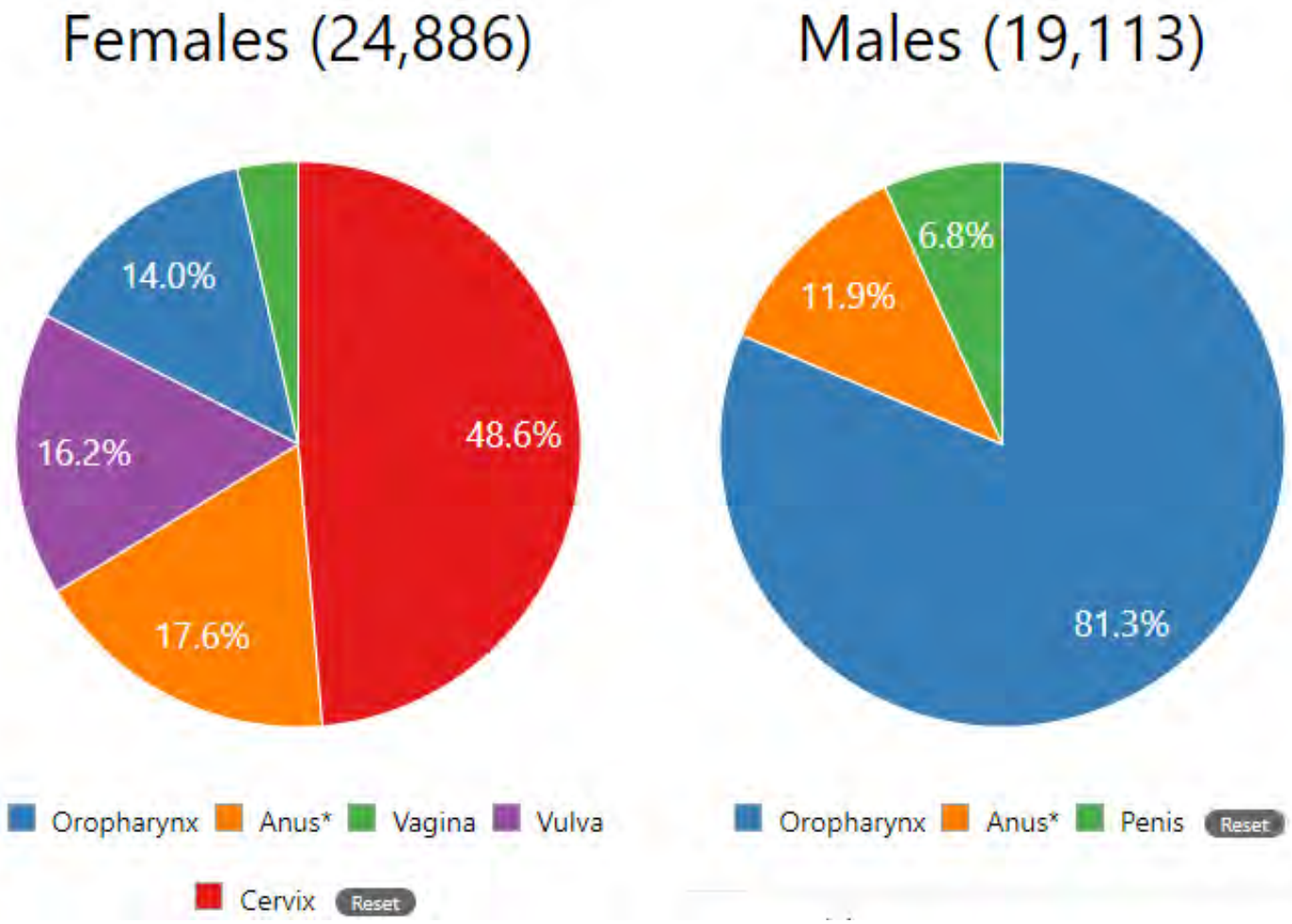
- 12,015 cases of cervical cancer
- 19,000 oropharyngeal cancers (men and women)
- ~13,000 other cancers (vaginal, vulvar, penile, anus)

34,800 (79%) of these cancers can be directly attributed to HPV

About 32,100 of these cancers can be prevented with the 9-valent HPV vaccine

Viens LJ et al. Human Papillomavirus–Associated Cancers United States, 2008–2012. MMWR Morb Mortal Wkly Rep 2016;65:661–666.
https://www.cdc.gov/cancer/uscs/about/data-briefs/no10-hpv-assoc-cancers-UnitedStates-2012-2016.htm

Average Number of New HPV-Associated Cancers by Sex in the U.S., 2012-2016



Centers for Disease Control and Prevention. Cancers associated with human papillomavirus, United States—2010–2014. USCS data brief, no. 1. Atlanta, GA: Centers for Disease Control and Prevention. 2017. https://www.cdc.gov/cancer/uscs/about/data-briefs/no10-hpv-assoc-cancers-UnitedStates-2012-2016.htm
Berman,Schiller:Cancer 2017;123:2219-29

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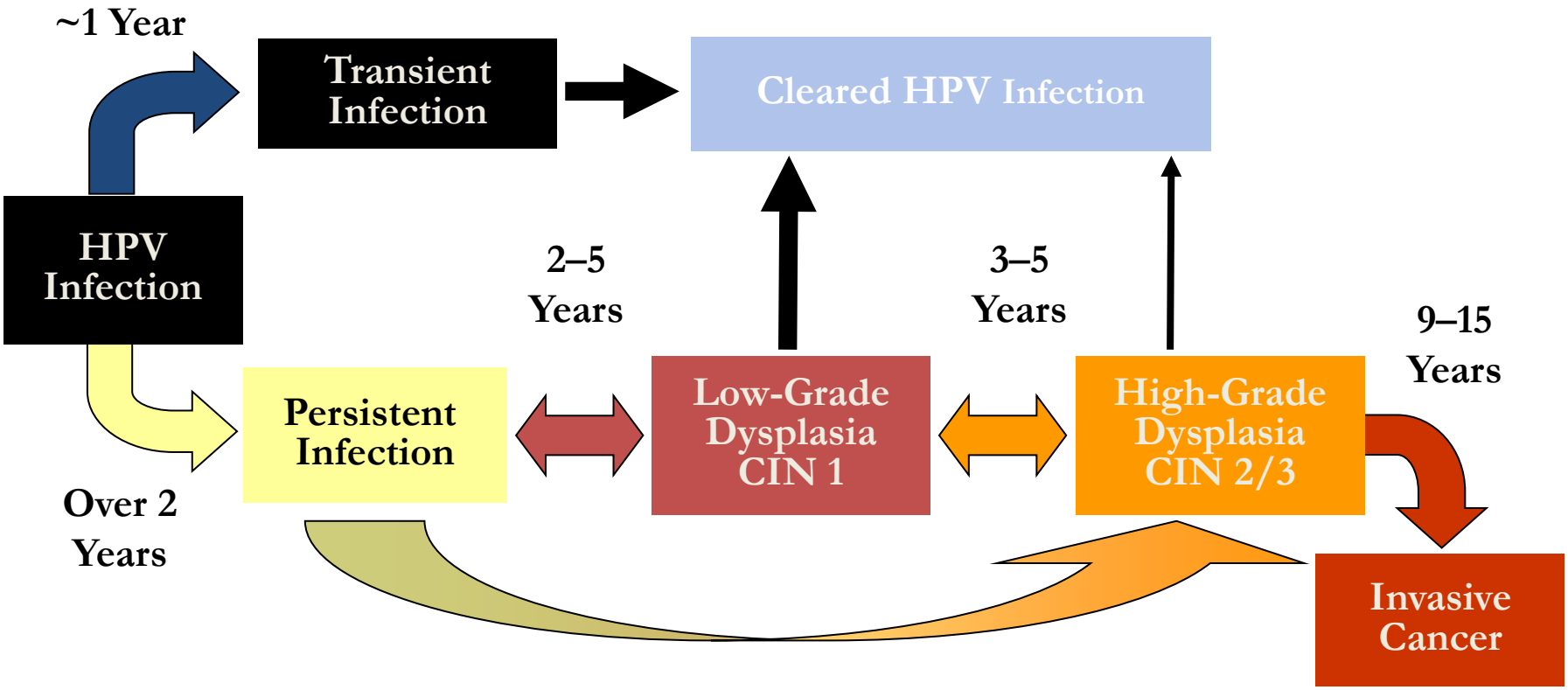
Natural History of High-Risk HPV



****HPV is necessary but not sufficient to develop cervical cancer**

Adapted from: 1. Pagliusi SR, Aguado MT. *Vaccine*. 2004;23:569–578. 2. Pinto AP, Crum CP. Clin Obstet Gynecol. 2000;43:352–362.

Human papillomavirus infection

- Infects basal layers of cutaneous and mucosal squamous epithelium, primarily in transition zones (endo-ectocervical junction)
- E6 and E7 are viral oncoproteins expressed with persistent infection and viral replication

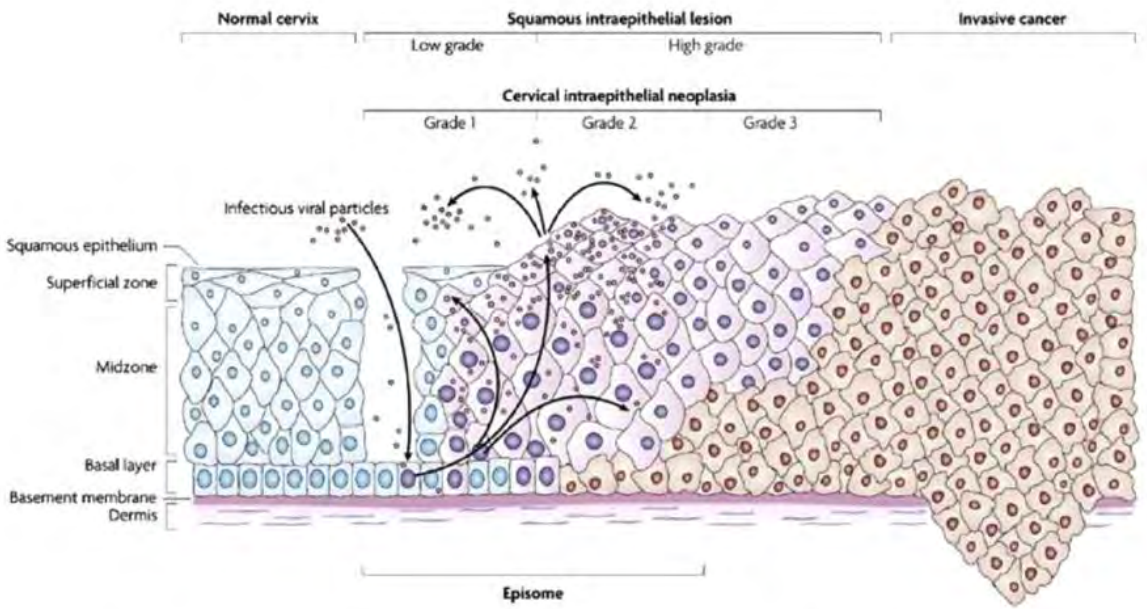
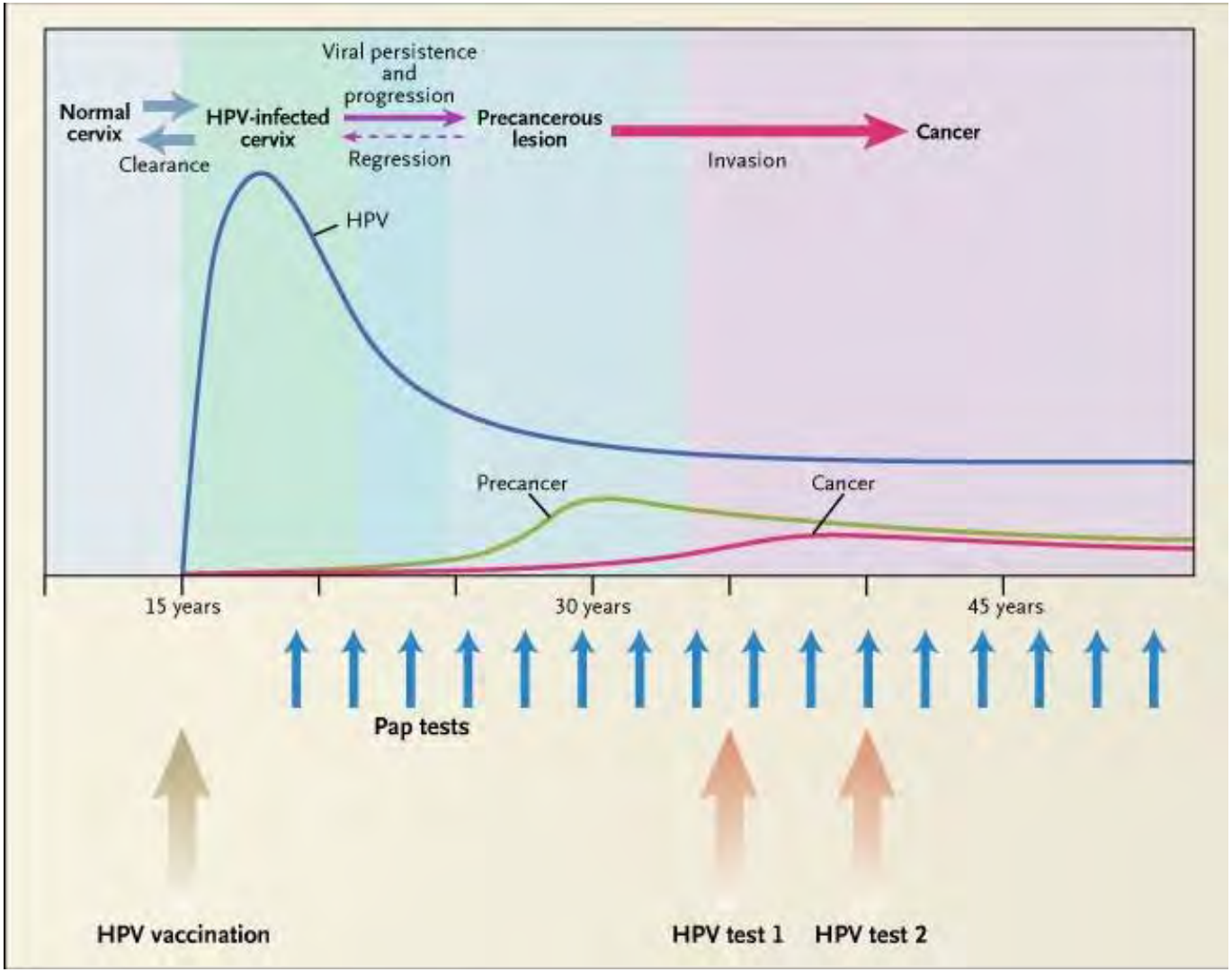


Fig. 2. Schematic representation of the HPV infection in cervical mucose and its different potential squamous intrepitelial lesions.

Sanjose. The natural history of human papillomavirus infection. Best Practice & Research Clinical Obstetrics and Gynaecology 47 (2018) 2-13

Li and Xu. Human Papillomavirus-related Cancers. Epidemiology and Molecular Biology 2017: 23-34.

Interventions for prevention of cervical cancer



Schiffman and Castle, NEJM, 2005

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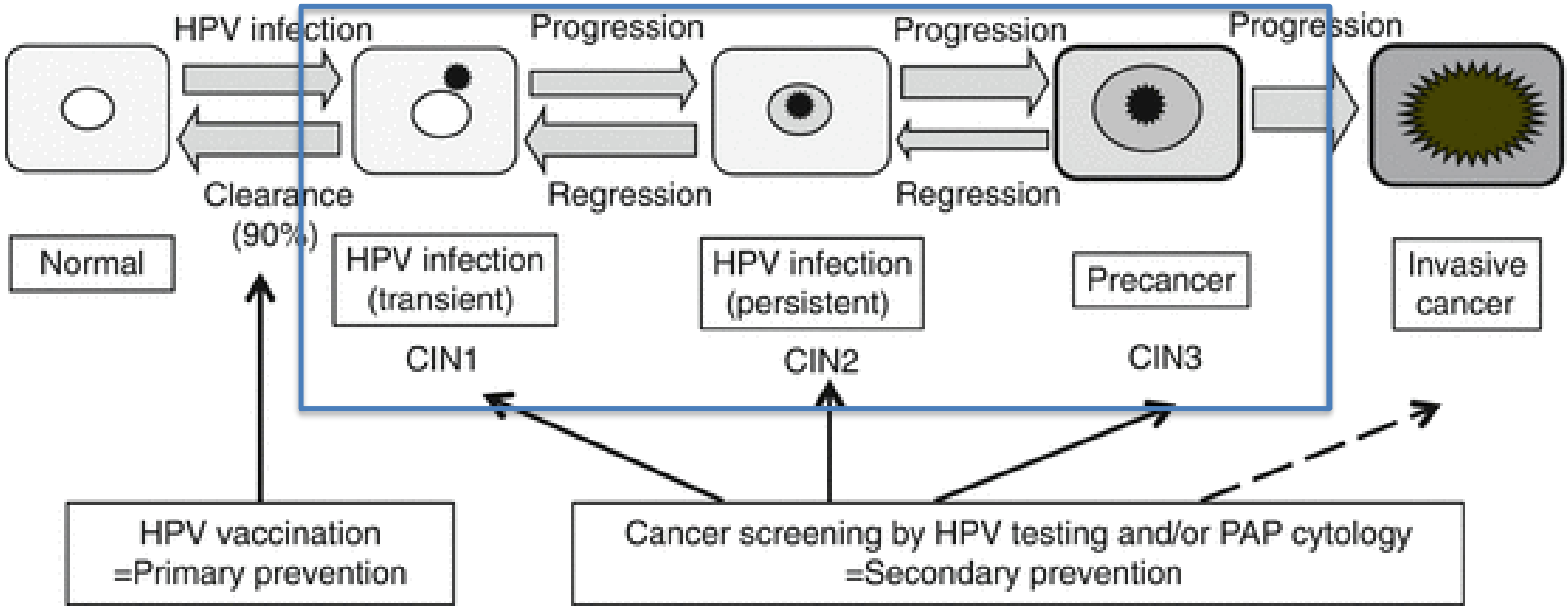
Cervical Cancer Prevention Strategies



Ino K. (2017) Prevention of Cervical Cancer: Era of HPV Testing and Vaccination. In: Konishi I. (eds) Precision Medicine in Gynecology and Obstetrics. Comprehensive Gynecology and Obstetrics. Springer, Singapore

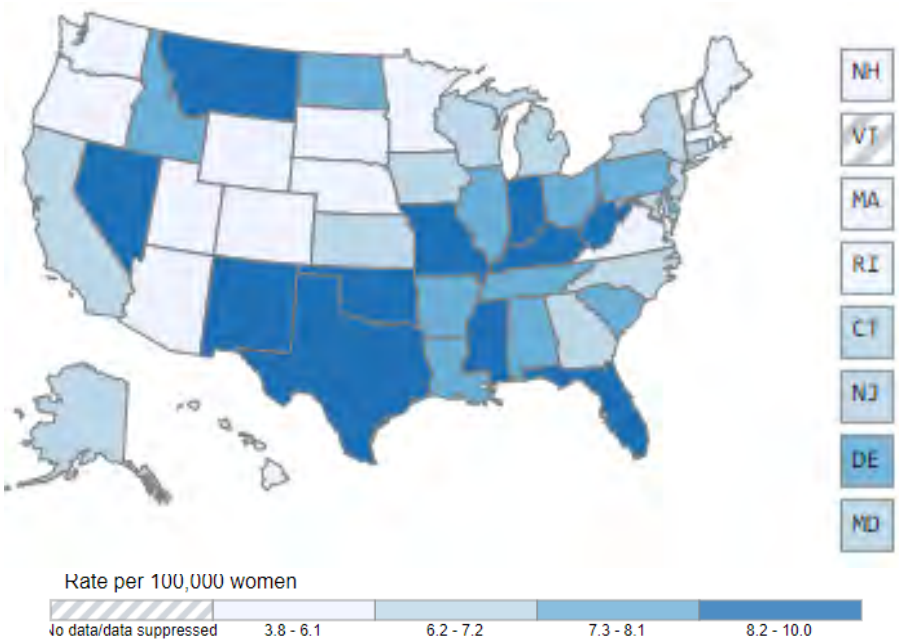
Cervical Cancer

US Incidence/Mortality
7.3/2.3 per 100,000

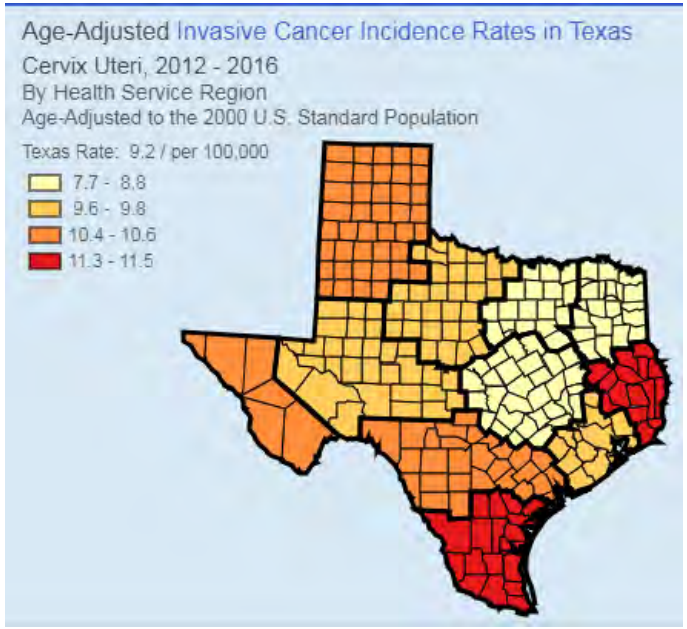
~290,000 women living with cervical cancer in the US

https://seer.cancer.gov/statfacts/html/cervix.html

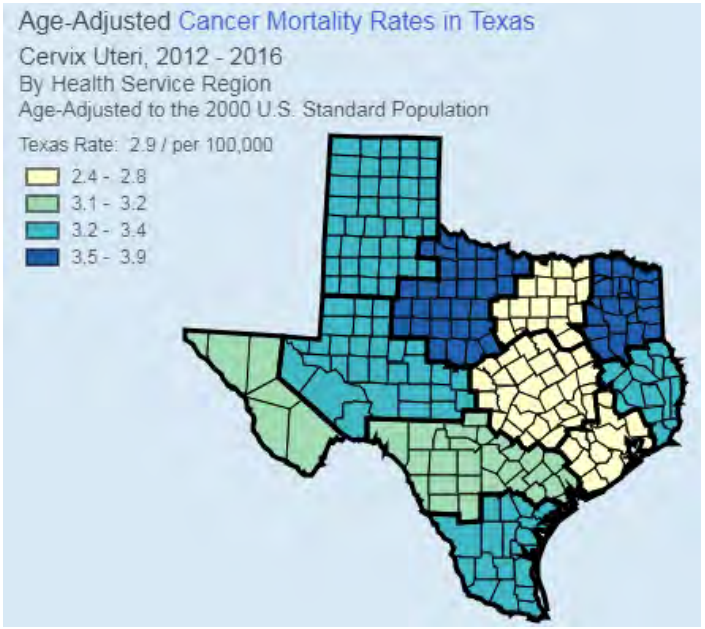
Texas Incidence/Mortality
9.1 (#6 in the US)
2.9 (#8 in the US)



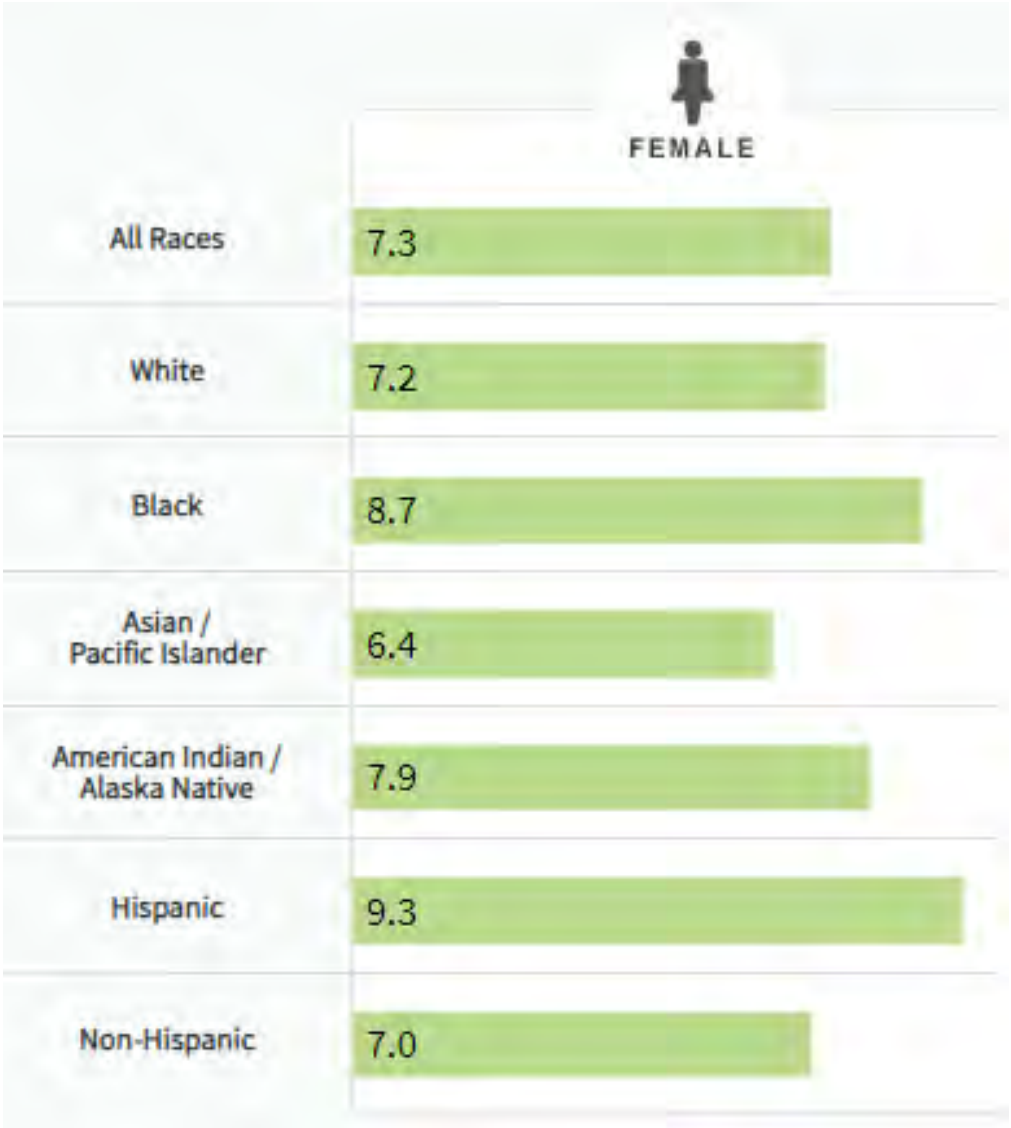
www.cdc.gov/cancer/dataviz, June 2019



https://gis.cdc.gov/Cancer/USCS/DataViz.html



https://www.dshs.texas.gov/tcr/data.shtm



Number of new cases of Cervical Cancer per 100,000 persons by race/ethnicity

13,170 new cases (2019)

https://seer.cancer.gov/statfacts/html/cervix.html
SEER 21 2012-2016, Age-Adjusted

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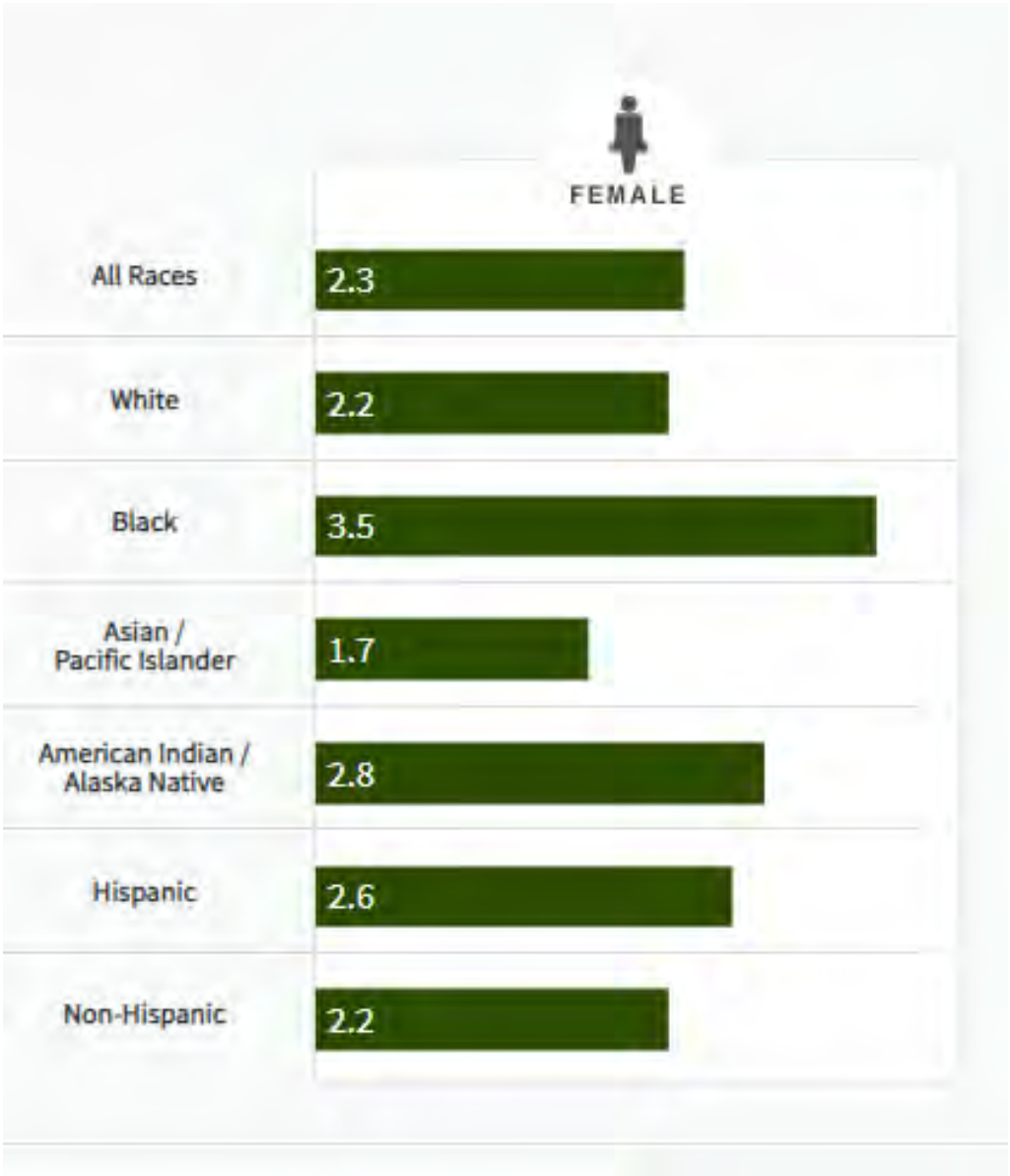

Number of deaths from Cervical Cancer per 100,000 persons by race/ethnicity

4,250 deaths (2019)

https://seer.cancer.gov/statfacts/html/cervix.html
SEER 21 2012-2016, Age-Adjusted

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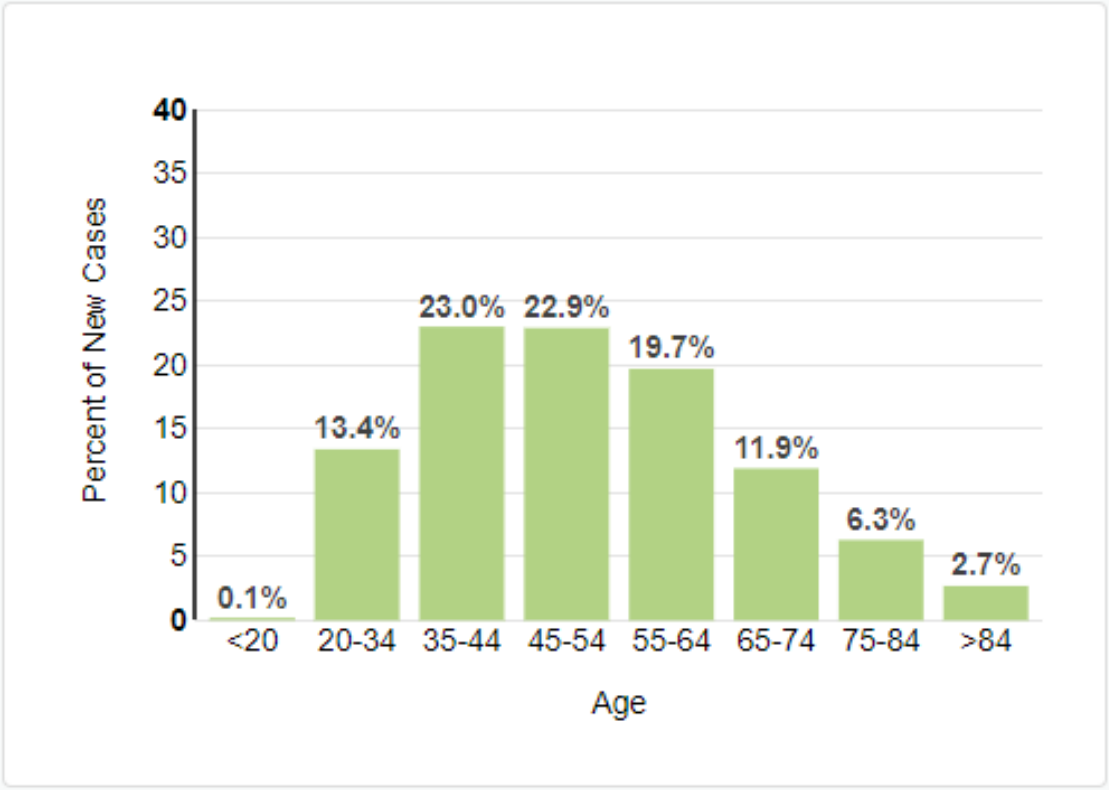
Percent of New Cases by Age Group: Cervical Cancer



Cervical cancer is most frequently diagnosed among women aged 35-44.

Median Age At Diagnosis

50

Median Age At Death

58

SEER 21 2012-2016, All Races, Females

https://seer.cancer.gov/statfacts/html/cervix.html
SEER 21 2012-2016, Age-Adjusted

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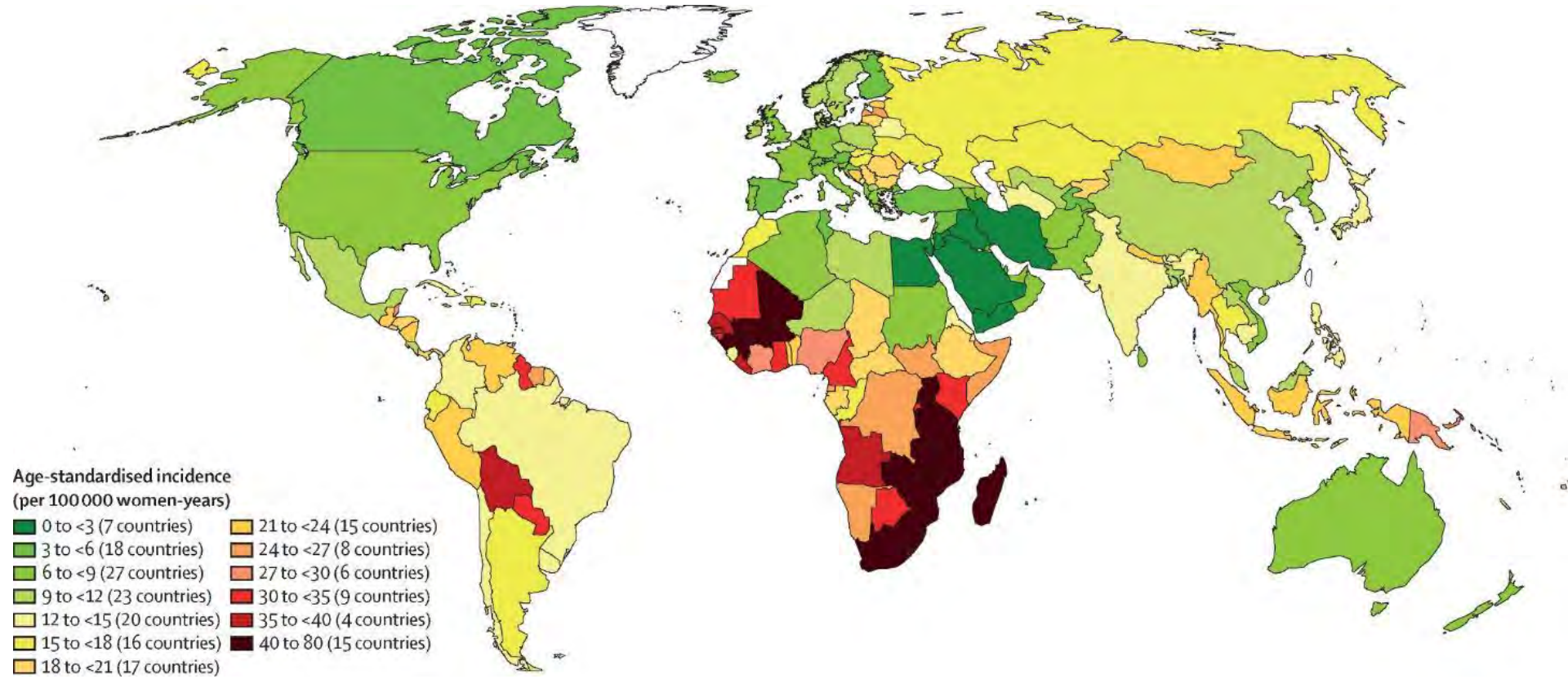
Costs of prevention and treatment of HPV related disease in the US

- ~52,000,000 screening tests/year
- 2-3,000,000 women/year have abnormal tests
  - Evaluation requires repeat visits, repeat testing
- ~350,000 women/year will have pre-cancerous lesions that require treatment and follow-up
- Cost of prevention and treatment of HPV related disease
  - ~$8 billion/year
    - $1 billion for cancer care
    - $6.6 billion for screening
    - $1.2 billion for follow up and treatment of abnormal results

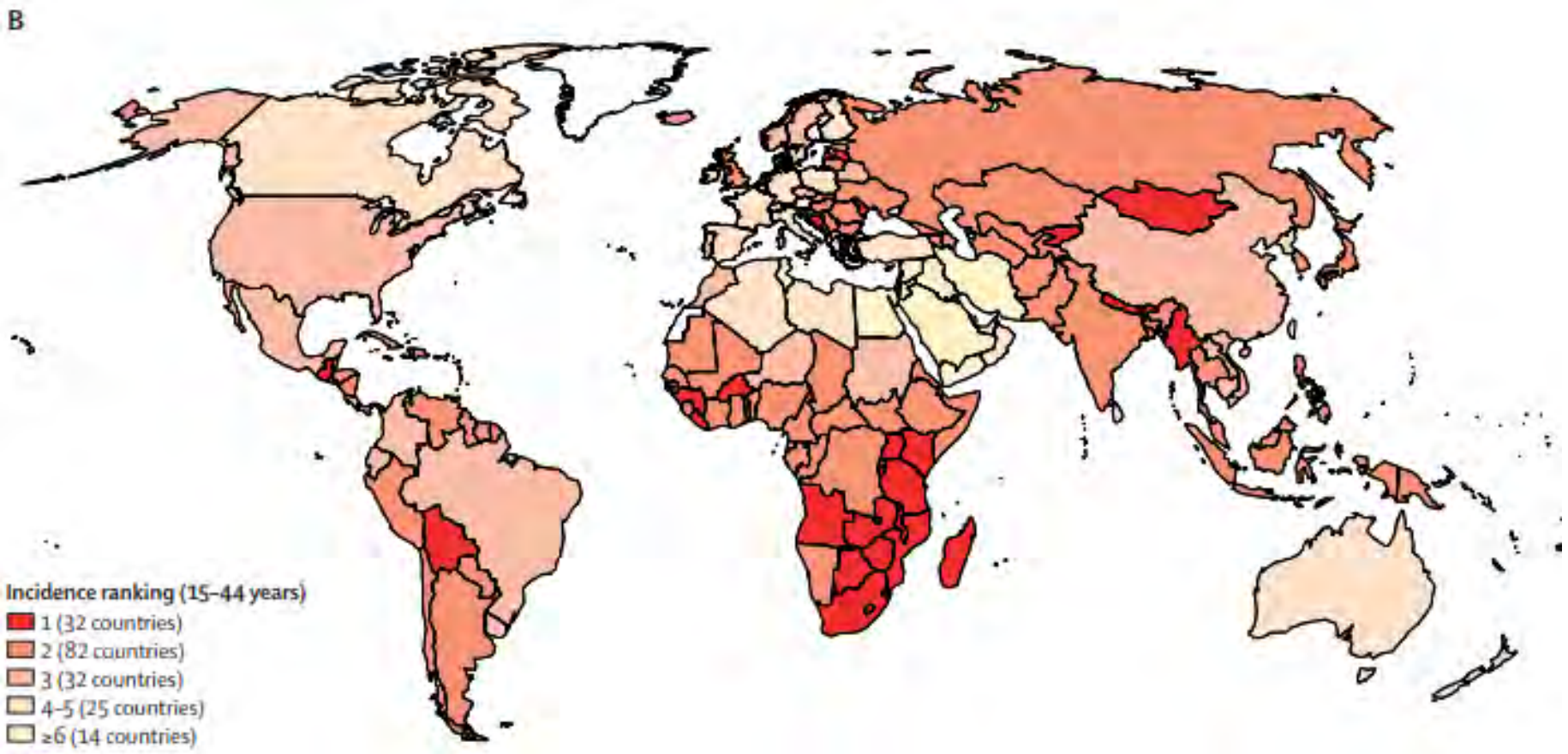
Chesson et al. Estimates of the annual direct medical costs of the prevention and treatment of disease associated with human papillomavirus in the United States.Vaccine 30:2012:6016-6019.
Chesson et al. Updated Medical Care Cost Estimates for HPV-associated Cancers: Implications for Cost-Effectiveness Analyses of HPV Vaccination in the United States.Hum Vaccin Immunother 15(7-8), 2019:1942-48.

Age Standardized Incidence of Cervical Cancer



The Lancet Global Health 2020 8, e191-e203DOI: (10.1016/S2214-109X(19)30482-6

Ranking of cervical cancer incidence in women 15-44 years (2018)



www.thelancet.com/lancetgh Vol 8:e191-203 February 2020

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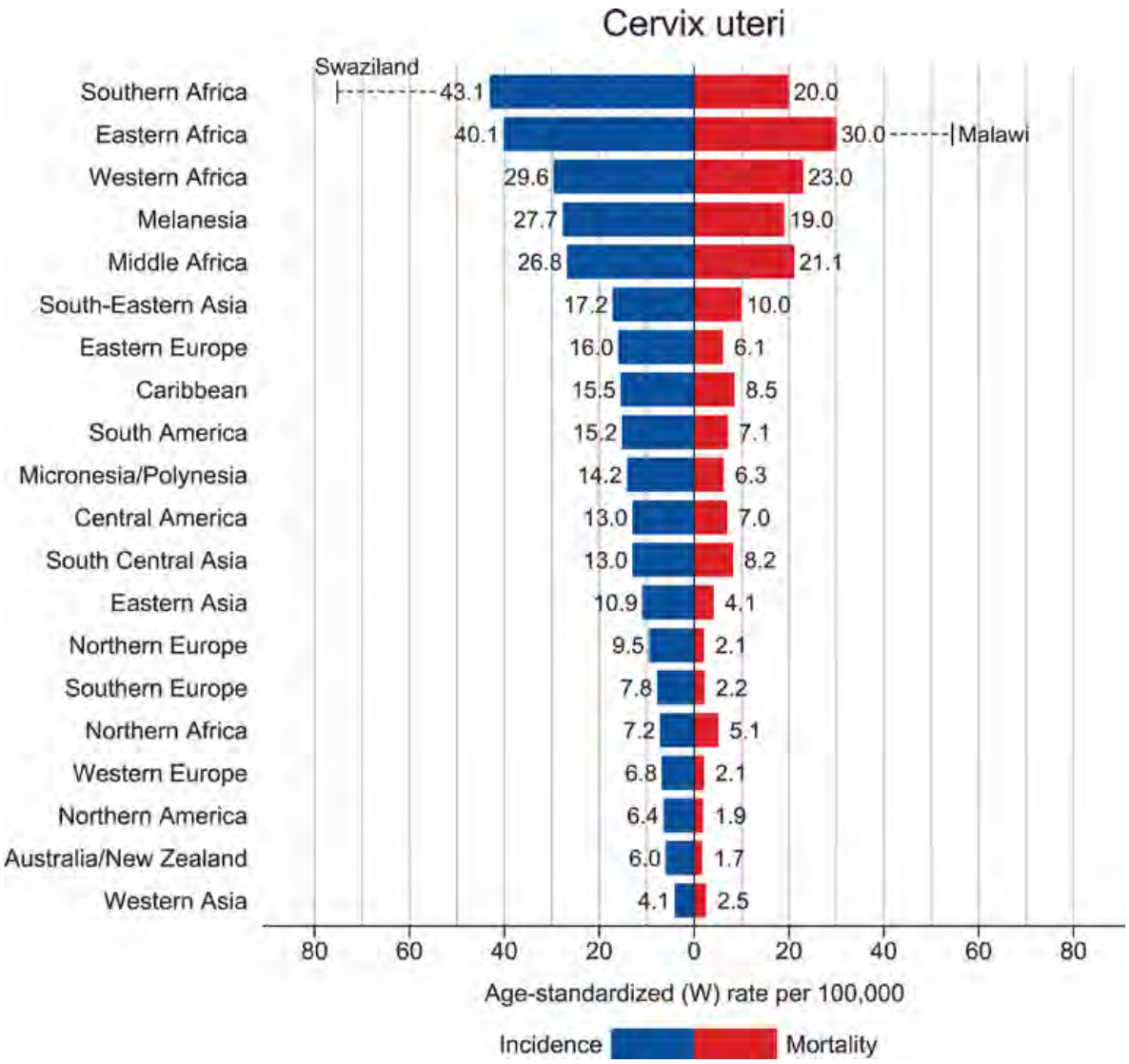

Bray et al, Global cancer statistics 2018, Cancer 2018

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HPV Prophylactic Vaccines

Recombinant L1 capsid proteins that form "virus-like" particles

Non-infectious and non-oncogenic

Antibodies prevent basement membrane binding

Produce higher levels of neutralizing antibody than natural infection

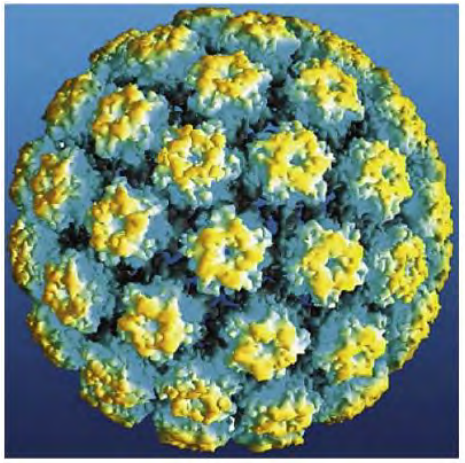
Vaccine not effective to treat an existing infection

Available vaccines:

Bivalent : Types 16,18

Quadrivalent: Types 6,11,16,18

Nonavalent: Types 6,11,16,18,31,33,45,52,58



HPV Virus-Like Particle

Schiller J. Lowy D. Explanations for the high potency of HPV prophylactic vaccines Vaccine 35 (2018)4768-73

HPV Vaccine Recommendation

Preteens should finish HPV vaccine series by 13th birthday

Plus girls 13-26 years old who haven't started or finished HPV vaccine series

Plus boys 13-26 years old who haven't started or finished HPV vaccine series

https://www.cdc.gov/hpv/hcp/schedules-recommendations.html

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Immunization of Boys

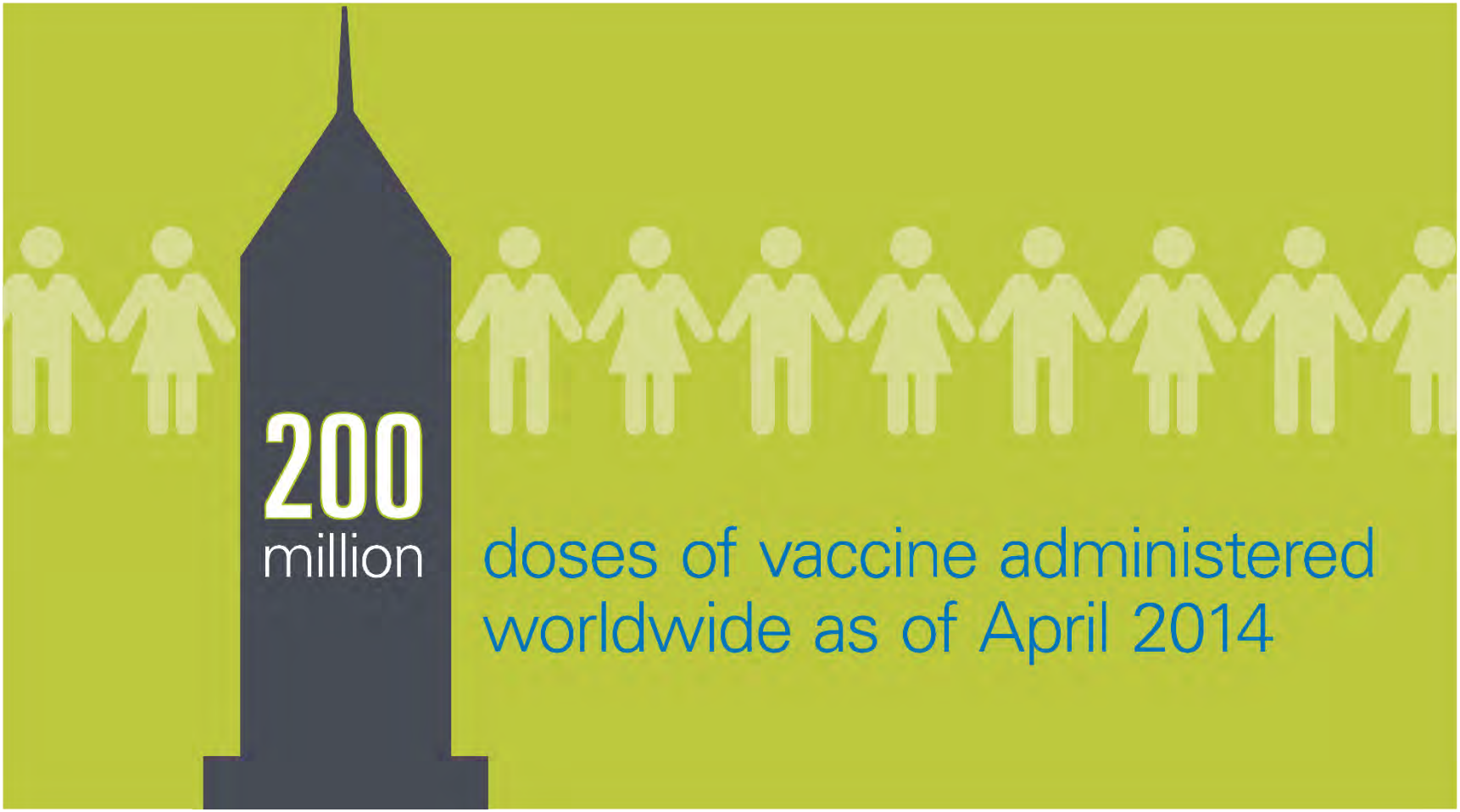
- Prevention of genital warts
- Potential prevention of oropharyngeal, anal, and penile cancer
- Decreased HPV transmission to female partners
- “Herd Immunity” - greater protection of the general public decreases infection in those who do not get vaccinated

Dosage and scheduling

Dose	Age range/ health condition	Schedule
2 dose	• Boys and girls prior to 15th birthday.	0, 6-12 months If 1st & 2nd dose administered <5 months apart a 3rd dose is required.
3 dose	• Boys and girls on or after 15th birthday. • Immunocompromised – HIV infection, cancer, autoimmune disease.	0, 1-2, 6 months

https://www.cdc.gov/hpv/hcp/schedules-recommendations.html

The HPV Vaccine is Safe



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HPV Vaccine Safety

Adverse Events:

- Injection site soreness
- Headache
- Fatigue
- Dizziness
- Fainting
- Nausea

Scheller *et al.*, *JAMA* 2015
Vaccine Adverse Event Reporting System (VAERS)

Reduced risk of high grade dysplasia

Denmark : Risk of CIN 2/3 significantly reduced among vaccinated women (Baldur-Felskov)

Scotland : Risk of CIN 1/CIN2/CIN3 reduced by 29%, 50% and 55% in women 20-21 (Pollock)

USA: Estimated vaccine effectiveness for prevention of HPV 16/18 attributable CIN 2+ was 21%-72%, with greater reduction for vaccination >48 mos prior to screening (Hariri)

Australia: 73-93% reduction in genital warts (Garland)

JNCI: Journal of the National Cancer Institute, Volume 106, Issue 3, March 2014, djt460,https://doi.org/10.1093/jnci/djt460

Pollock, K., Kavanagh, K., Potts, A. *et al.* Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland. *Br J Cancer* **111,** 1824–1830

Clinical Therapeutics/Volume 36, Number 1, 2014

S. Hariri et al. / Vaccine 33 (2015) 1608–1613

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Cervical cancer screening recommendations, ACOG, ASCCP, USPSTF

	ACOG[17]	ASCCP[18]	USPSTF[19]
Pap only	Every 3 years	Every 3 years	Every 3 years
Pap-HPV cotest	Every 5 years, age 30–65	Every 5 years, age 30–65	Every 5 years, age 30–65
High-risk HPV only	Every 3 years, age > 25	Every 3 years, age > 25	Every 5 years, age 30–65

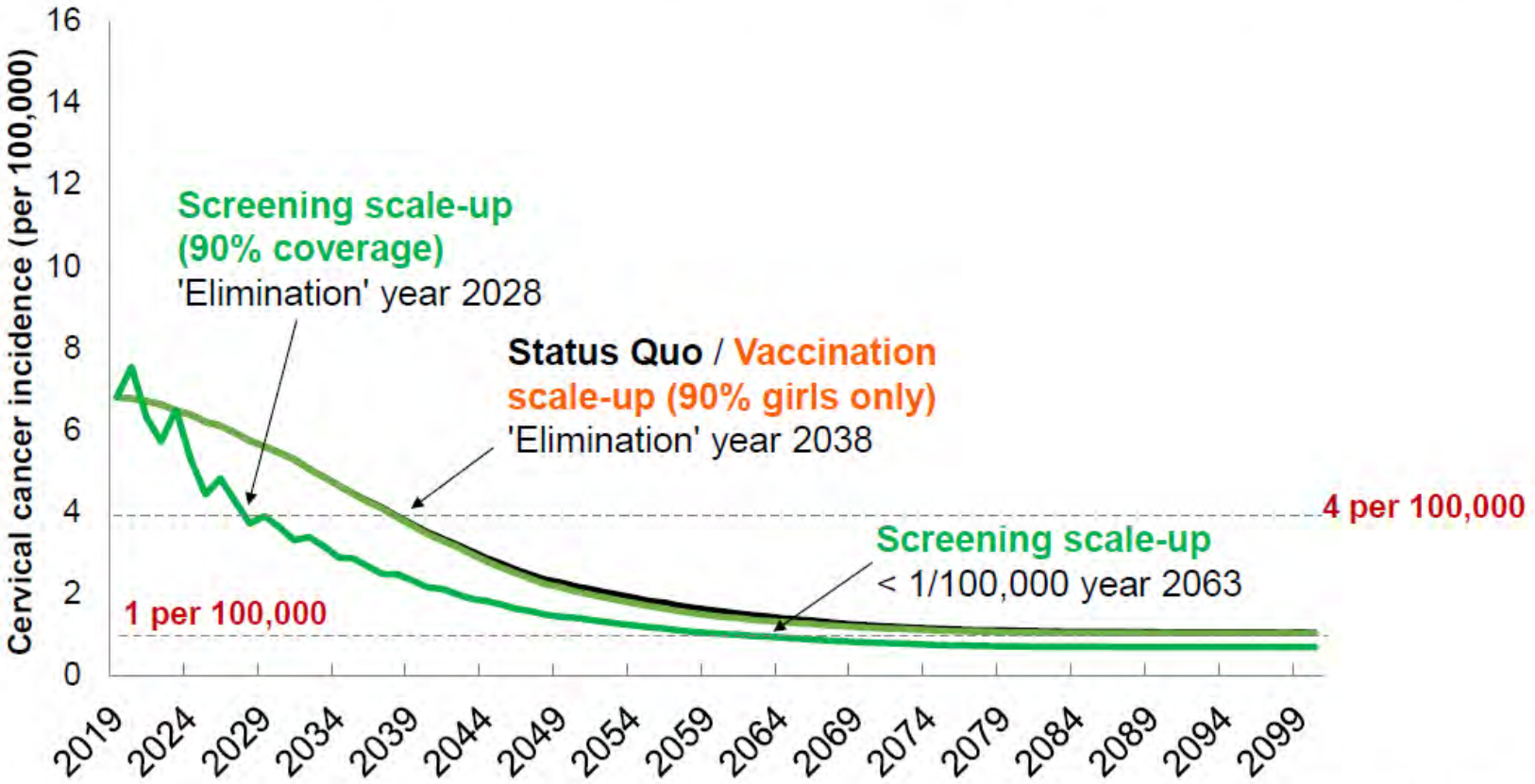
ACOG = American College of Obstetricians and Gynecologists; ASCCP = American Society for Colposcopy and Cervical Pathology; HPV = human papillomavirus; USPSTF = US Preventive Services Task Force

Why We Still Need Screening

- **Poor vaccine uptake…but improving**
- **Existing vaccines do not cover all high-risk HPV types**
- **Vaccines do not treat pre-existing HPV infections**

***Screening will be necessary for the foreseeable future and is still recommended after vaccination**

Cervical cancer incidence in USA will decline more rapidly by increasing screening than by increasing HPV vaccination



Courtesy of Jane Kim, Harvard School of Public Health

Courtesy of D. Lowy, NCI

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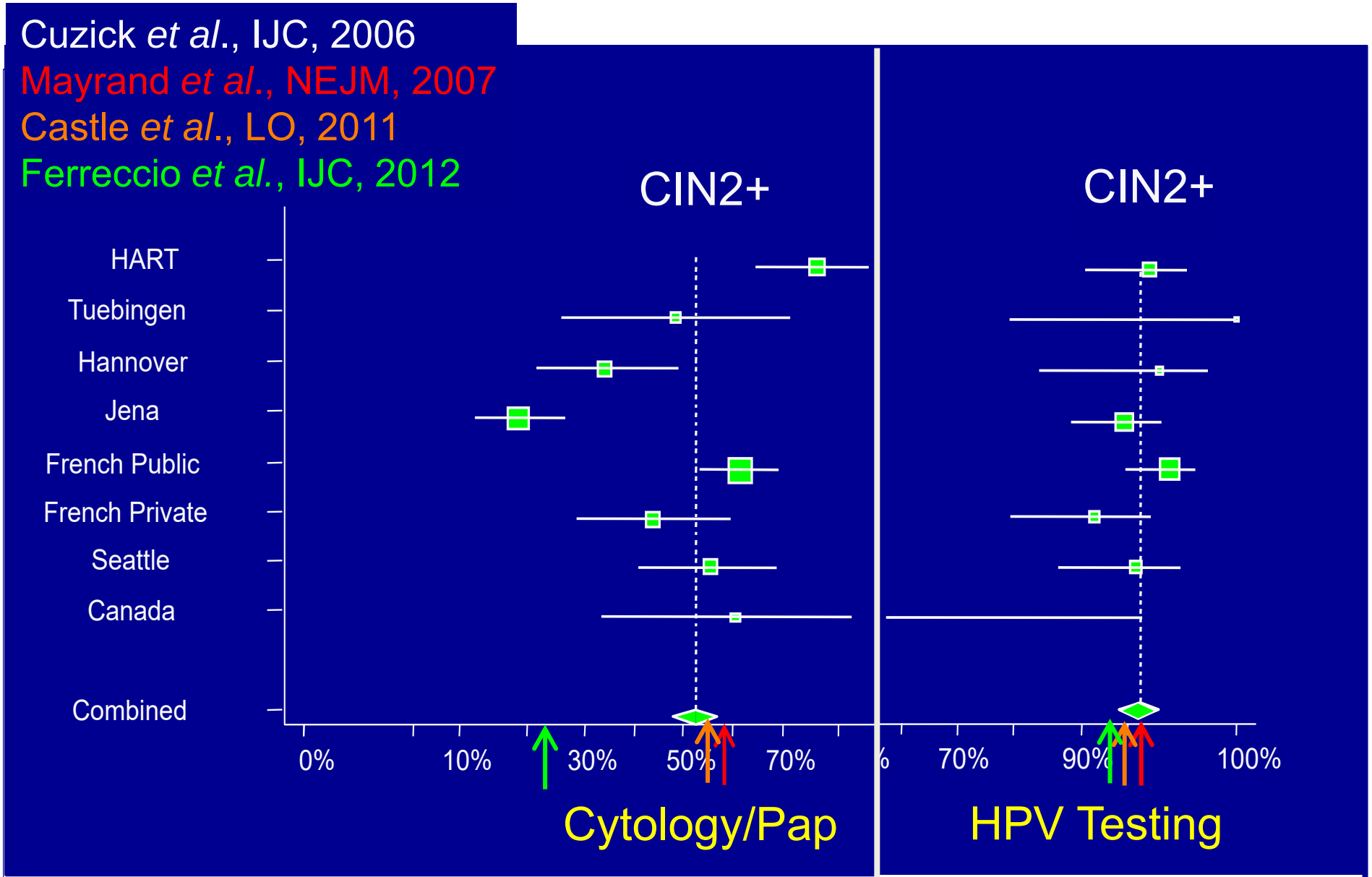
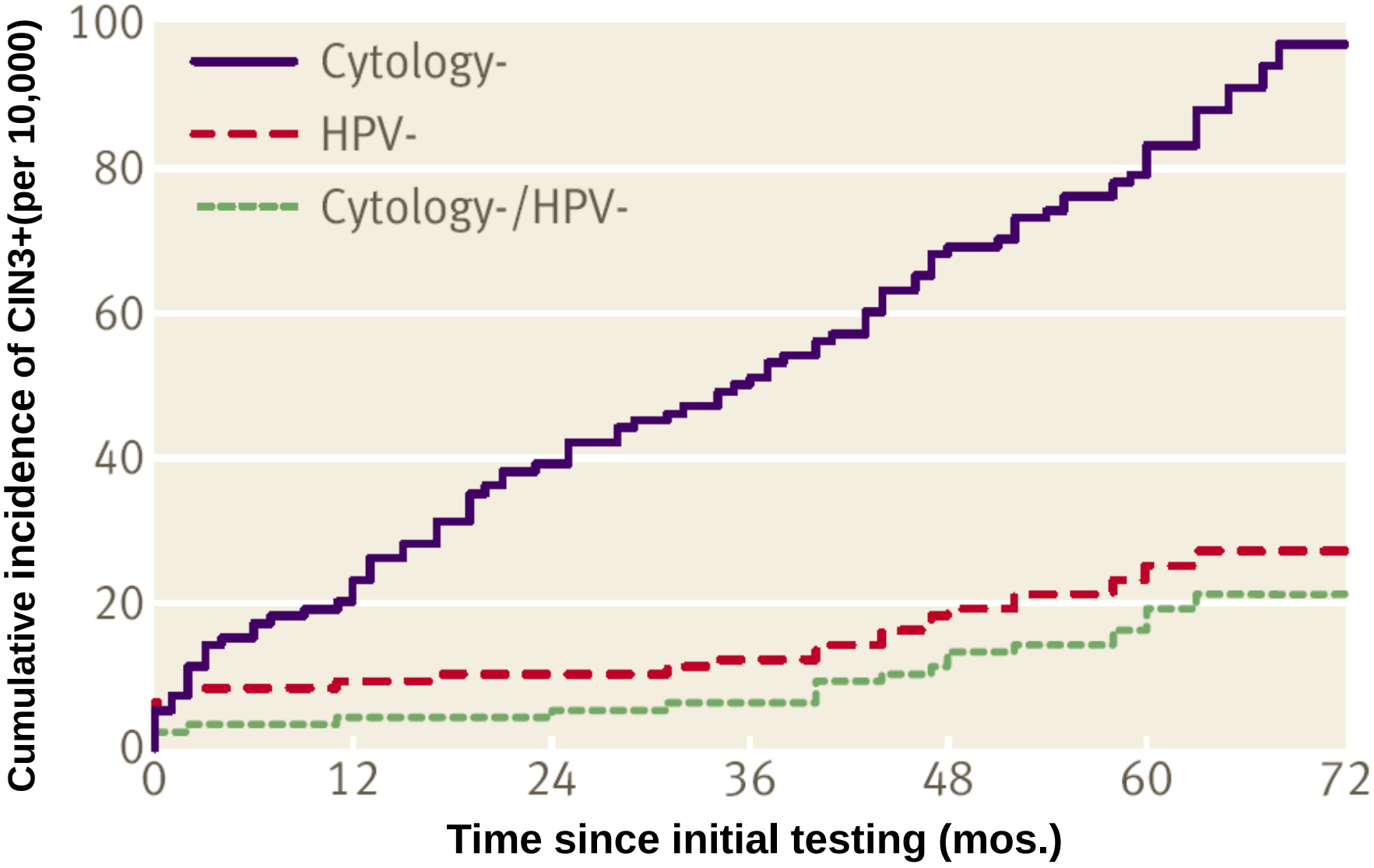
Sensitivity: CIN2+

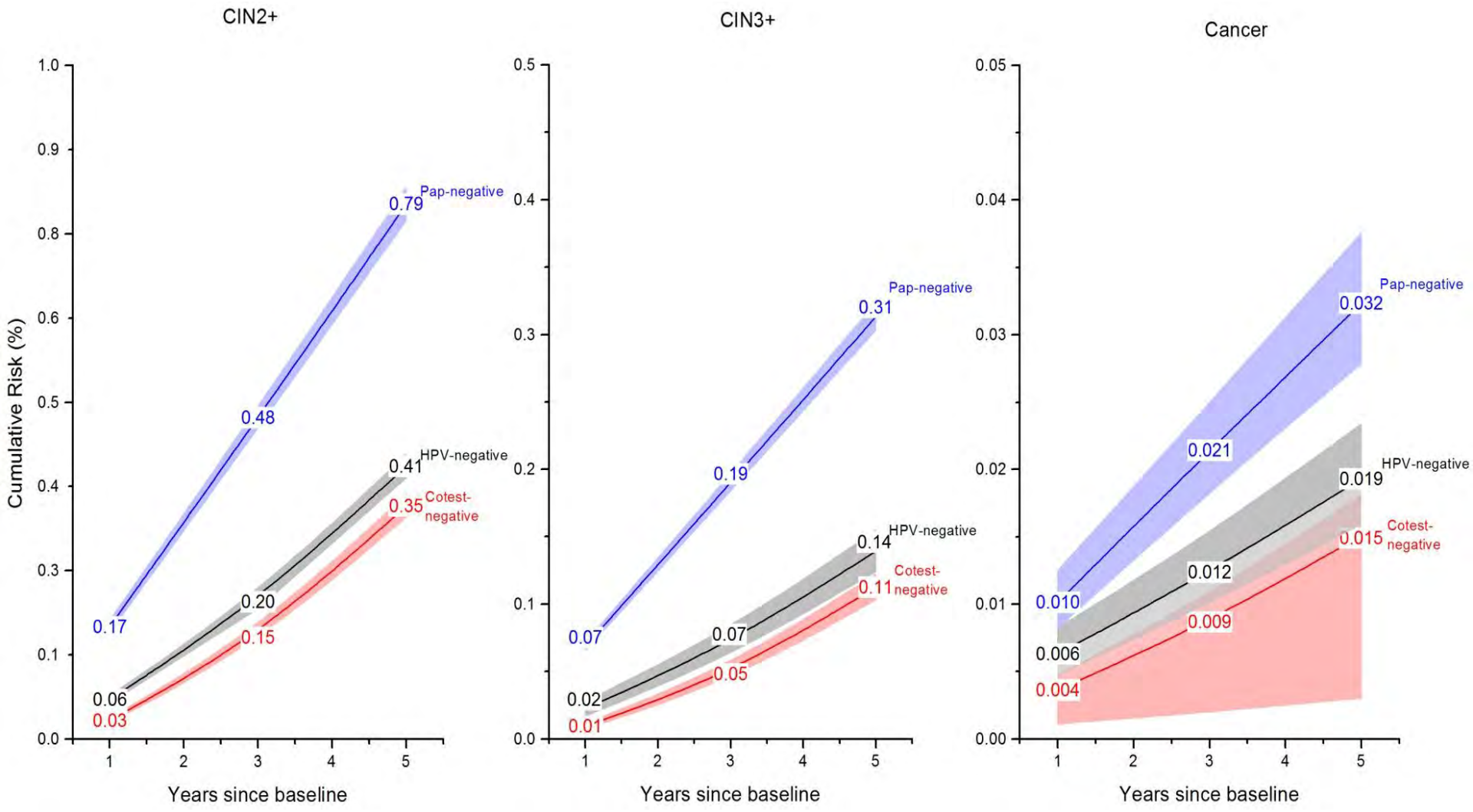


CIN3+ Risk Following a Negative Test



Dillner *et al*., BMJ, 2008

Reassurance Following a Negative Test in 1 Million Women Undergoing Routine Screening



Gage *et al*., JNCI, 2015

May 2018: WHO Director General's call to action to eliminate cervical cancer as public health problem

World Health Organization · UN WOMEN · unicef · UNFPA · UNAIDS · IAEA International Atomic Energy Agency

International Agency for Research on Cancer
World Health Organization

UNODC · Unitaid · The Global Fund · Gavi

CLINTON HEALTH ACCESS INITIATIVE · uicc global cancer control · GHO Global Health Objectives · unfm Université Numérique Francophone Mondiale · NYU Langone Health

World Health Organization

The Architecture to Eliminate Cervical Cancer

Vision: To build a world without cervical cancer

Threshold: < 4 cases of cervical cancer per 100,000 woman-years

2030 CONTROL TARGETS

90%

of girls fully vaccinated with HPV vaccine by 15 years of age

70%

of women screened with an HPV test at 35 and 45 years of age

90%

of women identifed with cervical disease receive treatment for precancerous lesions or invasive cancer

SDG 2030: Target 3.4 – 30% reduction in mortality from cervical cancer

The 2030 targets and elimination threshold are subject to revision depending on the outcomes of the modeling and the WHO approval process

Vaccinate your kids

….they grow up!

THANK YOU

BACK UP SLIDES

Key Output 2: Increased coverage of screening & treatment for pre-cancer lesions

WHO recommendations

- Women aged 30-49 be screeened at least once in their lifetime for cervical cancer, and rescreened every 5 years.
- HIV positive women should be screened every 3 years
- Immediate treatment where possible

Challenges

- *Expensive and complex screen and treat technologies complicate scaling-up*
- *New or optimized service delivery methods required for LMIC contexts*

Accelerators

- **Sufficient, affordable supply of screen and treat technologies & products**
  - Prompt certification of new products
  - Price reductions
- **National scale-up of screen & treat**
  - Simple algorithms need to be introduced for different settings
- **Increased quality and coverage of service delivery**
  - Countries detailed implementation plans to introduce and scale-up products and delivery models
  - Strengthen patient retention and linkage to treatment

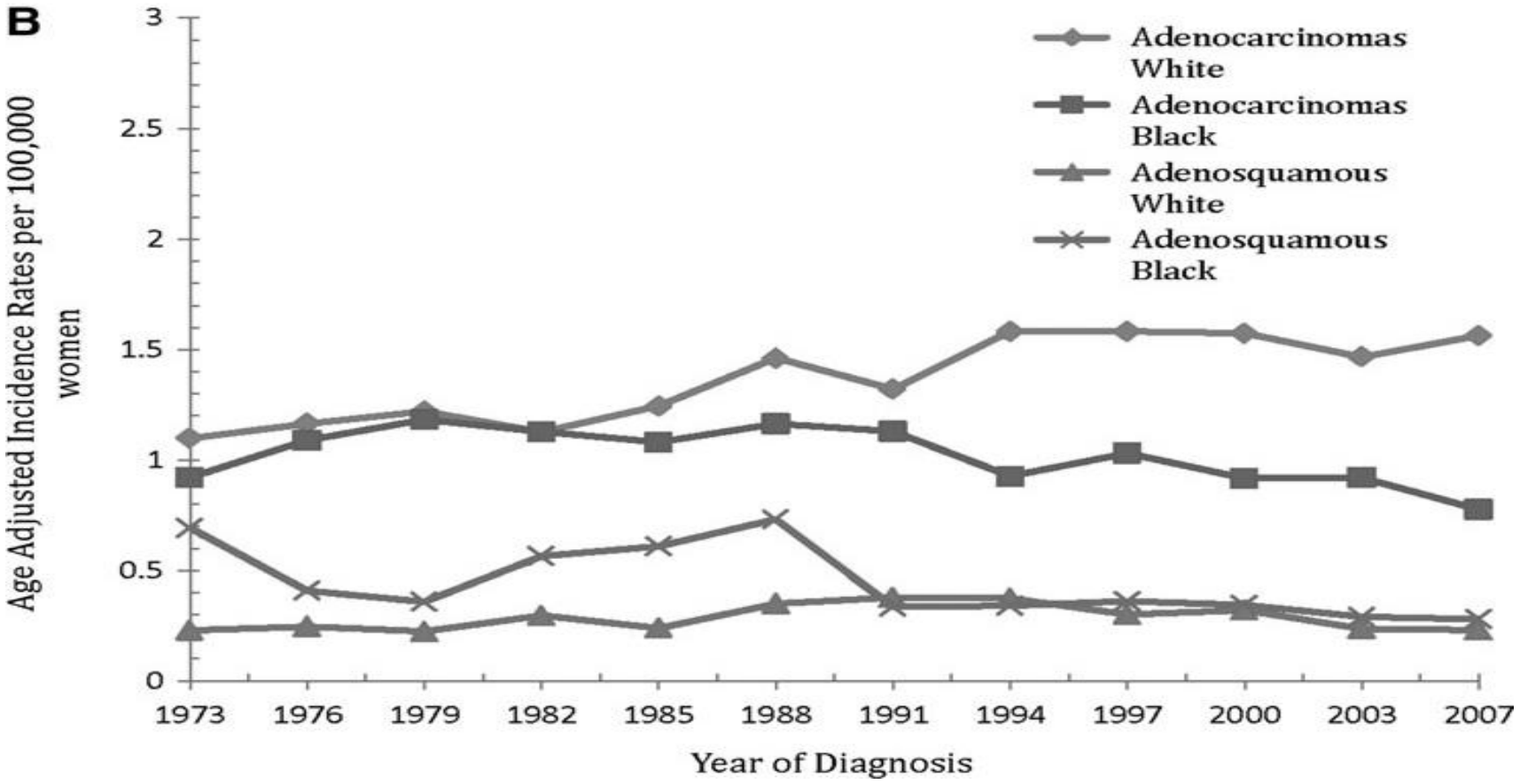
Comparison of Cervical Cancer Screening Tests

	Pap smear (cytology)	VIA	HPV testing
Cost	Moderate ($10-$15/test)	**Low (<$5/test)**	High, but lower in new formats (<$10/test)
Provider	Cytotechnologist and cytopathologist	**Nurses or mid-level providers**	**Lab technician**
Training/QA	++ (Significant)	++ (Significant)	**+ (Limited)**
Sensitivity	60-80%	50-80%	**80-95%**
Specificity	**85-95%**	70-80%	80-90%
Min. # of visits	2	**1**	1-2
Linking screening & treatment	Not possible in same visit	**Immediate treatment possible**	Possible in same visit or on same-day
Home testing	Not possible		**Self sampling possible**
Inter-obs.variation	++ (Significant)		**+ (Minimal)**
Reproducibility	Limited, unless using with digital imaging		**Easily achievable**
Technology	**Open source/public domain**		Proprietary

Sahasrabuddhe et al., Ca Prev Res (2012)

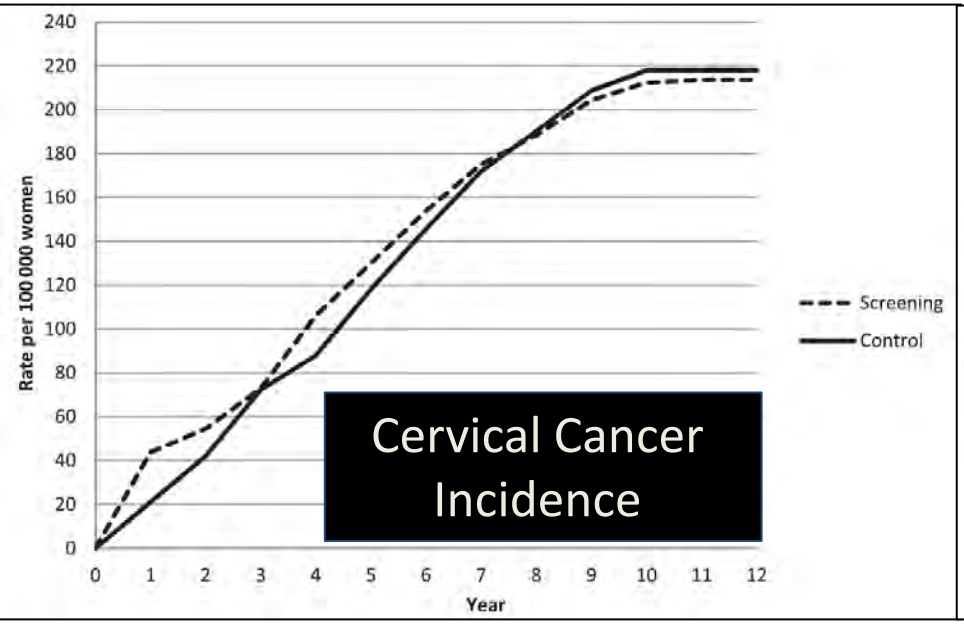
Slide Courtesy of V. Sahasrabuddhe.

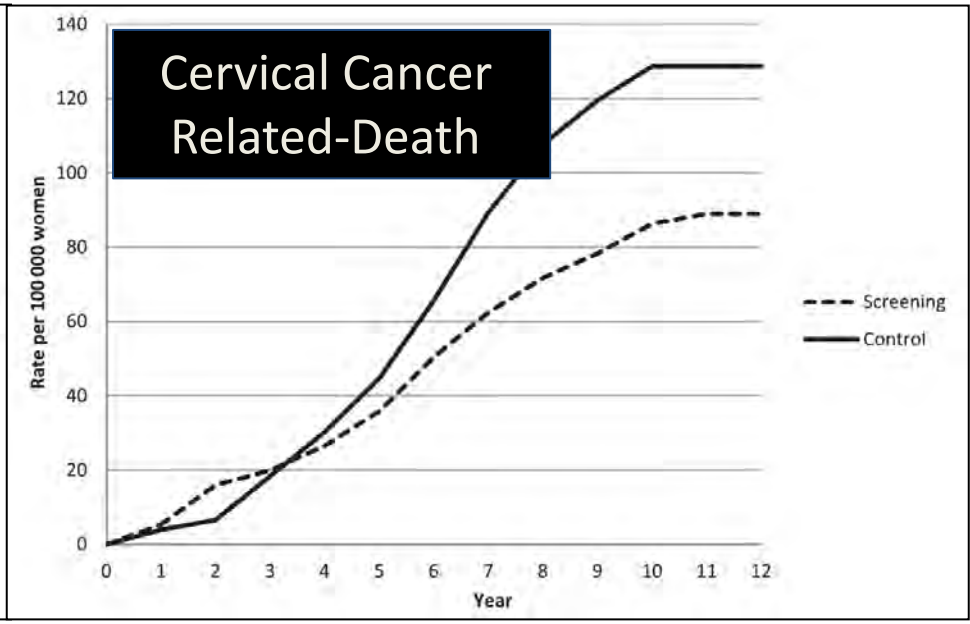
Pap and Adenocarcinomas



Adegoke, J Women's Health 2012

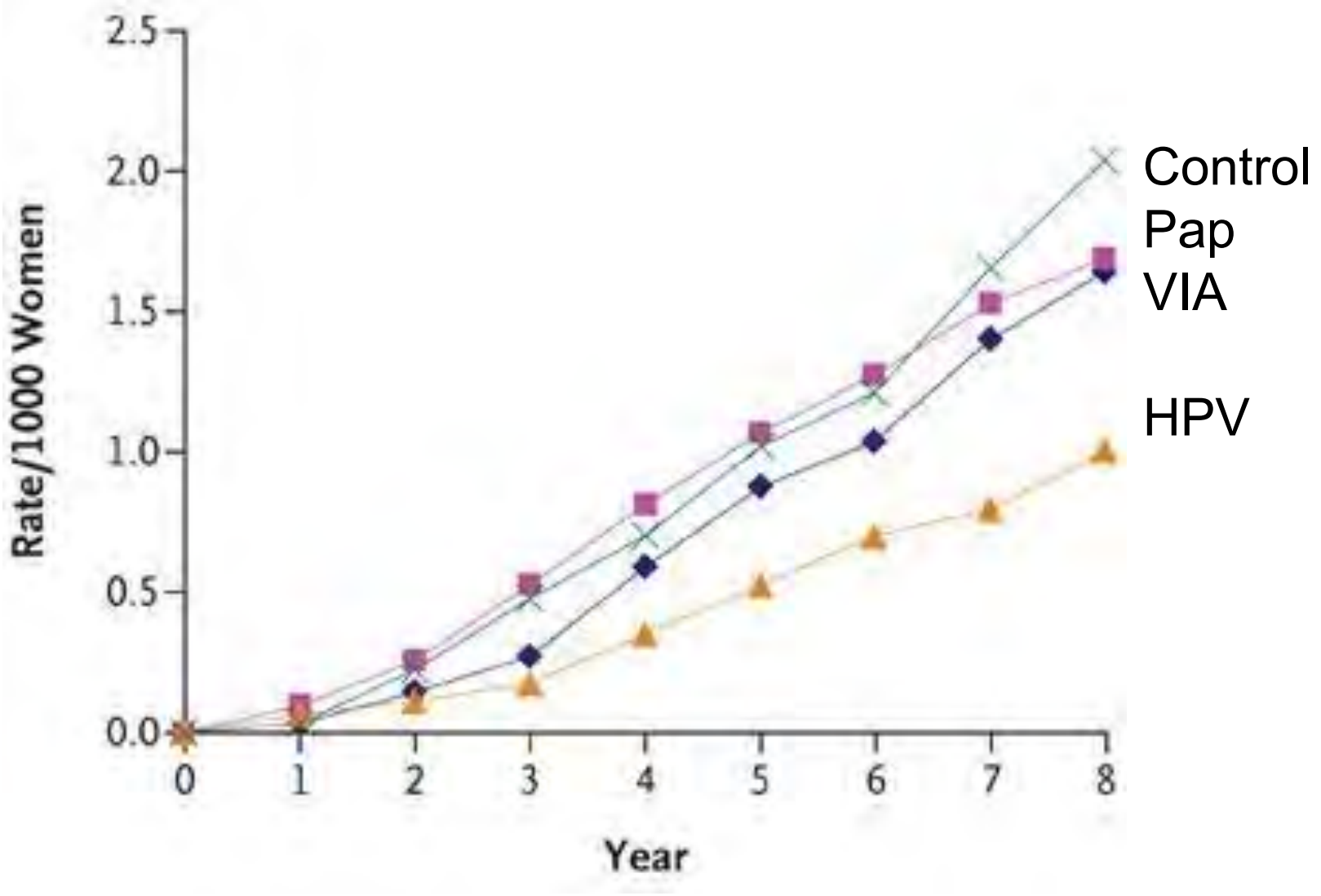
Four Rounds of VIA: Success or Failure?





Shastri *et al*., JNCI, 2014

HPV Testing Reduces the Risk of Cervical Cancer-Related Death in India



Sankaranarayanan *et al*., NEJM, 2009