Recent Updates for HPV Vaccination in Adults

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With thanks to, and slides adapted from:

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& Vice Chair, National HPV Vaccination Roundtable

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Objectives

Understand latest data on HPV vaccine effectiveness and safety in adolescents and adults

Understand new ACIP recommendations and how to approach shared decision-making around HPV vaccination of mid-adults

Review cervical cancer screening recommendations

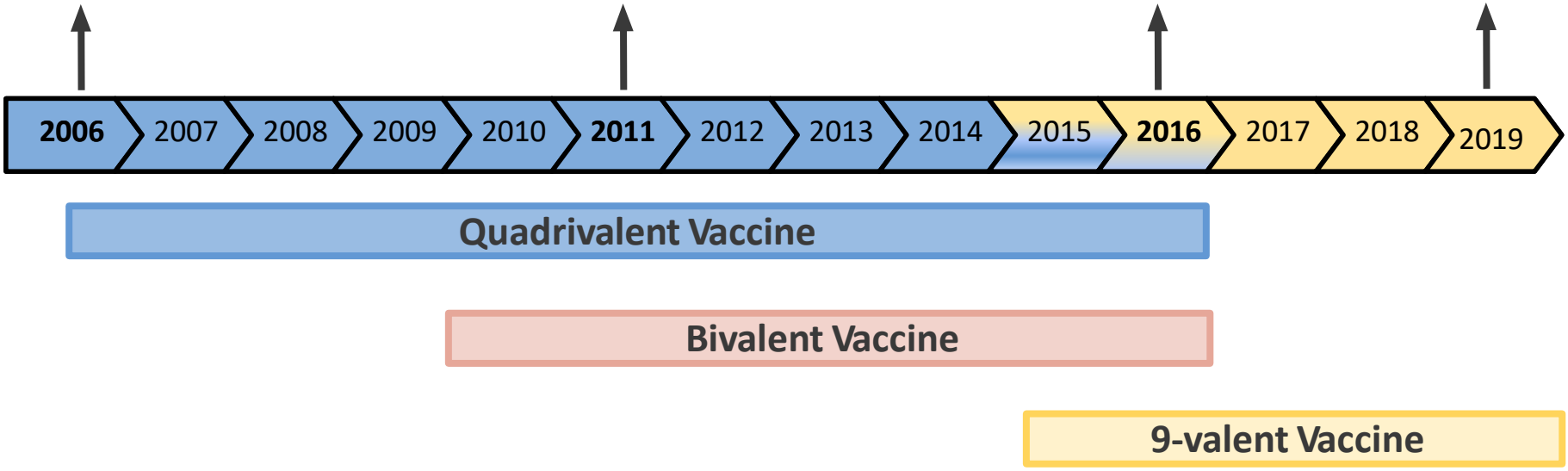
Evolution of HPV vaccination recommendations, vaccine availability and use – United States

Recommendation for Females
Routine: 11 or 12 years
Catch-up: through 26 years
3-dose schedule

Recommendation for Males
Routine: 11 or 12 years
Catch-up: through 21 years
3-dose schedule

2-dose schedule
if first dose age <15 years

Catch-up: through 26
Shared clinical decision-making: some adults 27 through 45 years



Slide credit Dr. Markowitz, CDC

Current ACIP Recommendations on HPV vaccination as of June 2019

- HPV vaccine now ***recommended*** for both males and females through age 26
- Routine age of vaccination remains 11-12
- Vaccination may start at age 9

- ***Individual decision making*** for individuals age 27-45

Recommended number of HPV vaccine doses and dosing schedule, United States

Population	Number of vaccine doses	Interval between doses
Persons initiating vaccination at **9 through 14** years, except immunocompromised persons	2	0, 6–12 months
Persons in the recommended age groups initiating vaccination at **age 15 or older** and persons with immunocompromising conditions	3	0, 1–2, 6 months

- No maximum interval between doses; schedule does not need to be restarted if there is longer than recommended number of months between doses

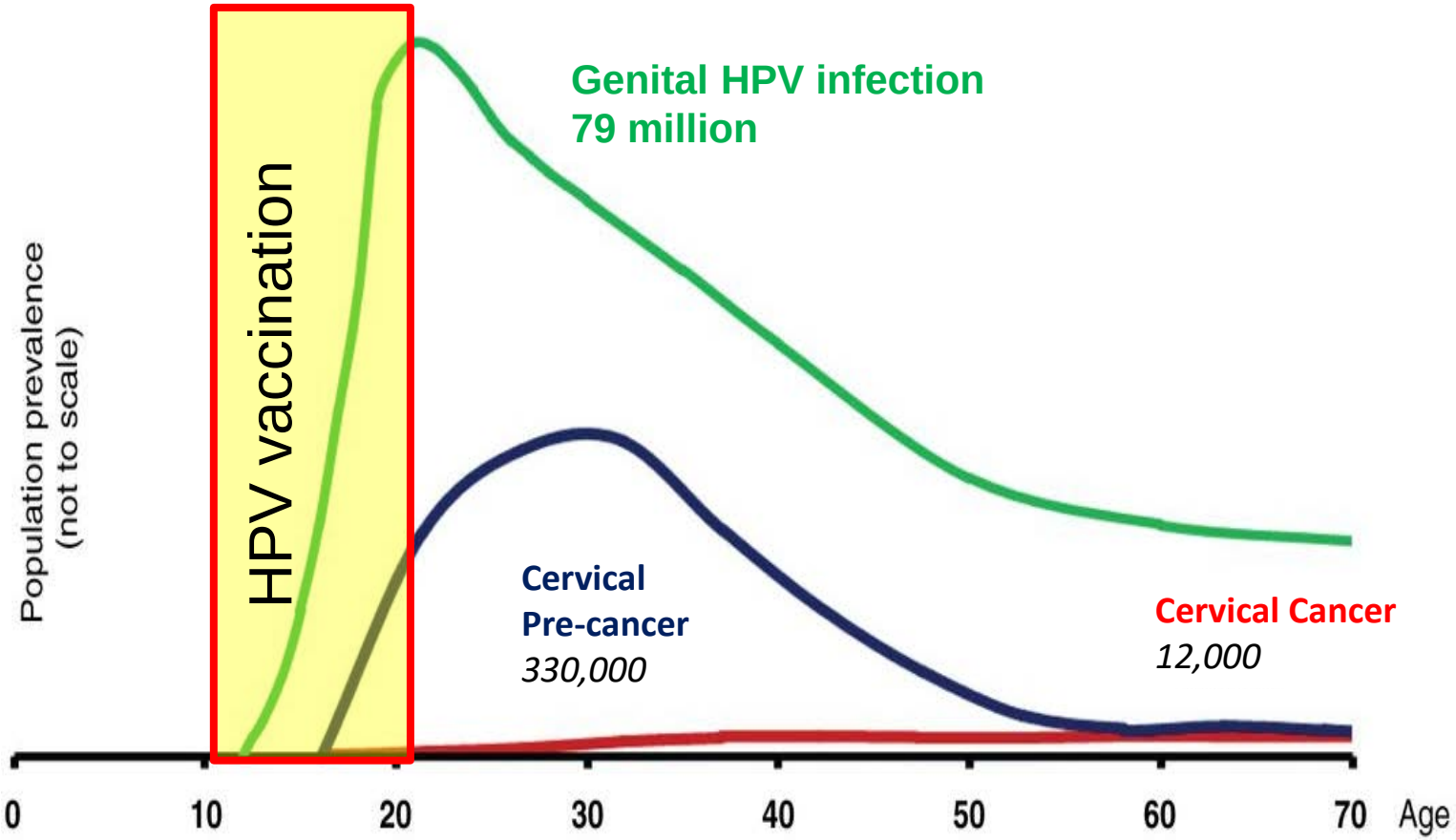
In a 2-dose schedule of HPV vaccine, the minimum interval between first and second doses is 5 months. In a 3-dose schedule of HPV vaccine, the minimum intervals are 4 weeks between the first and second doses, 12 weeks between the second and third doses, and 5 months between the first and third doses

Parents May Ask You:

- Will it work for my child?
- Will it work for me?

National HPV Vaccination Roundtable

HPV Vaccination of Kids Eliminates HPV Infection and the Downstream Consequences

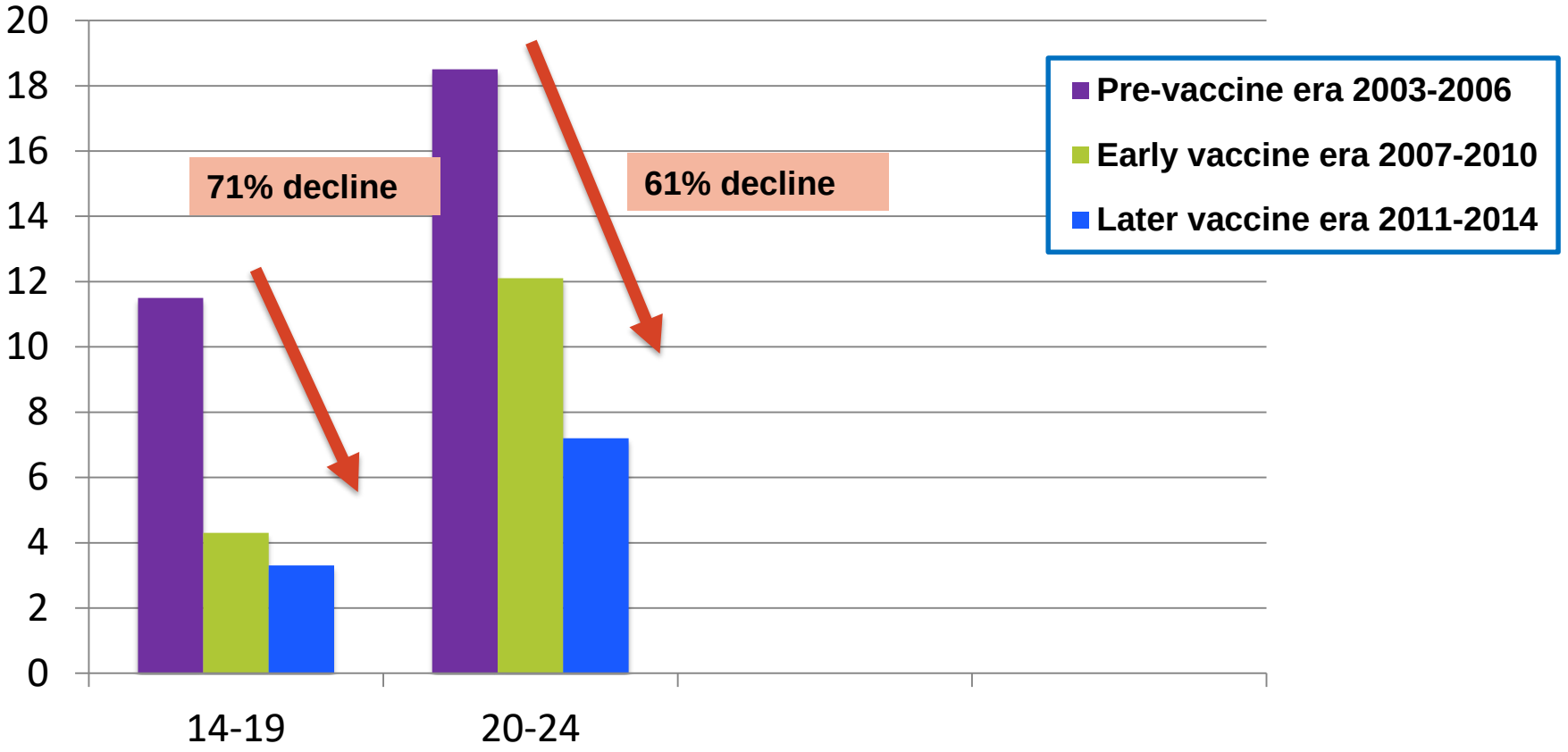


Source: Schiffman M et al., 2013

Powerful evidence of vaccine impact when vaccinating adolescents

Vaccine Type-HPV Infections, US Females

Pre-Vaccine Era, Early Vaccine Era and Later Vaccine Era

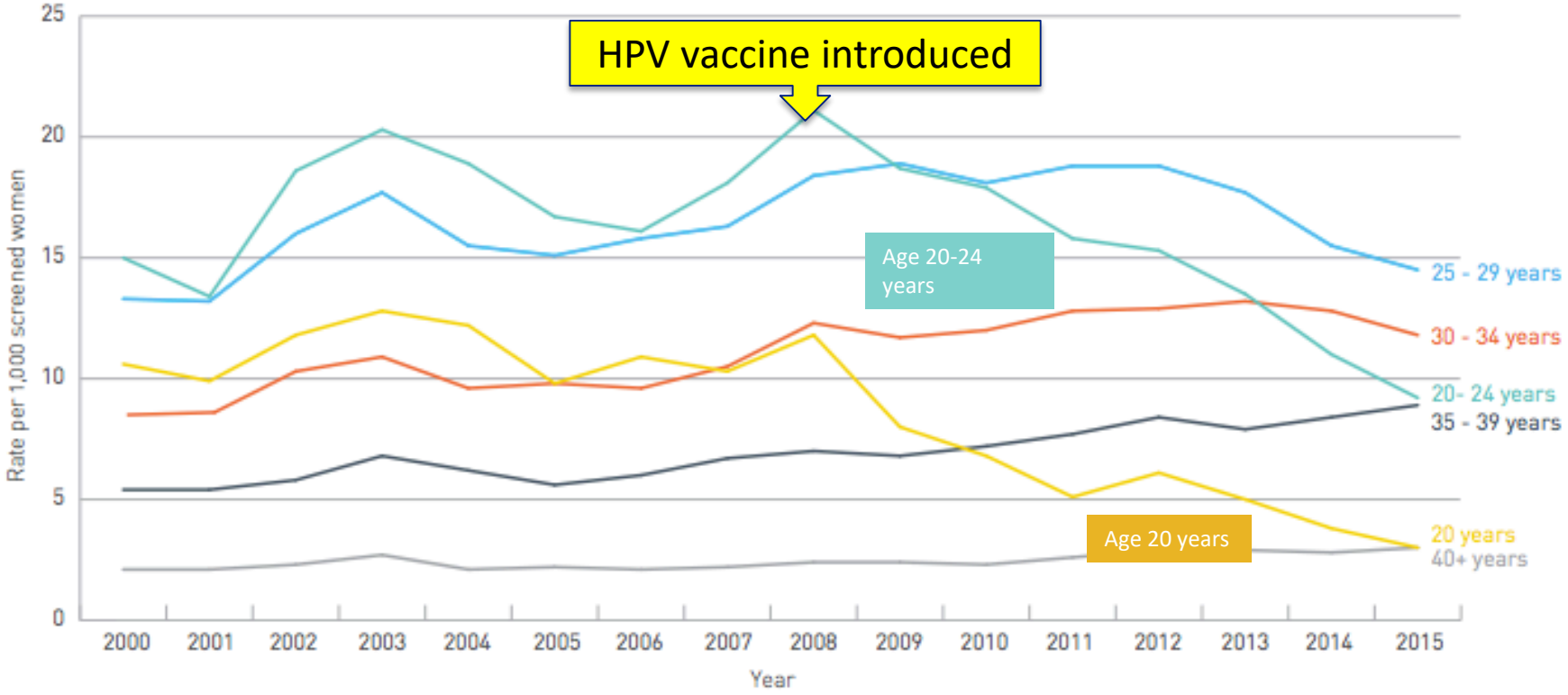


Study also found vaccine type-HPV decreased
89% for vaccinated girls, 34% for unvaccinated girls: herd immunity

Oliver, et al. JID 2017 https://academic.oup.com/jid/article/216/5/594/3892427

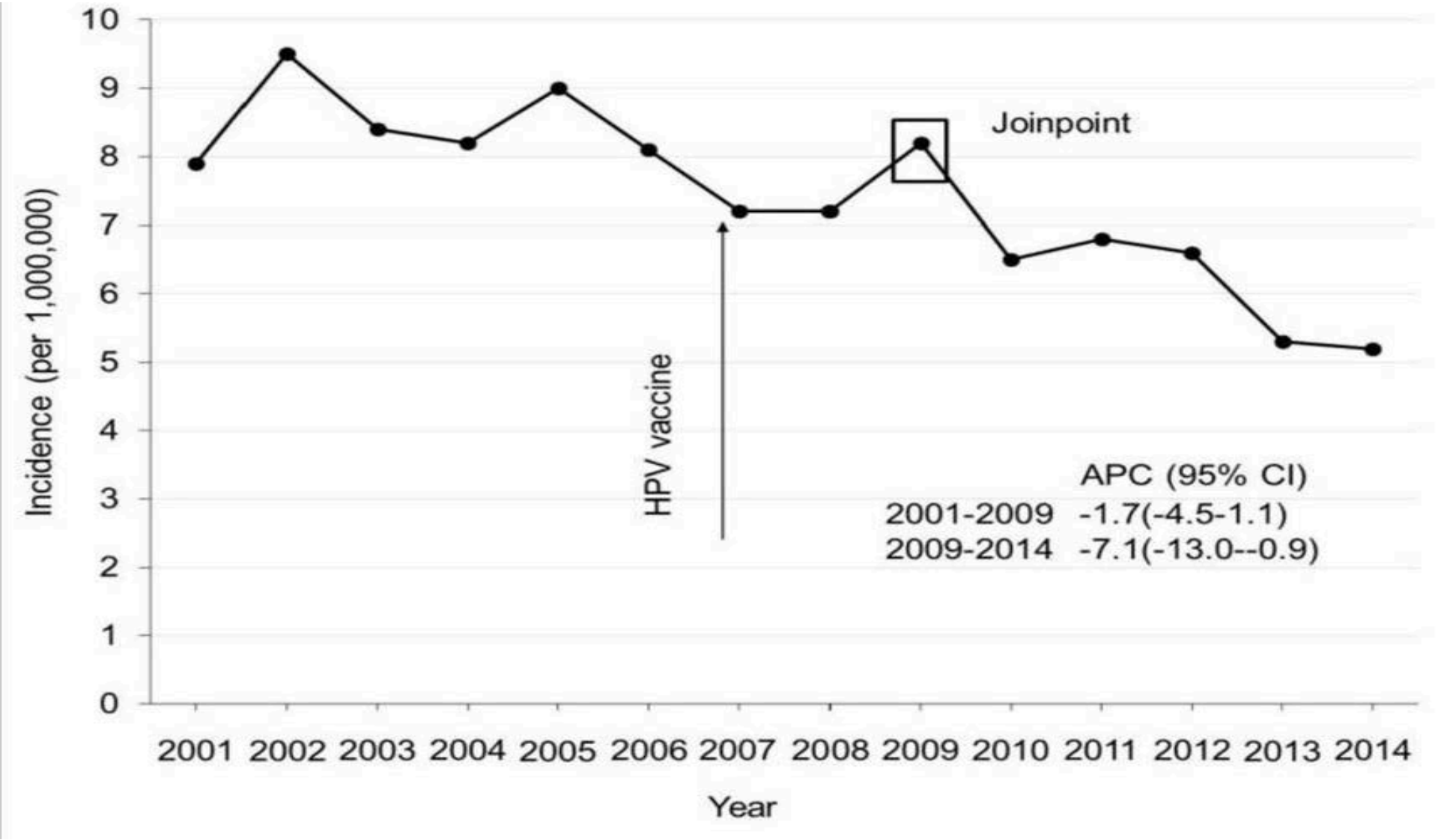
Decline in Pre-cancer in Australia for women ages 18-30

FIGURE 5.2 Trends in high-grade cervical abnormalities (histologically-confirmed) by age, 2000-2015, as recorded on the VCCR.



From the Victorian Cervical Cytology Report, 2015
http://www.vccr.org/site/VCCR/filesystem/documents/dataandresearch/StatisticalReports/17030_VCS_StatsReport15_ART.3.pdf

Decrease in cervical cancer among 15-24 year olds in the US



Guo et al, AJPM, 2018; *Note no decrease for ages 25-34

Early Data: Vaccination Protects Against Invasive HPV-associated Cancers

Data from the Finnish Cancer Registry, Helsinki, Finland

Malignancy	HPV Vaccinated women (65,565 person-years)		Non- vaccinated women (124,245 person-years)	
	N	Rate (95% CI)	N	Rate (95% CI)
Cervix	0	-	8	6.4 (3.1,13)
Vulva	0	-	1	0.8 (0.1, 5.7)
Oropharyngeal	0	-	1	0.8 (0.1, 5.7)
All HPV associated cancers	0	-	10	8.0 (4.3, 15)
Breast	2	3. (0.8,12)	10	8.0 (4.3, 15)
Thyroid	1	1.5 (0.2, 11)	9	7.2 (3.8, 14)
Melanoma	3	4.6 (1.5, 14)	13	10.5 (6.1, 18)
Non-melanoma skin cancer	2	3.0 (0.8, 12)	3	2.4 (0.8, 7.5)

Source: Tapio Luostarinen, et al. Int J Cancer. 2017 Dec 26. doi: 10.1002/ijc.31231. https://www.ncbi.nlm.nih.gov/pubmed/29280138
Letter to editor

Is the HPV vaccine safe?

Yes!

Photo Credit: http://bit.ly/2Ewabb4

HPV Vaccine Long-term Safety Data

- No increase of
  - 2011- anaphylaxis, GBS, stroke, blood clots, appendicitis, or seizures (than unvaccinated or who received other vaccines)
  - 2013 –Blood clots or adverse events related to the immune system & central nervous system (almost 1 million girls)
  - 2014 – Venous thromboembolism or blood clots (>1 million women)
  - 2012 & 2014 – Autoimmune disorders
  - 2015 – Multiple sclerosis or other demyelinating diseases
  - 2018- Primary ovarian insufficiency, rheumatologic conditions
- And over 60 other conditions

Gee et al., 2016; Cameron et al, 2016; Chao et al., 2011; Suragh et al., 2018; Wise et al, 2018

Current ACIP Recommendations on HPV vaccination as of June 2019

- HPV vaccine now ***recommended*** for both males and females through age 26
- Routine age of vaccination remains 11-12
- Vaccination may start at age 9

- ***Individual decision making*** for individuals age 27-45

FDA: Approves vaccines

ACIP: Recommends vaccination

FDA Approval is based on:

- Safety
- Efficacy (in a clinical trial setting)

ACIP Recommendation also considers:

- Disease burden
- Effectiveness (in a real world setting)
- Cost-effectiveness

National HPV Vaccination Roundtable

Licensure of 9vHPV for use in expanded age range

FDA Summary Basis for Regulatory Action

- Results of a randomized, double-blind, placebo-controlled trial (base study) of 4vHPV that included women aged 27–45 years
- Observational follow-up through 10 years in a subset of women in the base study
- A cross-study immunogenicity analysis showing non-inferiority of immune responses to 4vHPV in males aged 27–45 years vs aged 16–26 years
- Extrapolation of data to 9vHPV in individuals aged 27–45 years

Munoz et al. Lancet 2009; Castellsague et al. Br J Cancer 2011 (end of study results); Luna et al. PLoS One 2013 (6 year follow-up); Luxembourg (10 year follow-up presented at ACIP June 2018); Giuliano et al. Vaccine 2015; Giuliano et al. N Engl J Med 2011; Palefsky et al. N Engl J Med 2011

https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM622941.pdf

Slide credit Dr. Markowitz, CDC

HPV vaccines licensed and age ranges, United States (FDA)

Since October 2018

Vaccine	HPV types	Licensure ages
Bivalent (2vHPV)	16,18	Females 9–25 yrs
Quadrivalent (4vHPV)	6,11,16,18	Females and males 9–26 yrs
9-valent (9vHPV)	6,11,16,18, 31,33,45,52,58	Females and males 9–45 yrs

- After the end of 2016, only 9vHPV has been distributed in the United States
- HPV vaccines have been licensed through age 45 years or older in other countries

Slide credit Dr. Markowitz, CDC

Efficacy

the percent reduction in disease incidence in a vaccinated group compared with an unvaccinated control group under experimental conditions

Example conditions: ≤6 lifetime sex partners, no HPV or antibodies detected

vs. Effectiveness

the reduction in disease outcomes in a “real world” setting

National HPV Vaccination Roundtable

How did ACIP decide on individual decision-making?

Types of ACIP recommendations

ACIP does not recommend the intervention	ACIP recommends intervention for individuals based on shared clinical decision-making	ACIP recommends the intervention
Vaccination is not recommended	Recommendation relies upon guidance of clinician in the context of individual clinician-patient interactions to determine whether or not vaccination is appropriate for a patient	Vaccination recommended for all persons in the age group or group at increased risk for vaccine preventable disease

https://www.cdc.gov/vaccines/acip/recs/grade/etr.html

Slide credit Dr. Markowitz, CDC

Changing ACIP terminology over time for similar type of recommendation

Permissive Recommendation	Category B Rec/ Clinical Decision Making	Shared Clinical Decision-Making
▪ 2009 HPV vaccine for boys	▪ 2015 Men B for adolescents and young adults	▪ 2019 HPV vaccine for adults age 27-45 years
"HPV4 may be given to males aged 9 through 26 years…"	"…adolescents and young adults may be vaccinated with a serogroup B meningococcal (MenB) vaccine…"	"…shared clinical decision-making regarding HPV vaccination is recommended for some adults aged 27 through 45 years who are not adequately vaccinated"

Slide credit Dr. Markowitz, CDC

Routine HPV vaccination of adults 27 through 45 years was not brought to ACIP for consideration

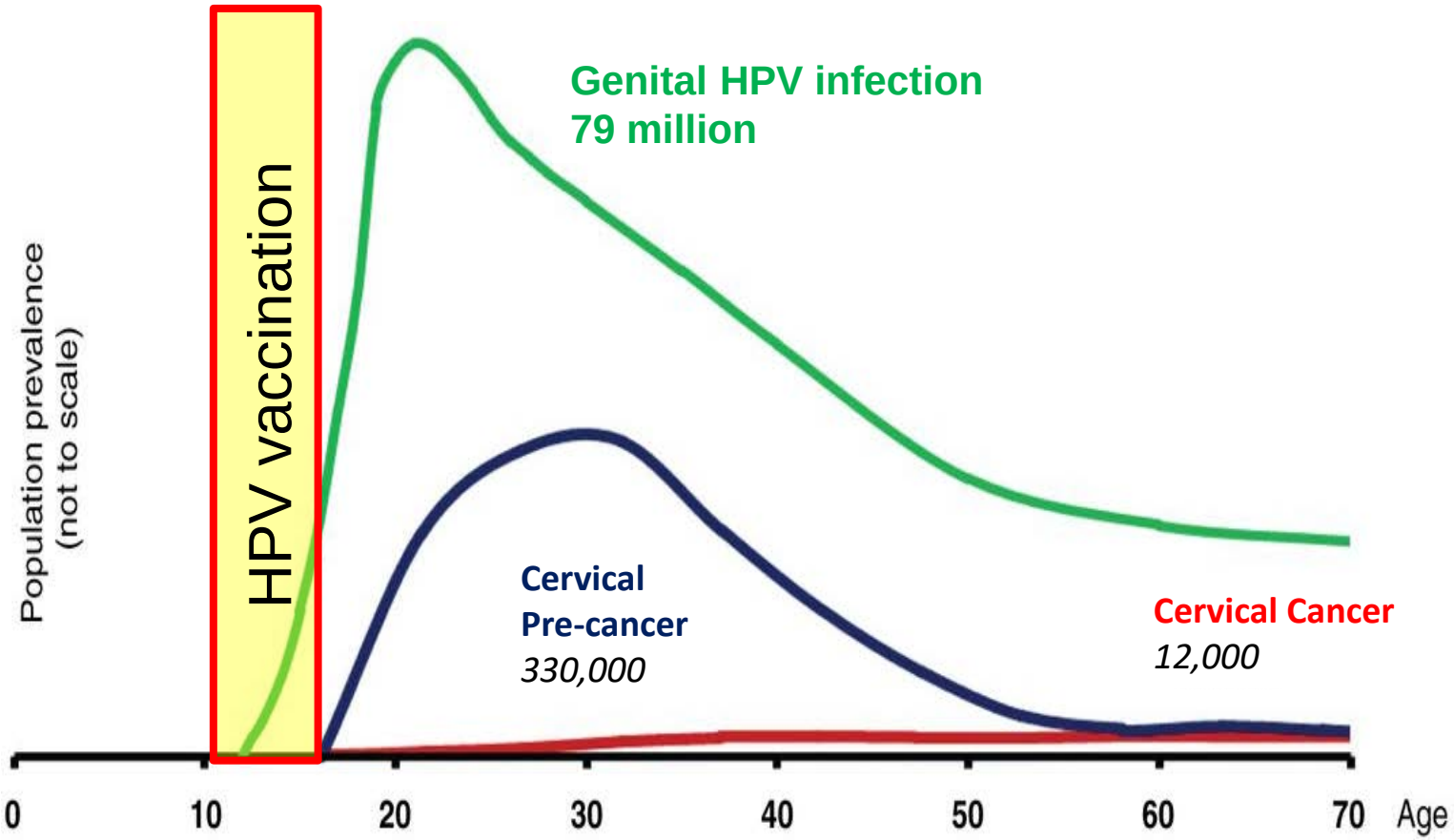
ACIP does not recommend the intervention	ACIP recommends intervention for individuals based on shared clinical decision-making	~~ACIP recommends the intervention~~
Vaccination is not recommended	Recommendation relies upon guidance of clinician in the context of individual clinician-patient interactions to determine whether or not vaccination is appropriate for a patient	~~Vaccination recommended for all persons in the age group or group at increased risk for vaccine preventable disease~~

https://www.cdc.gov/vaccines/acip/recs/grade/etr.html

Slide credit Dr. Markowitz, CDC

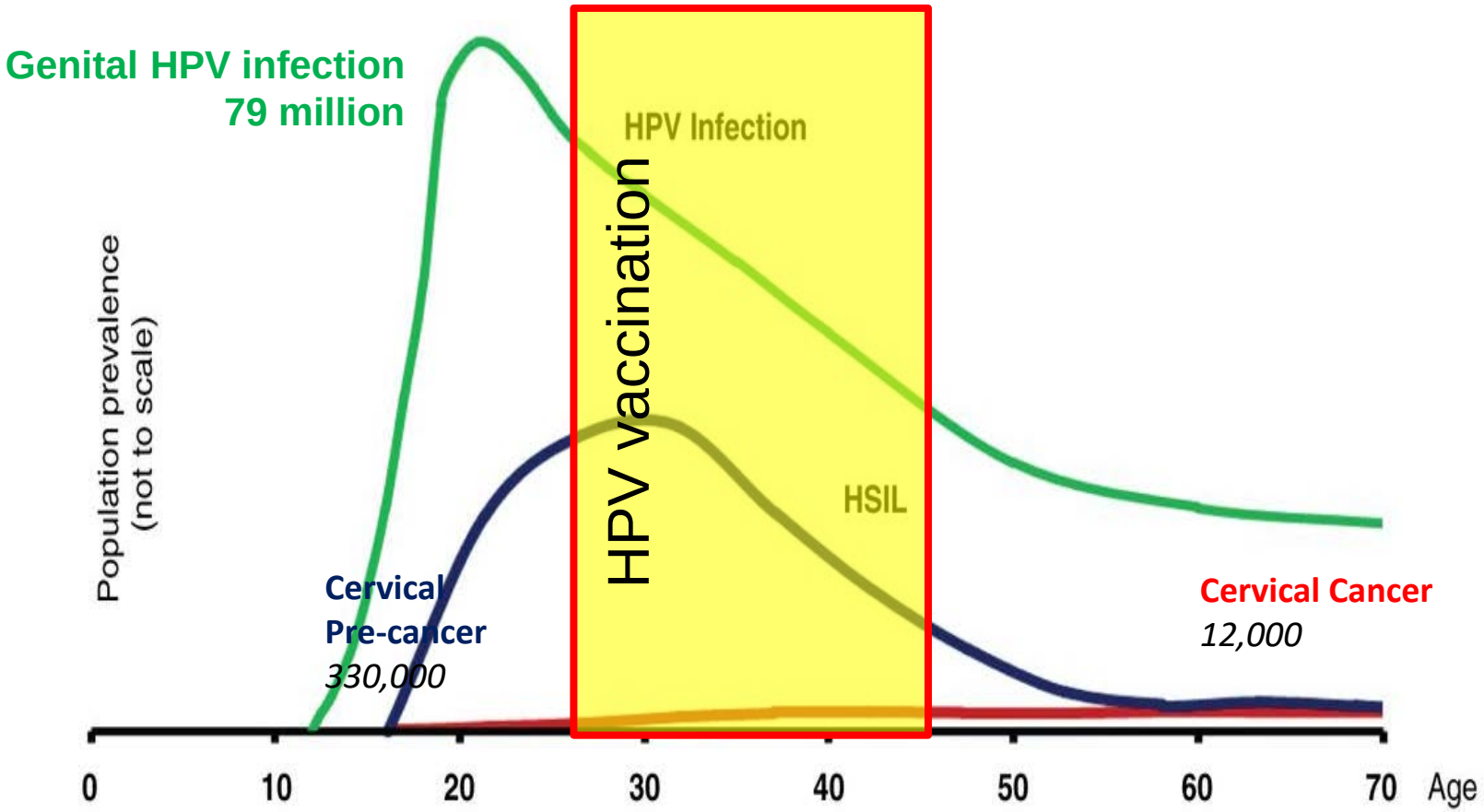
Why was routine recommendation not a consideration?

Vaccination of kids happens before infection



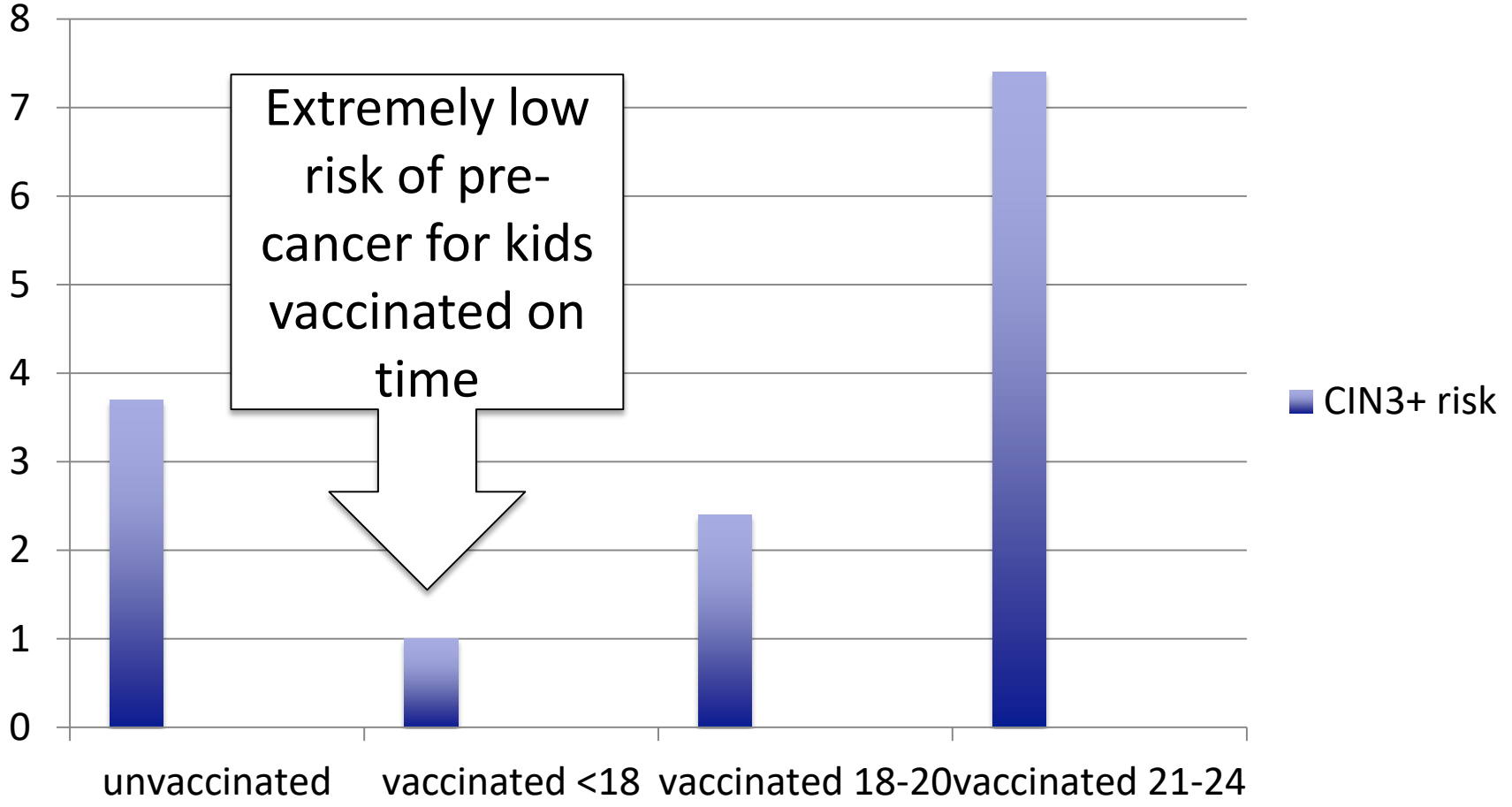
Source: Schiffman M et al., 2013

Vaccination of adults happens after infection



Source: Schiffman M et al., 2013

HPV vaccination works REALLY WELL for kids….
…. but less well after age 18



Castle, Prev Med, 2018, Kaiser Permanente Northern California

National HPV Vaccination Roundtable

Evidence: Effectiveness by age

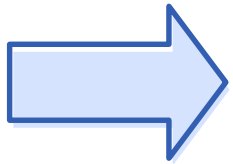
- 11 studies from 6 countries
- Endpoints: pre-cancer, genital warts, HPV infection
- In all studies, vaccine effectiveness decreased with age
- 2/3 of studies did not show effectiveness for women over age 20

National HPV Vaccination Roundtable

ACIP uses *Evidence to Recommendations* framework

Evidence to Recommendations Framework

- PICO question and background
- Problem
- Benefits and harms
- Values
- Acceptability
- Resource use
- Feasibility of implementation
- Balance of consequences
- Type of recommendation and recommendation text



Recommendation options

PICO: population, intervention, comparison, outcomes

https://www.cdc.gov/vaccines/acip/recs/grade/downloads/ACIP-evidence-rec-frame-508.pdf

Slide credit Dr. Markowitz, CDC

Understanding the burden of disease due to incident HPV infection in adults

- HPV incidence highest in late teens and early twenties
- New HPV infections do occur in mid-adults
  - New partner is risk factor; new partners decrease with increasing age
- Epidemiology of HPV infection differs for males and females
- Some uncertainty about immunity after clearance of natural infection
  - Immunity thought to be low; higher for females than males
- Progression to cancer occurs over years/decades
  - Some high risk HPV types more likely to progress to cancer

Rodriquez et al. JNCI 2010; Winer et al. CEBP 2011; Winer JID 2016; Beachler et al. JID 2016; Kahn et al. JNCI 2005; Giuliano et al. Int J Cancer 2015

Slide credit Dr. Markowitz, CDC

Evidence to Recommendations: Benefits and Harms

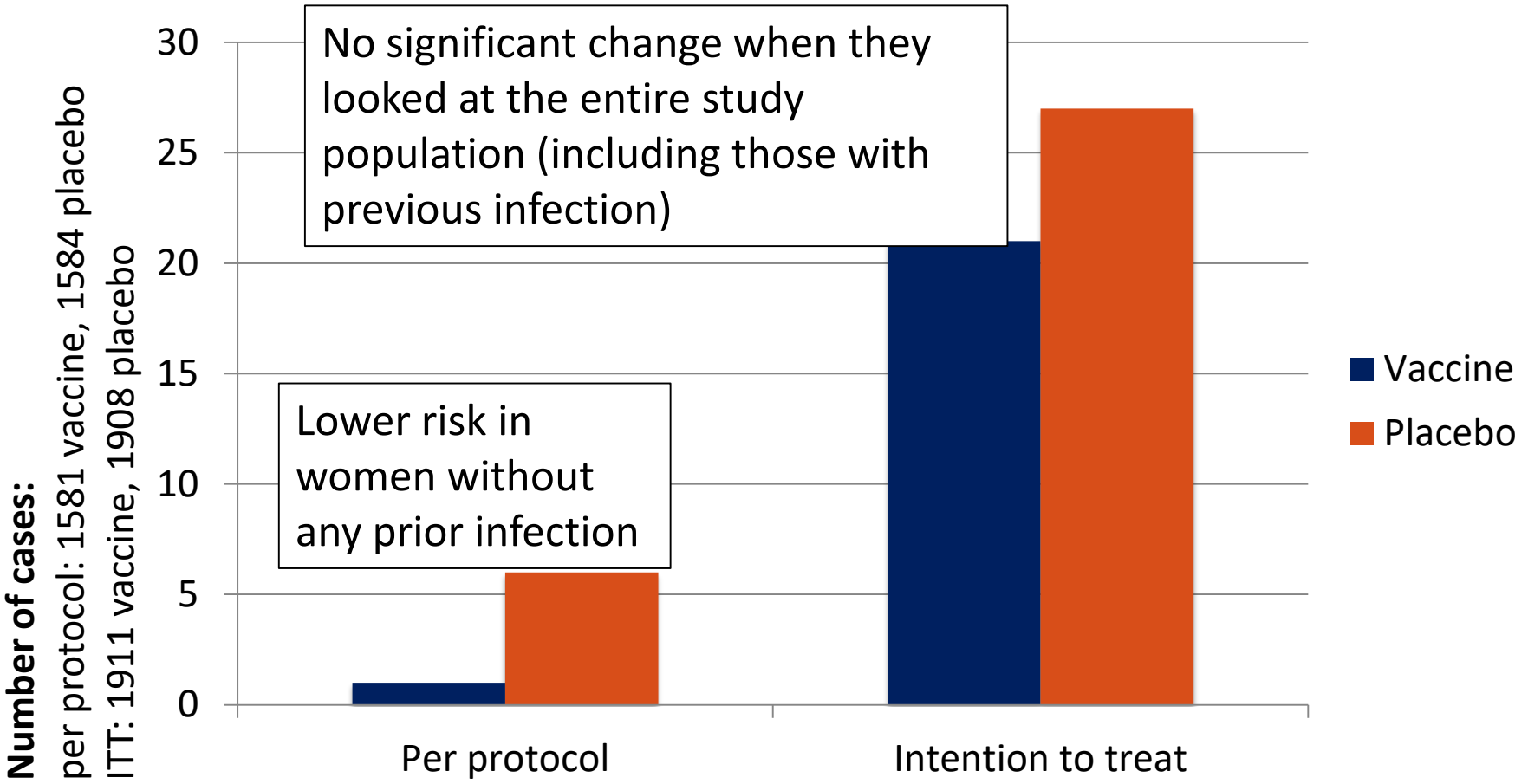
- 4vHPV efficacy trial in women ages 24–45 years (n=3,819)
  - Efficacy against endpoint of persistent HPV infection, extragenital lesions, CIN1+ (*not limited to precancer*)
    - Per-protocol efficacy: **88.7%** (95% CI: 78.1–94.8)
    - Intention-to-treat efficacy: **47.2%** (95% CI: 33.5–58.2)

- 9vHPV immunogenicity trial in women ages 27–45 years (n=640)
  - Antibody titers non-inferior compared to women ages 16–26 years
  - >99% of women in both age groups seroconverted to all 9vHPV types

Castellsagué X et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. Br J Cancer 2011
Luxembourg A. 9vHPV immunogenicity and safety trial in mid-adult females. Presentation to ACIP, Atlanta, GA. June 26, 2019.
CIN, cervical intraepithelial neoplasia

Slide credit Dr. Markowitz, CDC

Few cases of Cervical Pre-cancer Prevented by Vaccination in 27-45 Year-Old Women



Source: Castellague et al. Br J Cancer, 2011

Evidence to Recommendations: Benefits and Harms

- Evidence on benefits:
  - Efficacy: 3 RCTs of 4vHPV and/or 2vHPV
  - Immunogenicity: 3 RCTs, 6 observational trials
- Evidence on harms:
  - Safety: 5 RCTs, 4 observational trials

GRADE for HPV Vaccination of Mid-Adults http://www.cdc.gov/vaccines/acip/recs/grade/table-refs.html.

RCTs, randomized controlled trials

Evidence to Recommendations: Resource use

- **5 health economic models of HPV vaccination in the U.S. were reviewed**
  - The cost-effectiveness ratio for the HPV vaccination ages 9-26 ranged from cost-saving to about $35,000 per QALY gained
  - In the context of the existing program, expanding vaccination through age 30, 35, 40 or 45 years would provide relatively small additional health benefits
  - The incremental cost per QALY for also vaccinating adults through age 30 years exceeded $300,000 in 4 of 5 models
  - Variation in results across models was due to factors such as uncertainties about HPV natural history

QALY, quality-adjusted life year

Chesson HW. Overview of Health Economic Models for HPV Vaccination of Mid-Adults. Presentation to ACIP, Atlanta, GA. June 2019.

Estimated number needed to vaccinate

- HPV vaccines are most effective when given before exposure to HPV
- Population benefit would be minimal, yet some individuals in this age range might be able to benefit from vaccination
- Estimated number needed to vaccinate to prevent one case of **anogenital warts, cervical precancer, or cancer**, is:

Vaccinating ages 9-26	Vaccinating through age 45 years
9, 22, and 202	**120, 800, and 6,500**

Cervical precancer is CIN2+

NNV results from HPV-ADVISE, per Chesson HW, Overview of Health Economic Models for HPV Vaccination of Mid-Adults, presentation to ACIP, June 2019

Slide adapted from Dr. Markowitz, CDC

Burden of Disease

- Vaccinating through age 26
  - Estimated to prevent **25,000** HPV-related cancers annually

- Vaccinating through age 45
  - Estimated to prevent only 193 more cancers

ACIP Public hearings, 2018

National HPV Vaccination Roundtable

Shared clinical decision-making

- Shared clinical decision making category addresses situations where
  - vaccination may benefit some individuals, but
  - ***will have relatively minimal population-level impact***

Identifying who may benefit from vaccination is not always straight forward

Slide credit Dr. Markowitz, CDC

Shared clinical decision-making for HPV vaccination of adults age 27 through 45 years

- **HPV vaccination does not need to be discussed with most adults aged >26 years**
- For adults aged 27 through 45 years who are not adequately vaccinated, clinicians can consider discussing HPV vaccination with persons who are most likely to benefit
- Ideally, vaccination should be given in early adolescence because vaccination is most effective before exposure to HPV through sexual activity

MMWR 2019; 68; 698-702

Slide credit Dr. Markowitz, CDC

Considerations for shared clinical decision-making for HPV vaccination of adults age 27 through 45 years

- HPV is a very common sexually transmitted infection. Most HPV infections are transient and asymptomatic and cause no clinical problems.

- Although new HPV infections are most commonly acquired in adolescence and young adulthood, some adults are at risk for acquiring new HPV infections. At any age, having a new sex partner is a risk factor for acquiring a new HPV infection.

MMWR 2019; 68; 698-702

Slide credit Dr. Markowitz, CDC

Considerations for shared clinical decision-making for HPV vaccination of adults age 27 through 45 years

- Persons who are in a long-term, mutually monogamous sexual partnership are not likely to acquire a new HPV infection.
  - "New" infections are most likely reactivations in this situation
- Most sexually active adults have been exposed to some HPV types, although not necessarily all of the HPV types targeted by vaccination.
- No clinical antibody test can determine whether a person is already immune or still susceptible to any given HPV type.

MMWR 2019; 68; 698-702; FuTC et al, Int J Cancer 2016

Slide adapted from Dr. Markowitz, CDC

Considerations for shared clinical decision-making for HPV vaccination of adults age 27 through 45 years (con't)

- HPV vaccine efficacy is high among persons who have not been exposed to vaccine-type HPV before vaccination.
- Vaccine effectiveness might be low among persons with risk factors for HPV infection or disease (e.g., adults with multiple lifetime sex partners and likely previous infection with vaccine-type HPV), as well as among persons with certain immunocompromising conditions.
- HPV vaccines are prophylactic (i.e., they prevent new HPV infections). They do not prevent progression of HPV infection to disease, decrease time to clearance of HPV infection, or treat HPV-related disease.

MMWR 2019; 68; 698-702

Slide credit Dr. Markowitz, CDC

What do I do with my patient?

JAMA Clinical Guidelines Synopsis

Human Papillomavirus Vaccination for Adults Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Lauren D. Oshman, MD, MPH; Andrew M. Davis, MD, MPH

Which persons older than 26 years should receive vaccination?

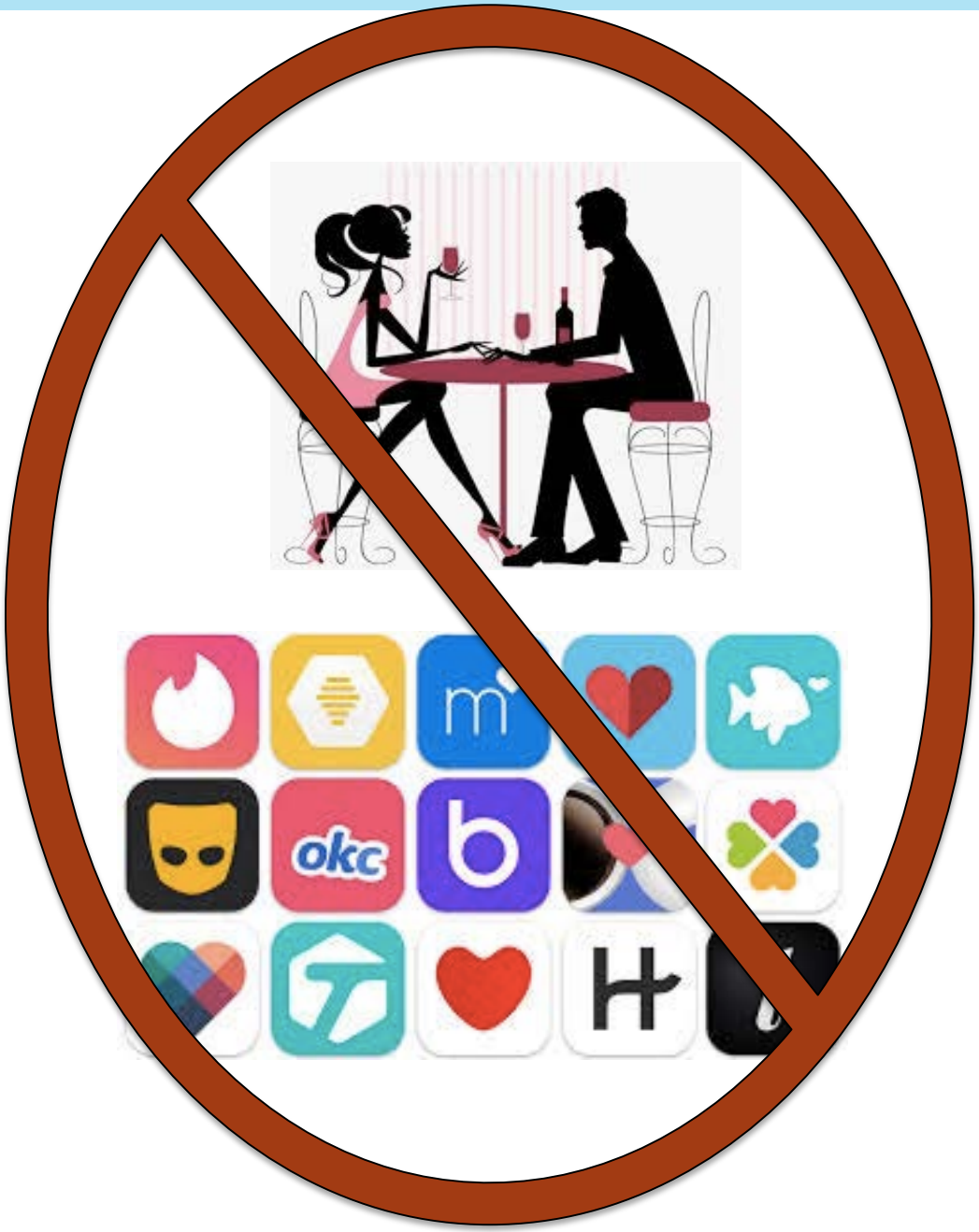
Oshman & Davis, Jan 13, 2020, JAMA

How should clinicians discuss this issue with patients potentially eligible for HPV vaccination in the 27- to 45-year age range?

"Persons who are in a long-term, mutually monogamous sexual partnership are not likely to acquire a new HPV infection or benefit from vaccination."

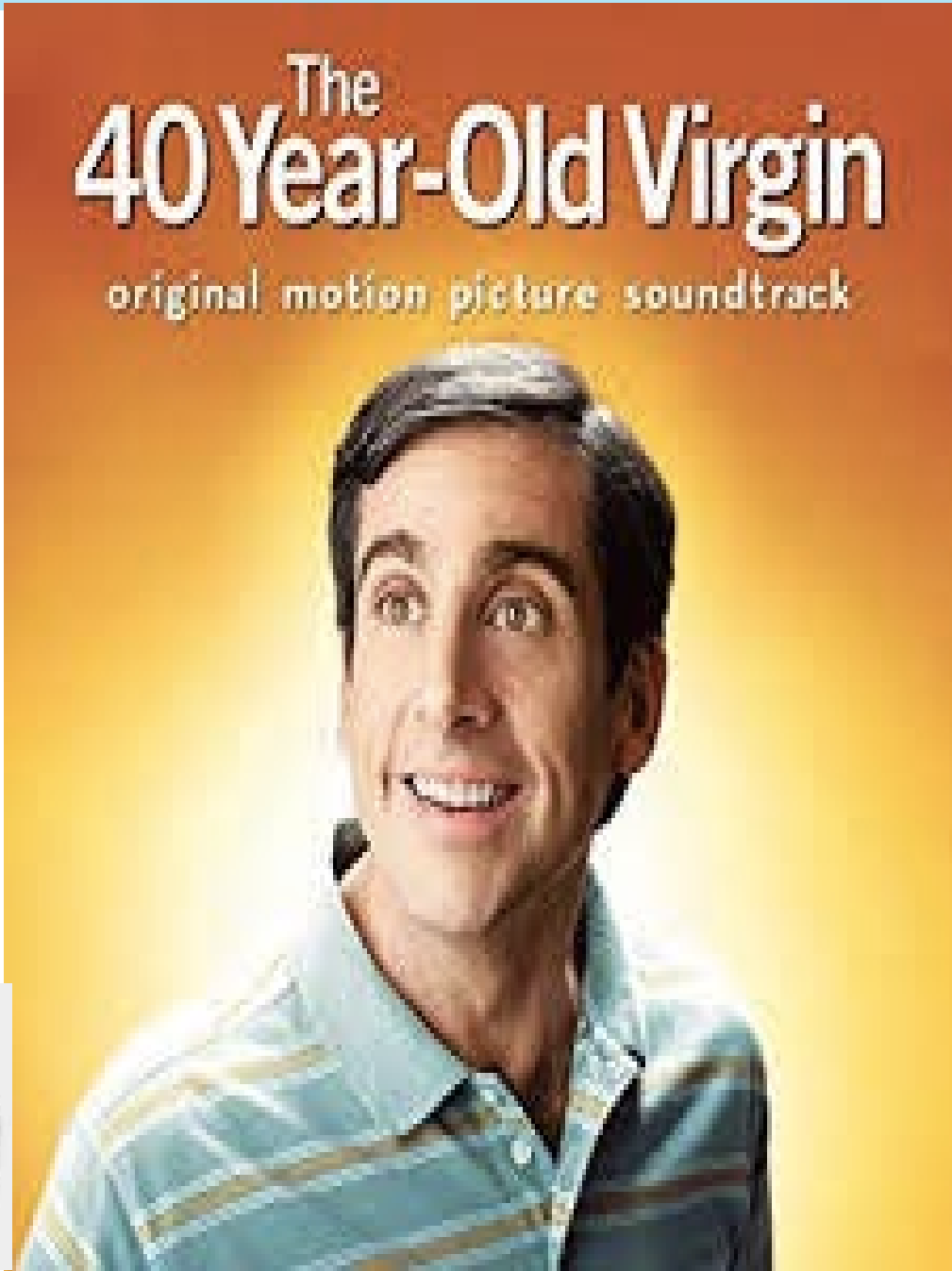
Oshman & Davis, Jan 13, 2020, JAMA

"Individuals with multiple prior sex partners are likely to have been exposed to the vaccine serotypes in the past, reducing usefulness."



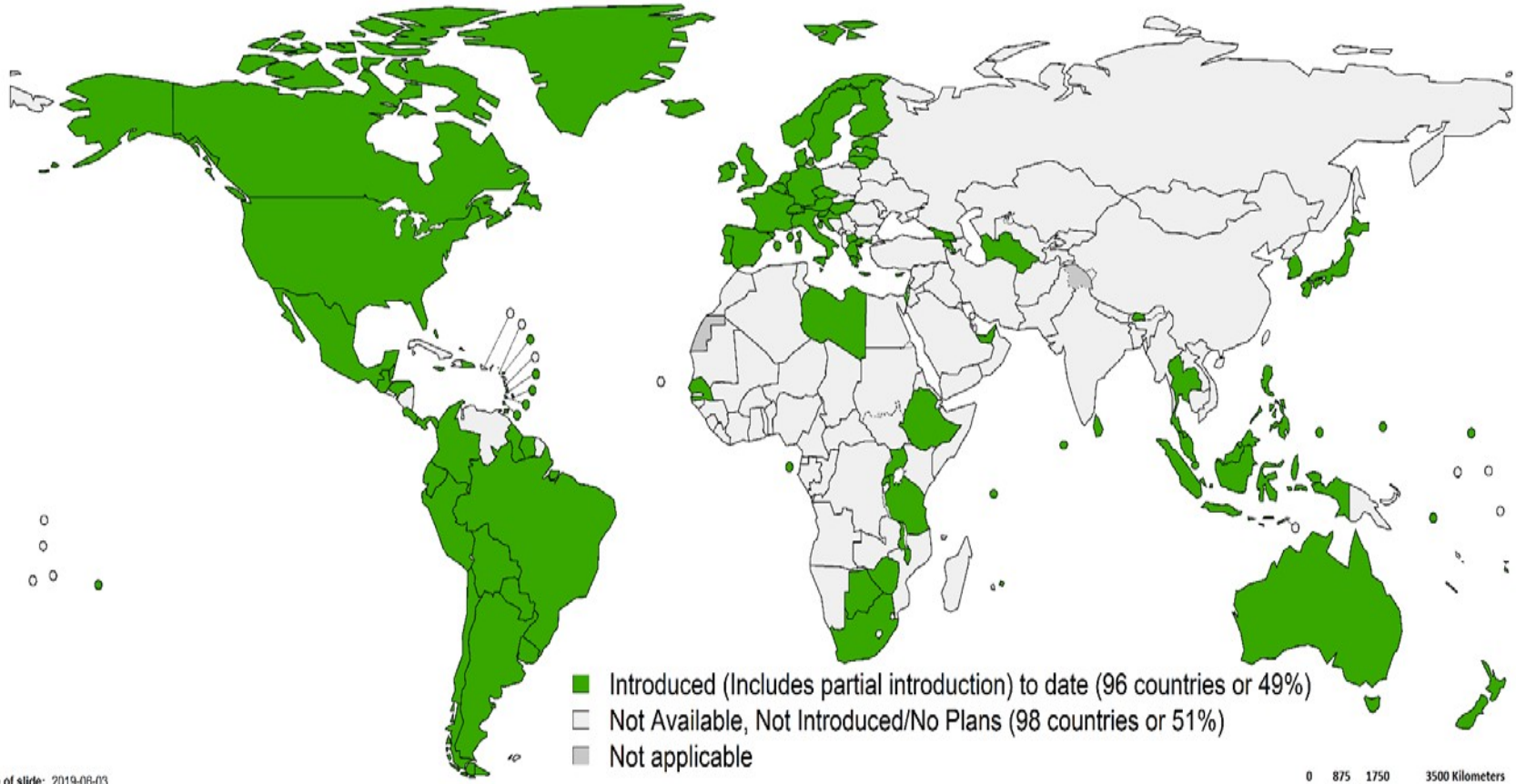
Oshman & Davis, Jan 13, 2020, JAMA

"The vaccine may be more beneficial for persons who have had few prior sex partners and who are at greater risk of acquiring unencountered strains of HPV from new sex partners."



Oshman & Davis, JAMA, 2020

Countries with HPV vaccine in the national immunization program, 2019



Date of slide: 2019-06-03
Map production: Immunization, Vaccines and Biologicals (IVB), World Health Organization(WHO)
Data source: IVB database as at 3rd June 2019

Disclaimer:

The boundaries and names shown and the designations used on this map do notimply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area nor of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

World Health Organization

Slide credit Dr. Markowitz, CDC

Current global HPV vaccine demand/supply imbalance

- **World Health Organization recommendations**
  - 2009 - HPV vaccination of girls for single age cohort of girls
  - 2016 - Multi-age cohort vaccination (age 9-14 years in first year)
    - Increased vaccine demand
- **HPV vaccine demand/supply imbalance**
  - Projected to last 3-5 years
  - Delay introduction in some countries
  - Prevent multi-age cohort vaccination
- **No HPV vaccine shortage anticipated in United States**
- **WHO has issued recommendations for more equitable, global allocation of the limited HPV vaccine supply**

https://www.who.int/immunization/programmes_systems/procurement/v3p/platform/module2/WHO_HPV_market_study_public_summary.pdf
https://www.who.int/wer/2019/wer9447/en/

Slide credit Dr. Markowitz, CDC

Summary of HPV vaccination

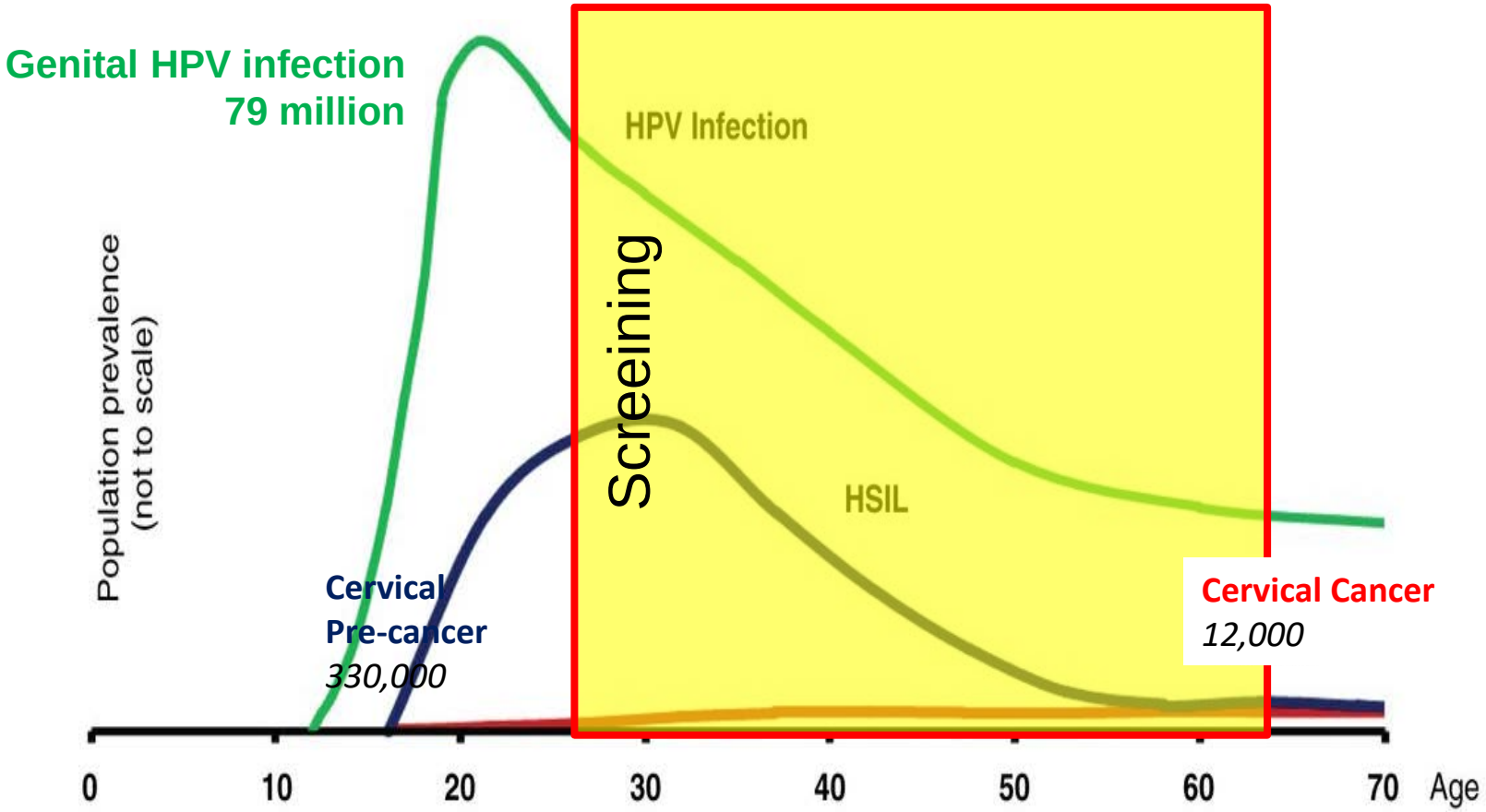
- **Adolescents remain the focus of US HPV vaccination program.**
  - HPV vaccination is most effective when given before exposure to any HPV
  - Changes in recommendations in 2019 include:
  - Catch-up harmonized across genders through age 26 years.
    - Simplifies the immunization schedule and may be more feasible to implement.
- Shared clinical decision-making for some persons aged 27 through 45 years.
  - Providers do not need to discuss HPV vaccination with most adults > age 26 years.
  - CDC is not actively promoting vaccination of adults > 26 years.

Slide credit Dr. Markowitz, CDC

What is the best way to prevent cervical cancer in adults?

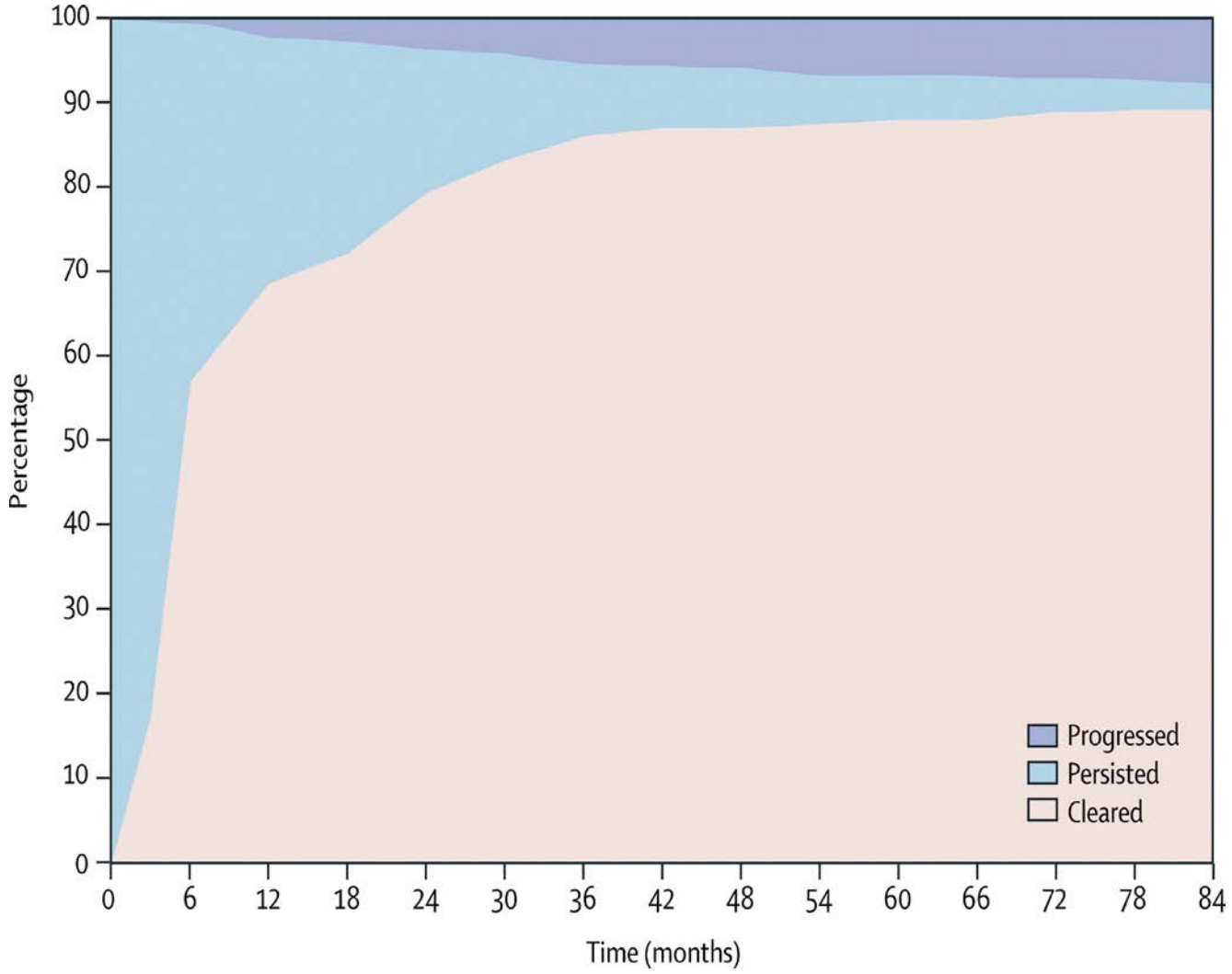
- 12,000 cases annually
- 4,000 deaths annually

Screening and treatment of precancers prevents cancer



Source: Schiffman M et al., 2013

Most HPV infections become undetectable… those that persist cause precancer (CIN3+) over time

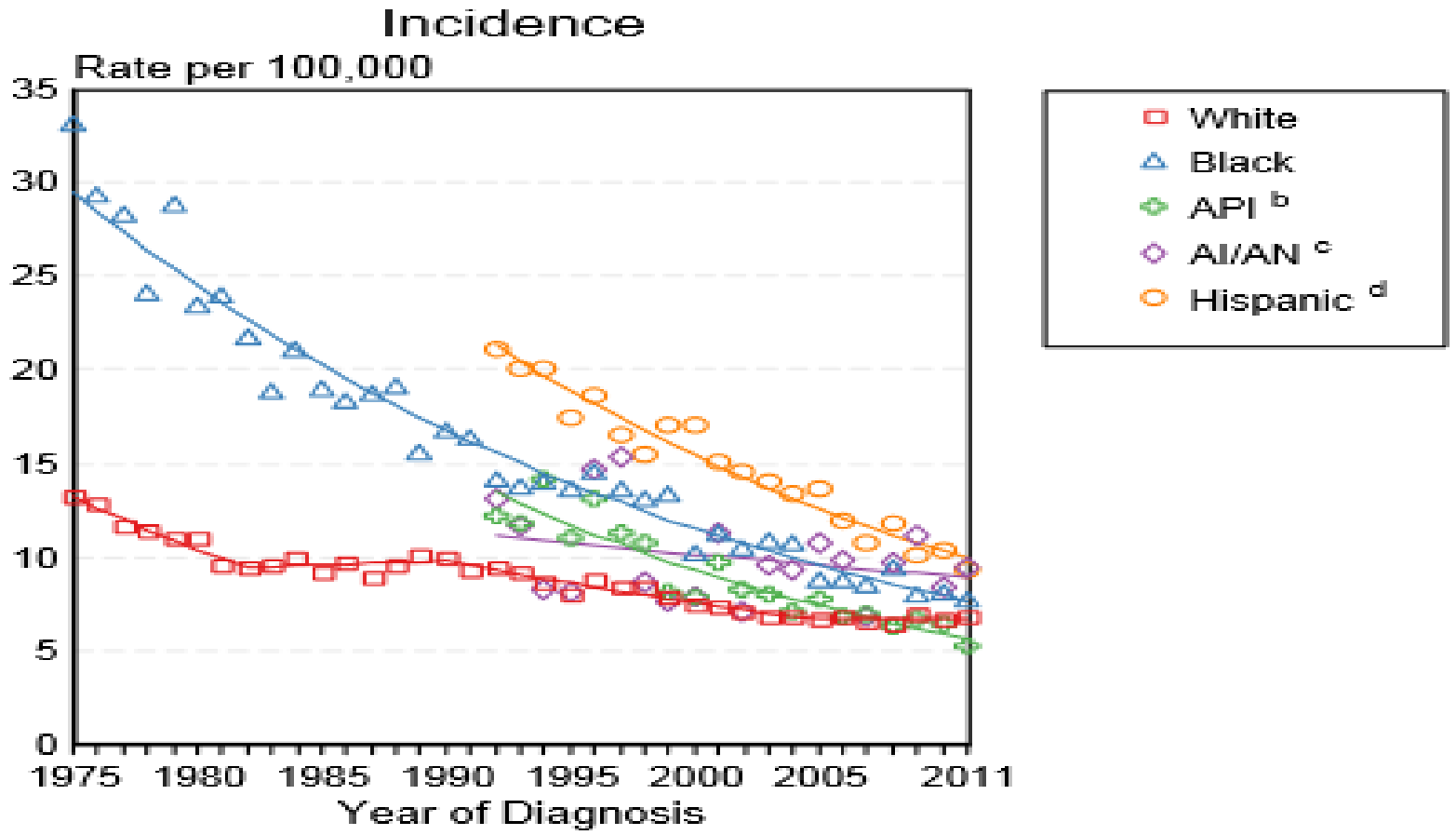


Screening detects pre-cancer

Treating precancer prevents cancer

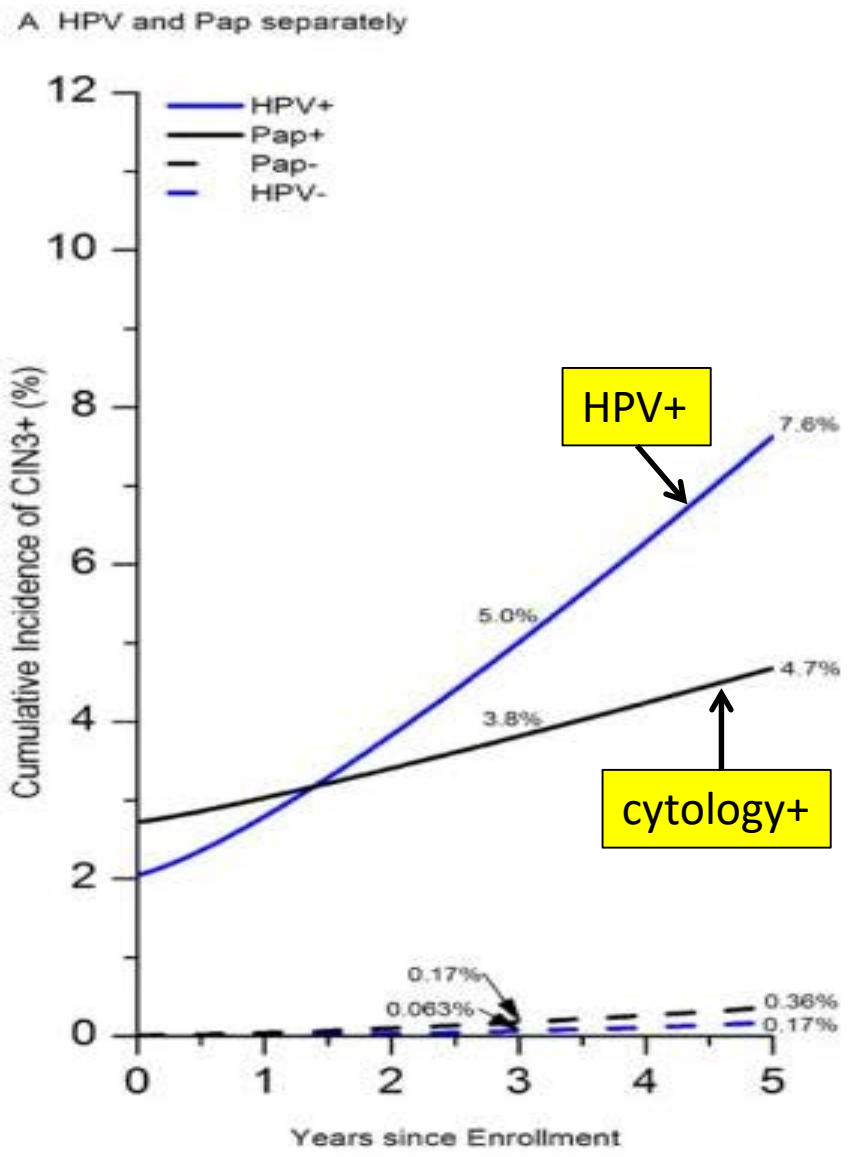
Goal of screening is to detect precancer and *prevent* cervical cancer

Screening Prevents Cervical Cancer



HPV Testing Predicts Future Risk Better than Cytology (Pap tests)

- Both HPV and cytology predicted risk on the date of screening
- HPV predicted 5-year risk of CIN3 and cancer



Katki et al J Low Genit Tract Dis. 2013

Current recommendations

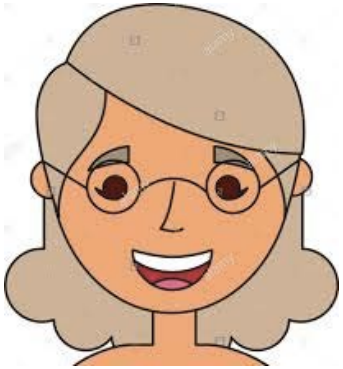
- **Age 21-24**
  - Pap testing only every 3 years*
  - HPV vaccination if not already vaccinated**
- **Age 25-29**
  - Pap testing* or HPV testing*** every 3 years
- **Age 30-65**
  - HPV testing or Pap/HPV cotesting every 5 years*
  - Pap testing every 3 years*
- **Age >65**
  - Discontinue screening if no prior abnormalities and 10 years of documented normal screening*

*USPSTF 2018; **ACIP 2006, 2019; ***ASCCP interim guidance for primary HPV screening 2015

Cervical cancer prevention throughout the lifespan

- **Ages 9-20**
  - **HPV vaccination**

- **Ages 21-26**
  - **Screening + catch-up vaccination**



- **Ages 27-65**
  - **Screening**
  - *May offer vaccination to select patients age 27-45 on an individual basis using shared clinical decision-making*

Questions?

Photo credit:
https://www.flickr.com/photos/travelinlibrarian/223839049