Updates on HPV Vaccination & Cervical Dysplasia

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Objectives

- List the updated indications for HPV vaccination
- Describe the clinical outcomes of the HPV vaccination
- Review alternate therapeutic benefits of the HPV vaccine
- Discuss updates in screening for cervical cancer

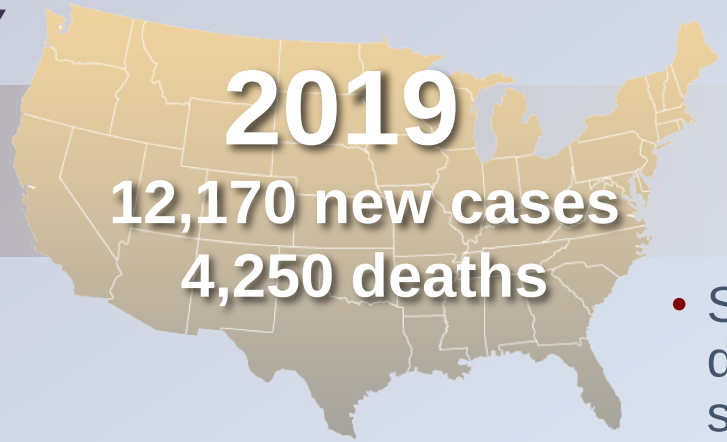
Disclosures

- Royalties – UpToDate, Inc. (Author)
- I have no other conflicts of interest to report

Cervical cancer

Epidemiology

Peak incidence
ages 40–60 yo



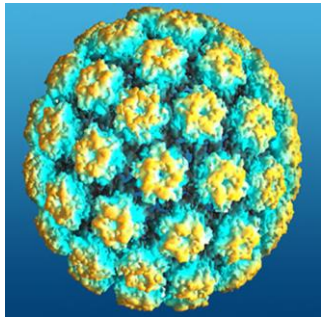
- Significantly reduced incidence due to implementation of screening with Pap
- **>50%** of cases in US due to inadequate or absent screening

Worldwide

>85% of all cases of cervical cancer occur in low-resource countries

Siegel RL et al. *CA Cancer J Clin* 2019.
Global Cancer Facts & Figures, 4th ed.

Human Papilloma Virus (HPV)

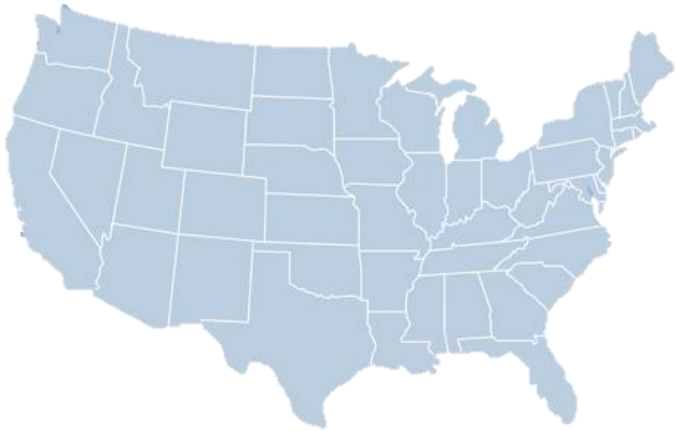


- Well-known as causative agent of >99% cervical cancers, majority of anogenital cancers in women and men
- **Risk factors associated with:**

Increased acquisition of high-risk HPV	Decreased ability to "clear" HPV
Multiple and/or high-risk sexual partners	HIV/AIDS
Early age at coitarche, first birth	Immunosuppression (i.e. transplant)
Smoking	Age?
Sexually transmitted infections	
History of genital tract or anal dysplasia	
Use of OCPs	

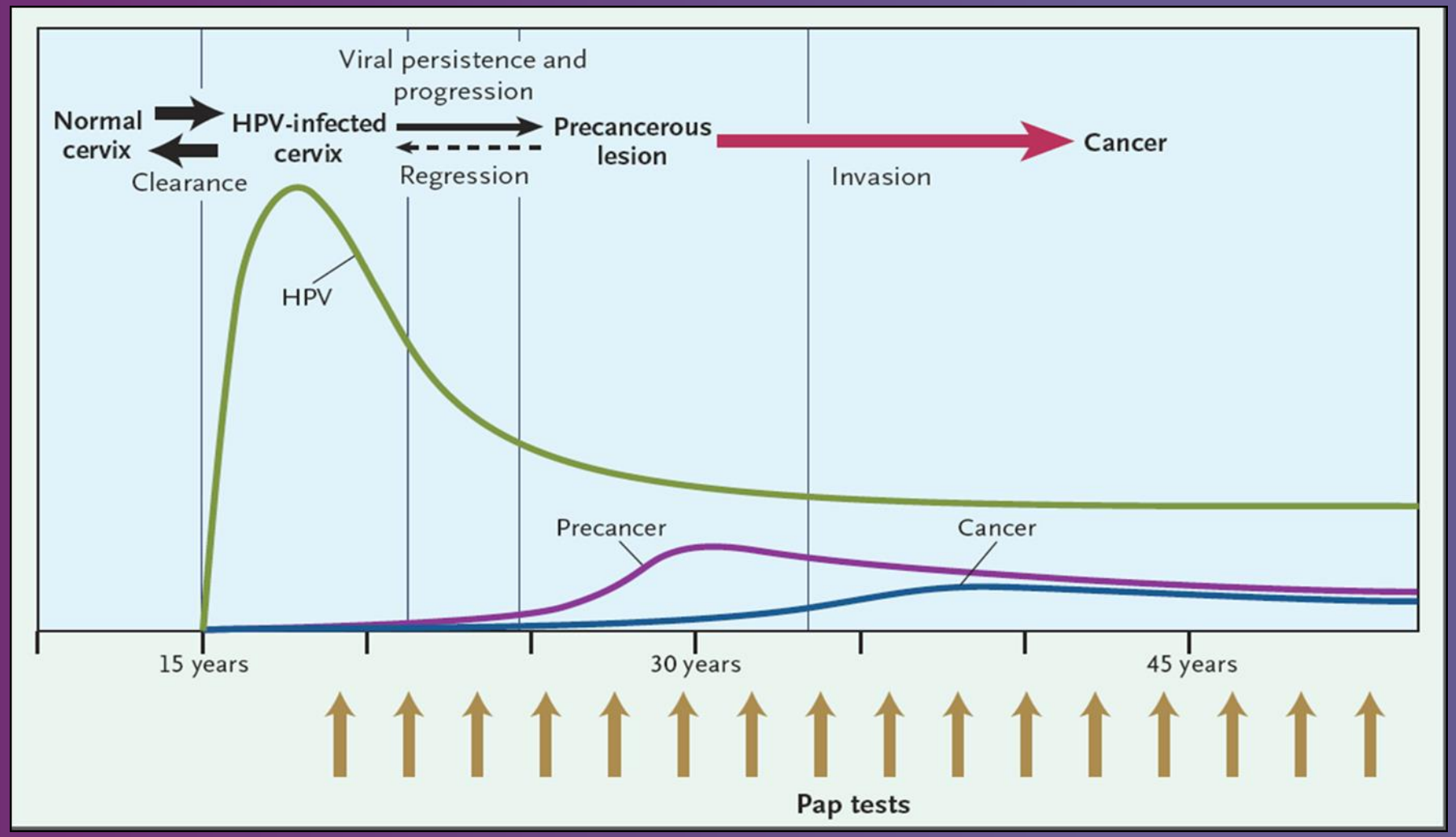
HPV
Epidemiology

- US Prevalence: 20 million adults
- US Incidence: 5.5 million
- 40% infection rate within 3 years of onset of sexual activity
- Peak prevalence:
  - Approximately 45% for women
  - Approximately 53% for heterosexual men



Dunne EF et al. *JAMA* 2007.

Natural History of HPV & Cervical Cancer



Runowicz CD. *N Engl J Med* 2007.

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Value of Prophylactic HPV vaccination

SCOPE

- Most common STI globally
- 14 million people infected annually
- 8 billion U.S. medical costs for HPV-related issues
- Increasing rates of vulvar cancer in younger women

HPV-Related Diseases

- Linked to 6 cancers: cervical, vulvar, vaginal, anal, penile, oropharyngeal
- Genital warts in 1.1/1,000 U.S. men and women

Feldman S. *Obstet Gynecol* 2018.

HPV VACCINE

Gardasil: Quadrivalent *(types 6,11,16,18)*
Cervarix: Bivalent *(types 16,18)*
Gardasil 9: Nanovalent *(types 6, 11, 16, 18, 31, 33, 45, 52, 58)*

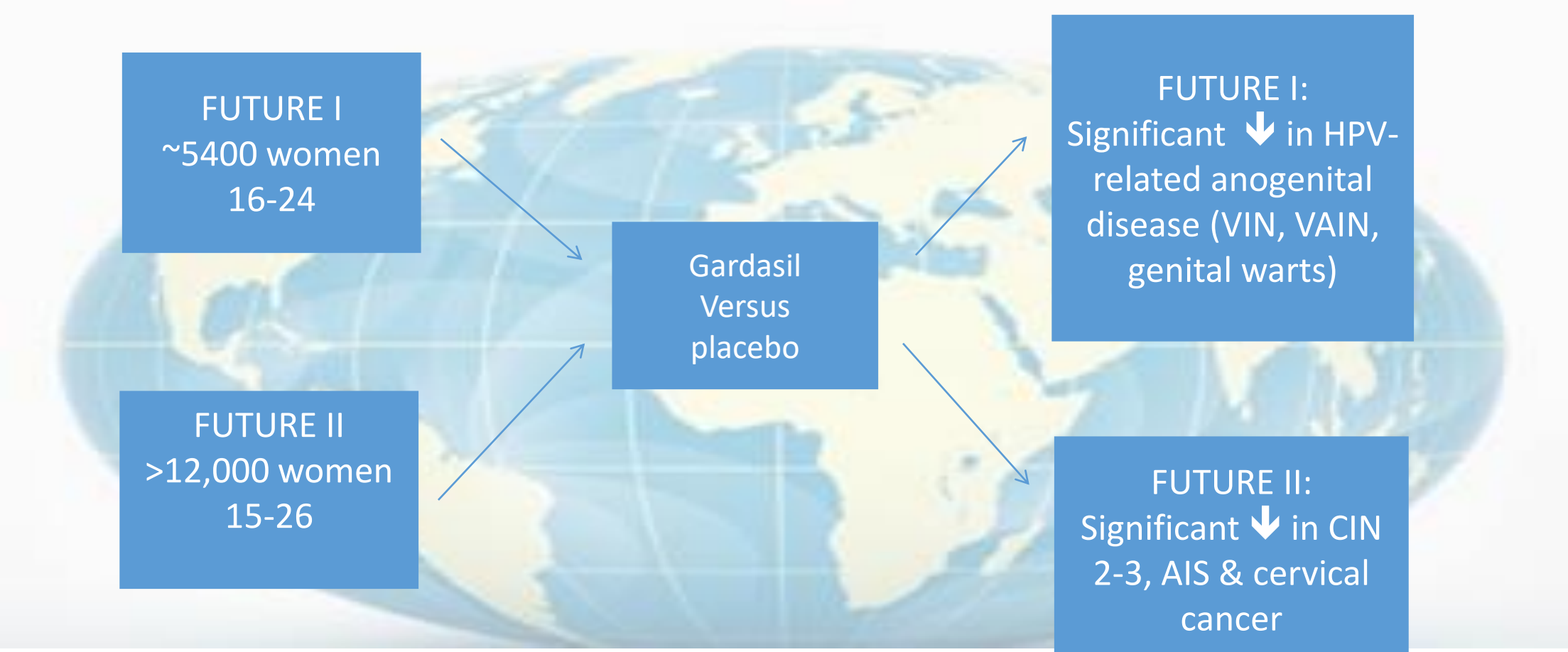
- As of 2016, only 9vvaccine available in U.S.
- Significantly ↓ incidence squamous and glandular dysplasia and carcinoma *in situ* of the cervix, vulva, vagina and anus

FUTURE II Study Group. *N Engl J Med* 2007; Joura EA et al. *Lancet* 2007. Joura EA et al. N Engl J Med 2015.

- Immunity persists >5 years

HPV Vaccine

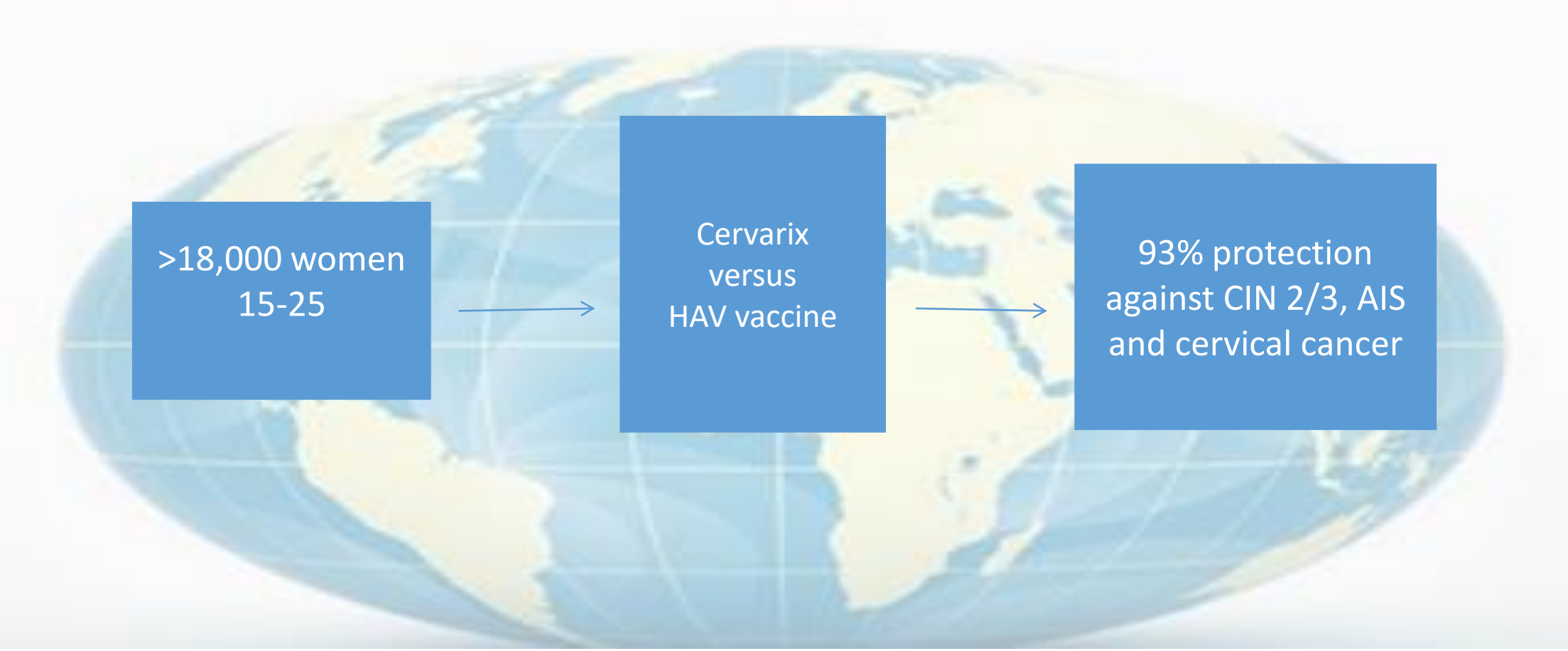
Clinical Trials – FUTURE I & II
Gardasil (HPV 6, 11, 16, 18)



FUTURE II Study Group. *N Engl J Med*. 2007.
Garland SM et al. *N Engl J Med*. 2007

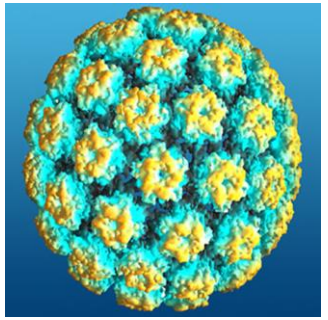
HPV Vaccine

Clinical Trials – PATRICIA
Cervarix (HPV 16, 18)



Paavonen J et al. *Lancet* 2009.

Human Papilloma Virus (HPV)
Updates on Vaccine Guidelines



- Oct 2018: FDA expanded approval of HPV vaccine for women and men between **27-45**
- **Recommendations based on result of FUTURE III**

~3800 women 24-45 → Quadrivalent vaccine vs placebo → 90% effective in reducing persistent HPV infection and cervical/genital HPV-related disease

- Analysis also demonstrated immunogenicity

Munoz N et al. *Lancet* 2009.
Castellsague X et al. *Br J Cancer* 2011.

Guidelines for HPV Vaccination

- FDA: approved for ages 9-45
- WHO
  - Ages< 15 → 2 doses (0 and 6 months)
  - Ages 15-45 → 3 doses
- ACIP/ACOG Practice Advisory: for ages >26, "decisions should be individual based on patient's circumstances, preferences, and concerns"
- Expert opinions
  - If "unexposed"….and intimacy situation has changed, vaccination?
  - If not previously sexually active, vaccination likely to be 100% effective
  - Continue screening in older women as vaccination unlikely to add much more to preventing cervical cancer

HPV Vaccine
Vaccination Schedule

- Two-dose series
  - Randomized studies have demonstrated that two vaccine doses (6 months apart) in young individuals have similar or greater immunogenicity compared with 3 doses in older individuals
- For women 15 and older, the three-dose series continues to be recommended
  - Immunologic responses to vaccine are not as substantial

Dobson SR et al. *JAMA* 2013.
Sankaranarayanan R et al. *Lancet Oncol* 2016.
Puthanakit T et al. *J Infect Dis* 2016.

HPV Vaccine Efficacy

HPV-Naïve (Incident infection / disease)

- 5+ year protection against HPV 16/18 infection, CIN 2+/AIS
- Gardasil has reduced immunogenicity for HPV 18/45 → need for long term surveillance

HPV-Exposed (Prevalent infection/disease)

- If HPV DNA +, vaccination did NOT induce clearance
- If seropositive, HPV DNA negative, vaccinations induced greater antibody titers → inferred future protection

DM Harper et al. *Gynecol Oncol 2017.*

EFFICACY OF 9VHPV VACCINE AGAINST RELATED DISEASES

- In HPV-naïve women, 9vHPV vaccination associated with
  - 98% reduction in CIN 2+, cervical procedures and treatments
  - 95% reduction in any grade vulvar and vaginal disease
  - 100% reduction in VAIN 2+, VIN 2+ caused by the 9 vaccine HPV types.
- Did not prevent disease related to “persistent” HPV infections
- Vaccination of HPV naïve patients ideal but "catch up" vaccine may be still beneficial

Guiliano AR et al. *Gynecol Oncol* 2019

HPV Vaccine
Safety

- Data on adverse events has been collected from prospective randomized trials, and continues to be reportable through the Vaccine Adverse Event Reporting System (VAERS)
  - https://vaers.hhs.gov
- Vast majority side effects mild; injection site reaction slightly more common with 9vHPV vaccine
  - Serious side effects: headache, dizziness, weakness, nausea, fever
  - No reported Guillain-Barre
- Questionable increased risk of postvaccination syncope with quadrivalent vaccine
  - 8.2/1000,000 qHPV doses

Slade BA et al. *JAMA* 2009
Phillips A et al. *Drug Saf* 2018
Chen W et al. *Vaccine* 2019.

HPV Vaccine
Risk of demyelinating disorders

- Social and news media have had varying focus on cases of multiple sclerosis and other demyelinating disorders after the HPV vaccine
- Recent cohort study in Denmark & Sweden showed no increased risk of MS or other demyelinating diseases following the quadrivalent vaccine
- In a cohort study using the same population, there was no association of the qHPV vaccine with an increased risk of autoimmune conditions

Scheller NM et al. *JAMA* 2015.
Hviid A et al. *J Intern Med* 2018.
Phillips A et al. *Drug Saf* 2018.

HPV Vaccine Pregnancy

- Combined analysis of five RCT's
  - 1,796 vaccine recipients became pregnant during course of the studies
  - No maternal adverse effects
  - Congenital anomalies: 40 in vaccinated group, 30 in placebo (p=0.20)

- Denmark: cohort study of vaccine exposure (qHPV)
  - No association with adverse pregnancy outcomes (miscarriage, preterm birth, small for gestational age, stillbirth)
  - Use of patient navigators and text messages improved completion rate

Garland SM et al *Obstet Gynecol* 2009.
Scheller NM et al. *N Engl J Med* 2017.

HPV Vaccine Postpartum

- Columbia University: HPV vaccine offered with 1st given after delivery
  - Only 30.6% completed the series
  - Prior knowledge of HPV or attitudes about HPV was not associated with completion of the series
  - 98.6% felt postpartum vaccination was convenient
  - 50.4% reported they would not have otherwise asked about the vaccine
- University of Texas: use of patient navigators to improve uptake & completion of HPV series
  - Only 15.5% had previously completed series prior to delivery
  - Use of patient navigators and text messages improved completion rate

Wright JD et al. Obstet Gynecol 2012.
Berenson AB et al. *Am J Obstet Gynecol* 2016.

Prevention → Therapy?

Patient Counseling

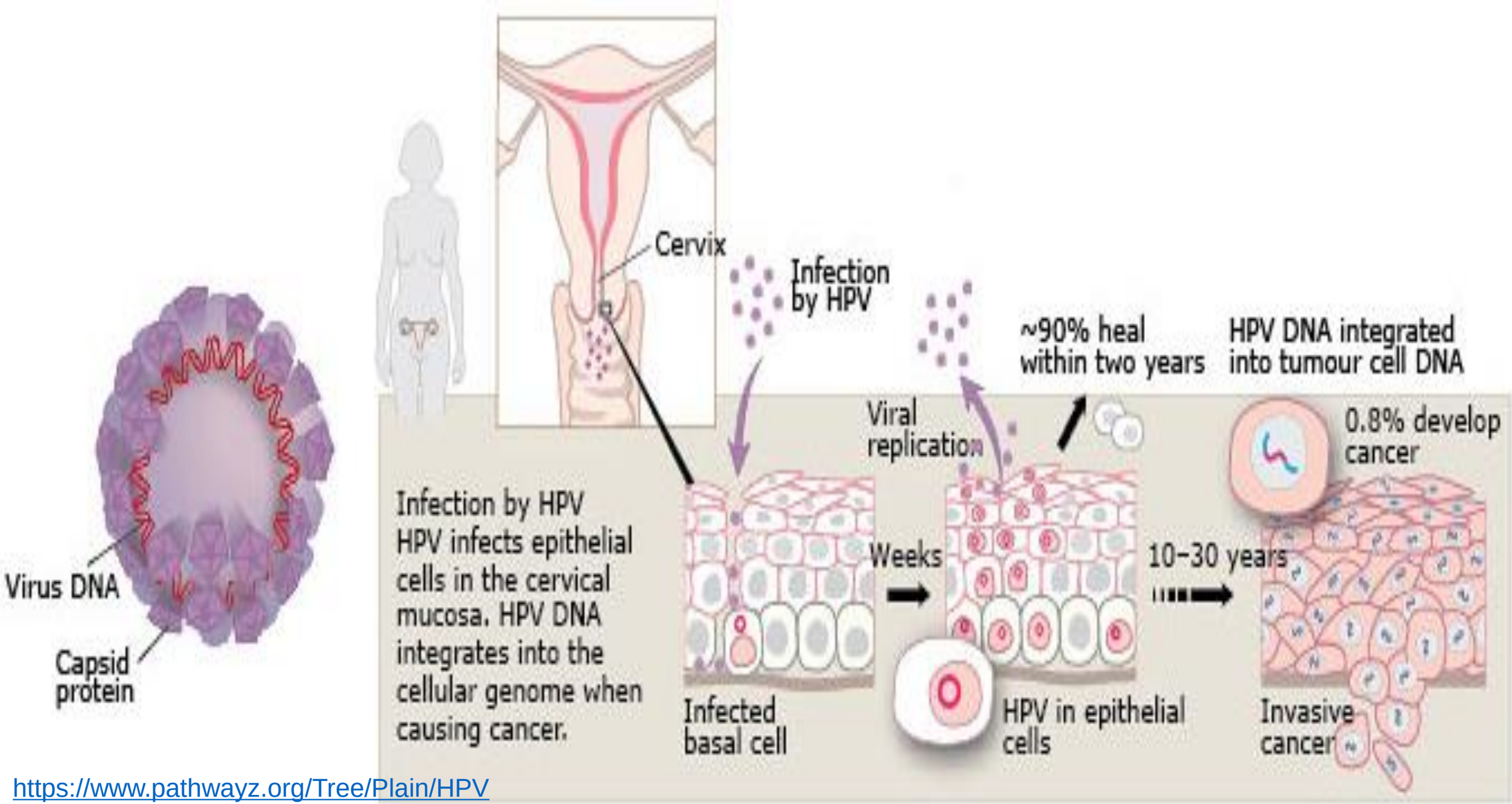
How would you respond to the HPV unvaccinated woman who asks:

- If I clear HPV, am I protected from future infection with the type of HPV that I cleared?
- Can I get the same HPV back from my partner after “clearance”?
- If I have HPV 16 or 18, will HPV vaccination help me clear this persistent infection?

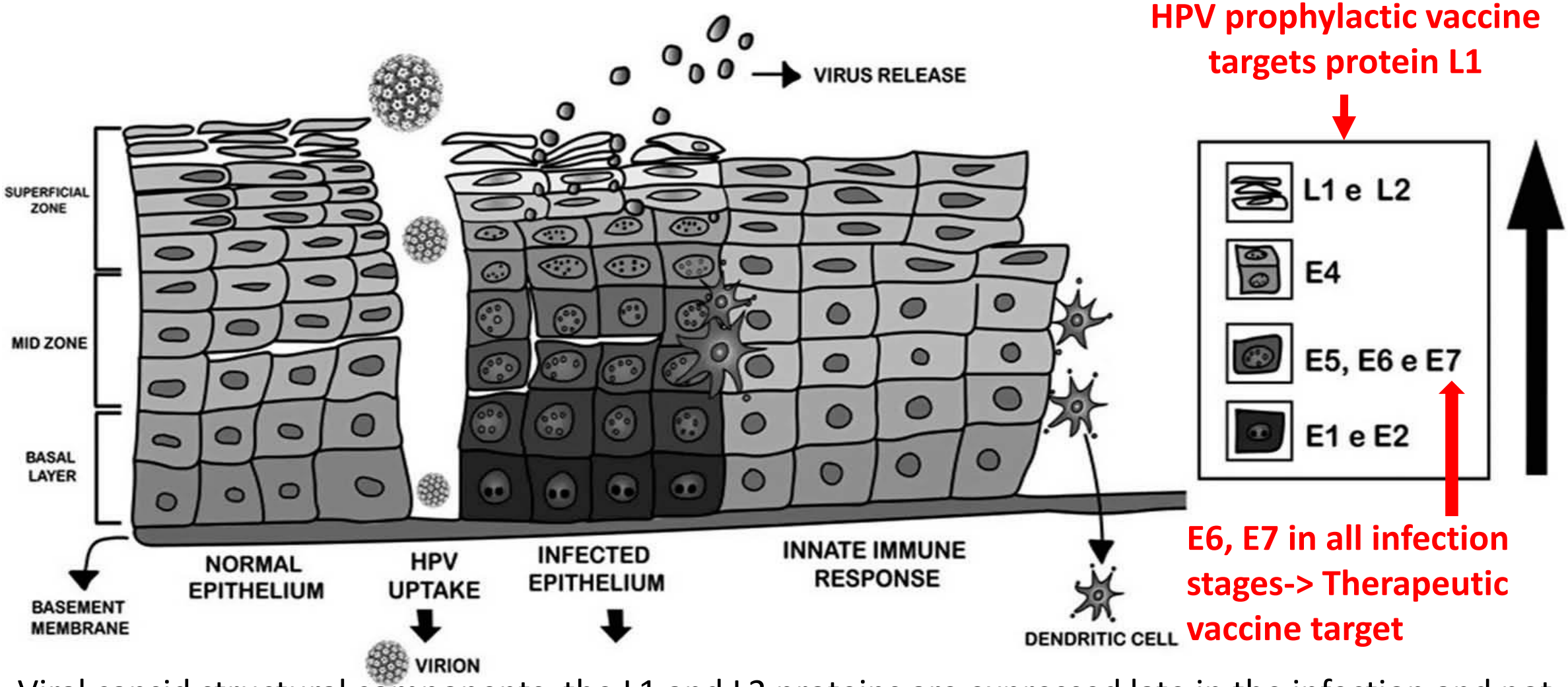
Virologic Considerations

Papillomaviruses uniquely produce virions only in the terminally differentiated layer of squamous epithelium

J Schiller. *Vaccine* 36 (2018) 4768-4773



https://www.pathwayz.org/Tree/Plain/HPV



Viral capsid structural components, the L1 and L2 proteins are expressed late in the infection and not on basal epithelial cells where primary keratinocytes are HPV hosts. Vaccines have recombinant L1 virus-like particles (VLP) targeting L1.

Why can't current HPV vaccination "clear" established HPV infection?

- L1 structural proteins produced in late stage of infectious cycle during epithelium terminal differentiation
- Recombinant L1 VLP → high neutralizing Abs can block NEW HPV infection
- T cell-mediated response can KILL infected cells expressing L1.
- L1 *not expressed* in basal epithelial cells where keratinocytes are HPV hosts

Preventive vaccines INEFFICIENT in established infection

MN Cordeiro et al. Expert Review of Anticancer Therapy, 2018 18(4): 365-76

Is HPV vaccination effective on Incident and Prevalent Infections after Treatment

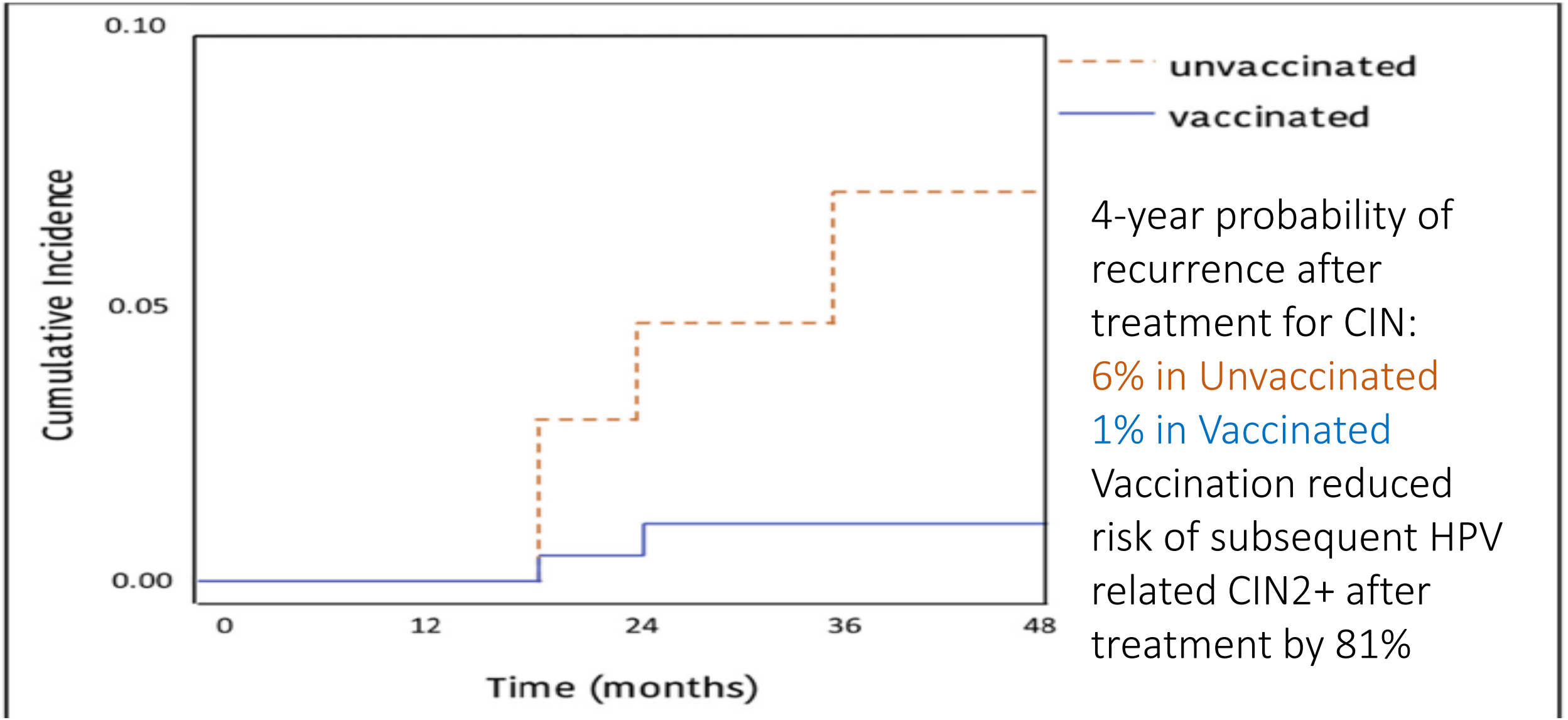
Clinical effectiveness (clinical disease relapse) of HPV vaccination after LEEP for CIN 2+ and microinvasive cervical cancer

A Ghelardi et al. *Gynecol Oncol* 2018.

SPERANZA

- Prospective case-control study in Italy
- 536 Women ages 18-45 with histology confirmed CIN 2+ had LEEP: vaccination (V) and non-vaccination (NV) arm
- V-arm: 4vHPV given at 1, 3, and 6 mos after LEEP
- Mean Follow up = 36 mos:
- HPV, pap, colposcopy q 6 mos x 2 years, the annual until year 4 post-treatment

A Ghelardi et al. *Gynecol Oncol* 2018.



4-year probability of recurrence after treatment for CIN:
6% in Unvaccinated
1% in Vaccinated
Vaccination reduced risk of subsequent HPV related CIN2+ after treatment by 81%

Impact of vaccination on disease relapse after excisional procedure

A Ghelardi et al. Gynecol Oncol 2018.

SPERANZA Results

Non-Vaccinated

- 81% cleared HPV infxn by 6 mos
- 6% clinical disease recurrence (CDR) rate after 1 year (n=6)
- In the clinical disease recurrence (CDR) group, 63% had HPV 16 and 54% had co-infection with >1 HPV type

Vaccinated

85% cleared HPV infxn by 6 mos

1% clinical disease recurrence rate after 1 yr (n=1)

In the CDR group, 100% efficacy (none had HPV types in the 4vHPV vaccine)

A Ghelardi et al. *Gynecol Oncol* 2018.

SPERANZA: Proposed Mechanisms for Vaccine Efficacy After Excision

- Primary prevention for vaccine HPV types not previously exposed: "incident" infection
- Excision of infected basal cells
- High local antibody response to vaccine may prevent self-infection of uninfected cells at surgical site
- Median interval relapse time: 36 months

A Ghelardi et al. *Gynecol Oncol* 2018.

SPERANZA Summary

- Vaccination not effective against prevalent infection ***except*** after surgical therapy
  - Reduction in post-treatment relapse for warts and CIN
- 4vHPV vaccine 30 days after LEEP reduced risk of recurrent disease by 81% (65% reduction in other trials)
  - Actual number is low : 6 vs 1cases
- May be effective as ***adjuvant*** to surgical treatment, not as therapy alone

Ghelardi A et al. Gynecol Oncol 2018.

HPV Vaccine
Other Examples of Therapeutic Benefit?

- Cervical dysplasia
  - Randomized phase II international trial of a novel HPV vaccine showed improved resolution of CIN 2,3
    - Gene delivery system of vaccine that includes genes for modified E6 and E7
  - Randomized phase 2B trial of vaccine targeting E6 and E7 showed improved resolution of CIN 2-3

- Vulvar dysplasia
  - Ongoing randomized VIVA trial: HPV Vaccine to Interrupt Progression of Vulvar and Anal Neoplasia
    - Vaccine vs placebo given **after** treatment for VIN and/or AIN

Harper DM et al. *Gynecol Oncol* 2019.
Trimble et al. Lancet 2015.
Stankiewicz Karita HC et al. *JAMA Netw Open* 2019.

Cervical Cancer Screening
Status Quo

- Test strategy based on age
  - 21-30 yo: Pap smear q3years
  - 30-65
    - **Every 5 years: "co-test" *or* primary HPV test** (preferred; ACS, ACOG, ASCCP)
    - Every 3 years: Pap smear with reflect HPV *or* Pap smear alone
  - Patients who have received an HPV vaccine should still have age-appropriate screening
- When to stop
  - After hysterectomy (where cervix removed) *if no prior genital tract dysplasia*
  - At 65, *if patient has had adequate prior screening*

ACOG Practice Bulletin No. 168, *Obstet Gynecol* 2016.

Screening

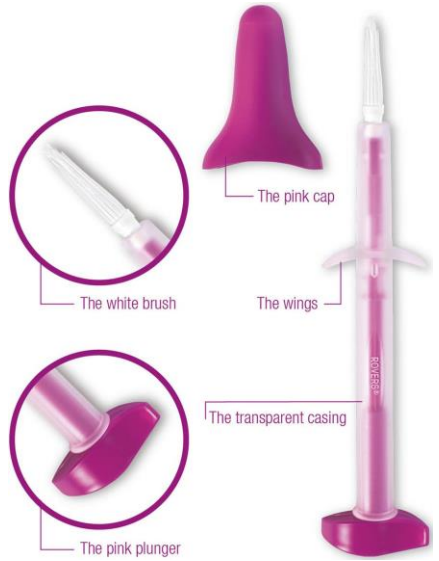
Technique

- Obtaining endocervical cells
- Liquid versus conventional
  - No difference in accuracy
  - However liquid prep may increase yield of adequate specimens
- Use of gel lubricant?
  - Four randomized trials have shown no effect of lubrication on the quality of cytology results

Amies AM et al. *Obstet Gynecol* 2002.
Harer WB et al. *Obstet Gynecol* 2002.
Gilson M et al. *J Am Board Fam Med*.
Griffith WF et al. *Contraception* 2005.

Primary HPV Screening

- Inclusion of HPV testing alone or combined with cytology is associated with increased detection of precancerous cervical lesions compared with cytology alone
  - HPV FOCAL: Randomized trial of primary HPV testing versus cytology alone
    - Primary HPV group: reflex to cytology if positive at start; if negative, repeat HPV & cytology at 4 years
    - Cytology: reflex to colpo if positive at start; if negative repeat cytology at 2 and 4 years
    - Fewer cases of CIN 2-3 at 4 years with primary HPV screening
- Self-testing?
  - IMPROVE: randomized trial of self-collected versus clinician collected in Netherlands
    - Self-collected cervico-vaginal sample with Evalyn Brush
    - Similar accuracy in detection of CIN2, 3 or 3+ lesions



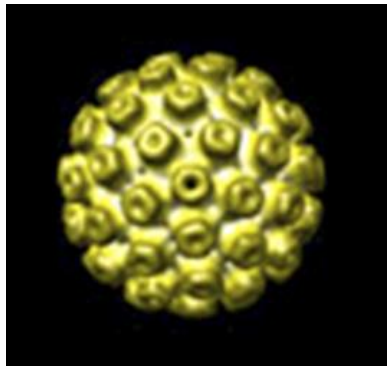
Ogilvie GS et al. *JAMA* 2018.
Polman NJ et al. *Lancet Oncol* 2018.

Special Considerations For….

- Women who are immunocompromised (i.e. solid organ transplant recipients)
- Women exposed to DES in utero
  - Initially approved 1947; Rx discontinued in 1971
- Women previously treated for CIN2, CIN 3 or cancer

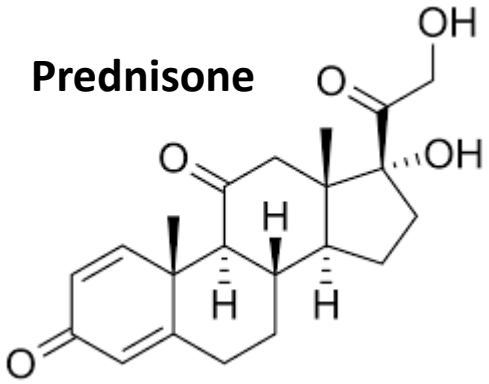
These patients remain at risk for persistent or recurrent disease for ≥20 years!
Continue routine age-based screening for 20 years after initial dysplasia diagnosis

Cervical Cancer Screening
HIV+

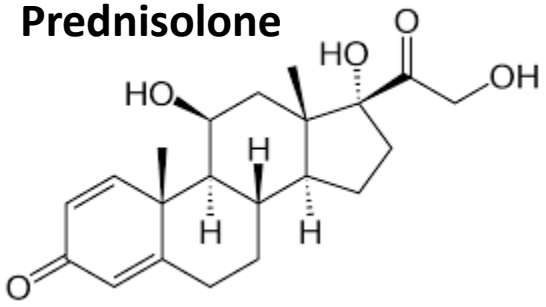


- **CDC** Recommendations
  - Initiate cytology screening within 1 year of HIV diagnosis if sexually active **OR** within 1 year of coitarche, regardless of age
  - Continue to screen beyond age 65
  - Recommendations endorsed by ACOG; differ from joint guidelines of ACS, ASCCP and ASCP

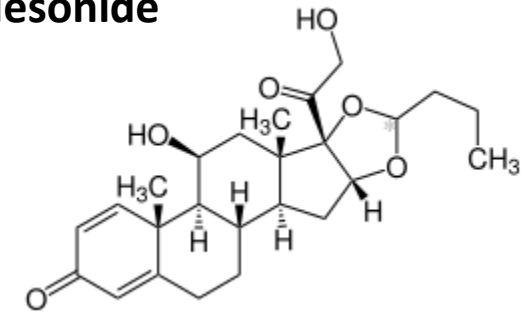
Prednisone



Prednisolone



Budesonide



Cervical Cancer Screening
Immunosuppressed (IS) women without HIV

Risk Group	Recommendation
Inflammatory bowel disease (IBD) – on IS Rx Systemic lupus erythematous (SLE) and rheumatoid arthritis (RA) – on IS Rx	- Younger than 30: cytology - 30+: Co-testing preferred, cytology acceptable - If cytology alone → annual cytology; can space out after 3 consecutive tests - If co-testing → repeat q3 years if normal - Continue screening throughout lifetime; discontinue screening based on shared discussion regarding quality & duration of life rather than age
Solid organ transplant recipient	Same as above *Screen patients on dialysis and posttransplant similarly*
Allogenic hematopoietic stem cell transplant	Same as above If patients develop new diagnosis of GVHD or chronic GVHD, resume annual cytology or perform initial baseline co-test
Type 1 Diabetes SLE and RA - not on IS Rx IBD - not on IS Rx	Follow general population screening guidelines

Moscicki AB et al. *J Lower Gen Tract Dis* 2019.

A 65 yo presents for routine care and asks if she can skip her Pap smear/HPV test

Guideline:
Screening by any modality should not be done after 65 yo in women with **prior normal screening** and no history of CIN2+

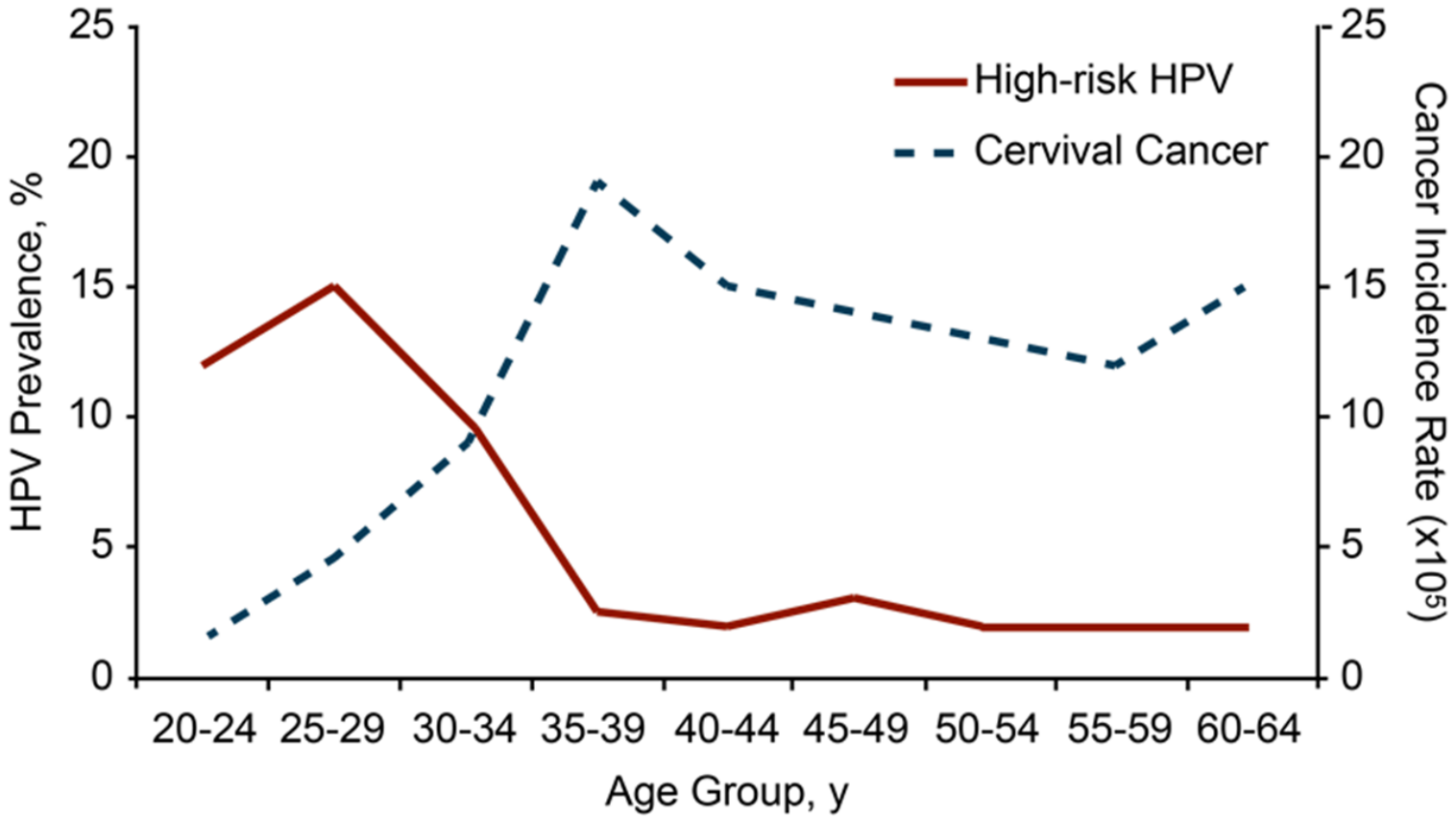
CERVICAL CANCER SCREENING

DEFINING ADEQUATE SCREENING

- **Review prior screening**
  - History of abnormal screening?
  - Is prior screening up to date?
  - Other HPV-related disease? (e.g. VIN, genital warts)
- **Adequate prior screening?**
  - Two consecutive (-) co-tests within past 10y; most recent test within last 5y
  - Two consecutive (-) HPV tests within past 10 y; most recent test within last 5y
  - Three consecutive (-) Pap tests within past 10y; most recent within last 3y
- **Complete pelvic exam**
  - Visualization of genitalia and cervical appearance
  - If abnormal cervical lesions present, *biopsy* is indicated

Saslow D et al. *CA Cancer J Clin* 2012.
Landy R et al. *Cytopathology*. 2016.

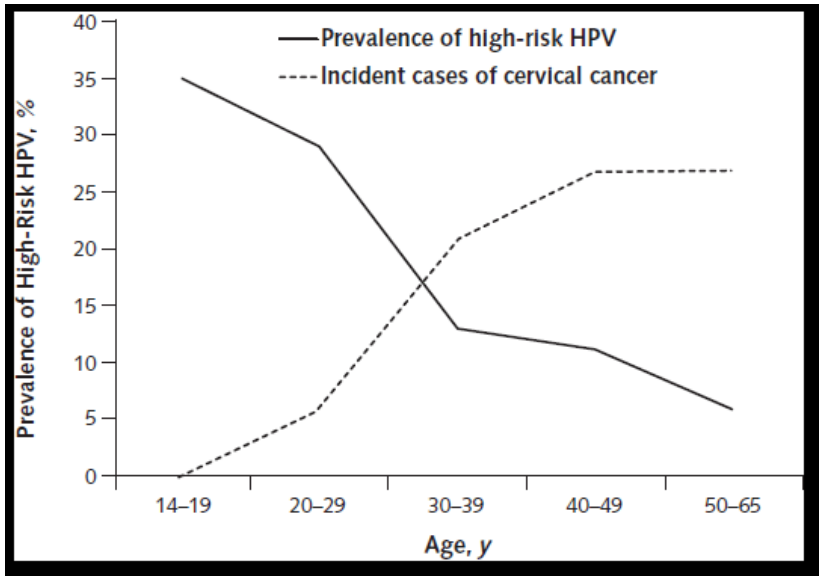
Age-Specific Rates of HPV Infection and Cervical Cancer



Bosch FX, et al. *J Clin Pathol*. 2002;55:244-265. Reproduced with permission from the BMJ Publishing Group.

Cervical Cancer Screening
Don’t be hesitant to keep your patient up do date!

- High incidence of cervical cancer in women over 65
  - In US population adjusted for hysterectomy, highest incidence of cervical cancer among women 65-69
    - Highest rates seen in black women 85 years or older
- Recent review of the National Health Interview Surveys found that the proportion of women not recently screened for cervical cancer increased with age



USPSTF, 2014.

Rositch AF et al. *Cancer* 2014.
White MC et al. *Am J Prev Med* 2017.

Cervical Cancer Screening

Stay current!

- UW experience
  - Cohort of women with cervical cancer ≥60
  - Length of time from last Pap smear significantly correlated with stage at diagnosis
- National Swedish registry
  - Cervical screening at age 61-65 for women who were unscreened, or screened with abnormalities, in their 50's, led to significant reduction in subsequent development of cervical cancer
- Finnish-based cohort study
  - Patients invited for cervical cancer screening at age 65
  - 50% reduction in cervical cancer mortality

Fox KV et al. *Gynecol Oncol* 2008.
Wang J et al. *PLoS Med* 2017.
Pankakoski M et al. *PLoS One* 2019.

Conclusions

- Be aware of updated indications for HPV vaccine – your patient may be eligible!
- The HPV vaccine is highly immunogenic & effective; single-dose schedule may be coming
- Future therapies in cervical dysplasia include novel HPV vaccine strategies
- Consider whether your patient requires adjusted screening and if their screening has been adequate before screening stops

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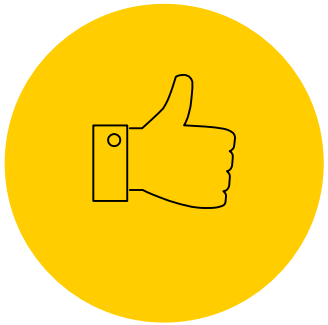
- **Medcon**: connects clinicians to specialty expertise at UW

  (800) 326-5300 or (206) 520-9700 (24/7)

  medcon@uw.edu (monitored 7AM-6PM)



Questions!