Human Papilloma Virus Infection in Adolescents and Young Adults

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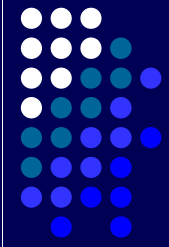
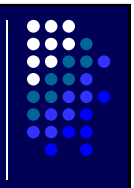


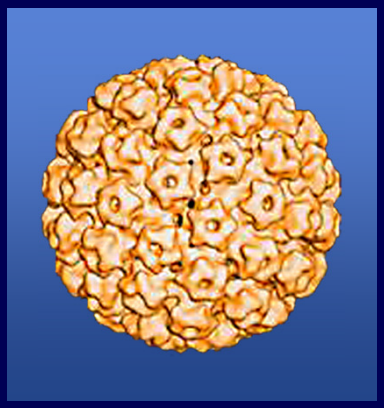
Learning Objectives



- Review background information on Human Papilloma Virus (HPV) and HPV infection in adolescents and young adults: epidemiology, clinical manifestations, diagnosis, and treatment
- Review short- and long-term sequelae of HPV infection
- Discuss strategies to prevent ano-genital HPV infections, including vaccination

HPV

Nonenveloped double-stranded DNA virus[1]

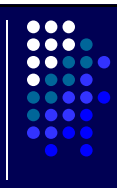


- >100 types identified
- ~40 infect anogenital area
  - 15–20 oncogenic ("high risk") types, including 16, 18, 31, 33, 35, 39, 45, 51, 52, 58
  - Nononcogenic ("low risk") types include: 6, 11, 40, 42, 43, 44, 54
    - HPV 6 and 11 are most often associated with external genital warts.

Mechanisms of HPV Transmission and Acquisition

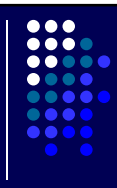
- Sexual contact
  - Through sexual intercourse: most common
    - Correct and consistent condom use helps reduce the risk of transmission, but it is not fully protective.
  - Genital–genital, manual–genital, oral–genital transmission: uncommon
    - Genital HPV infection in virgins is rare, but may result from nonpenetrative sexual contact.
- Nonsexual routes
  - Mother to newborn (vertical transmission): rare
  - Auto-inoculation (hand to genital, etc)
  - Fomites (eg, shared objects): extremely rare

Epidemiology of Genital HPV infection



- HPV is the most prevalent STI in the US
- About 75% of HPV infections occur in 15-24 yo
- Often acquired w/in months after first sexual intercourse
- Estimated that ~50% of sexually active women and men will have acquired genital HPV at some point (but most will never know they were infected)
- HPV is usually asymptomatic and is not a reportable STI—thus any incidence or prevalence numbers are certainly underestimates

Why is HPV so prevalent?



- Natural infection does not → immunity
  - Infection with HPV does NOT cause cell death or viremia → thus there is little stimulation of the host immune system
  - The host immune response that does develop is slow and weak
- Treatment of infection is difficult and often not curative; no anti-viral treatment exists

Risk factors for genital HPV infection

- Younger age at 1st intercourse (≤ 17 yo)
- Number of sex partners
- Number of partner's partners
- Older age of male partner
- Cigarette smoking
- Non-use of condoms
- Immunosuppression (impaired T cell numbers or function)

Clinical Manifestations:

from annoying to deadly

- Genital warts (condylomata) *[occur early p infxn]*
  - 90% are caused by types 6 and 11
  - Most common in those < 25 yo
- Cervical dysplasia *[occurs months later]*
  - Squamous intraepithelial lesion (dx by cervical cytology [Pap] screening)
  - Cervical intraepithelial neoplasia (dx by colposcopy with biopsy)
- Cervical cancer; squamous cell carcinomas of vulva, vagina, anus or male genitalia *[occurs 10-15 yrs later]*
- Oral-pharyngeal cancers *[occur many years later]*

Genital Warts In Women

Photo courtesy of The Cincinnati STD/HIV Prevention Training Center

Mild/ Inconspicuous

Photo courtesy of Dr.. **A. Ferenczy**

Moderate to Severe

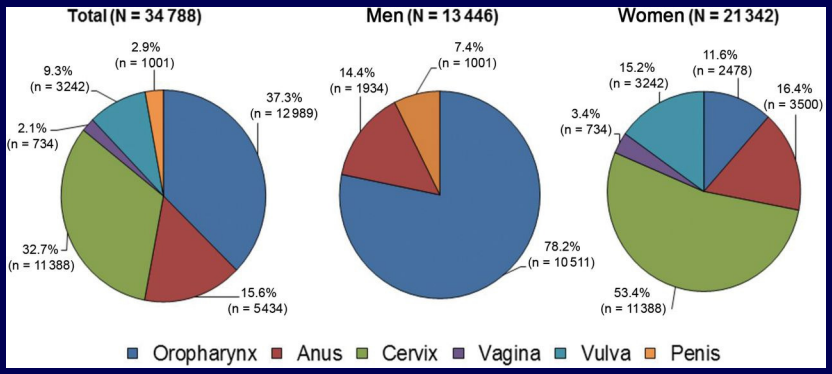
Genital Warts In Men

Cancers Caused by HPV Types 6, 11, 16, and 18

HPV TYPE	APPROXIMATE DISEASE BURDEN
16	90% of oropharyngeal cancers
16 and 18	-70% of cervical cancers and pre-cancers - 50% of vaginal, vulvar and penile cancers -80% of anal cancers

Number of new human papillomavirus (HPV)–associated cancers overall, and by sex, in the United States, 2009

Number of new human papillomavirus (HPV)–associated cancers overall, and by sex, in the



Jemal A et al. JNCI J Natl Cancer Inst 2013;jnci.djs491

JNCI

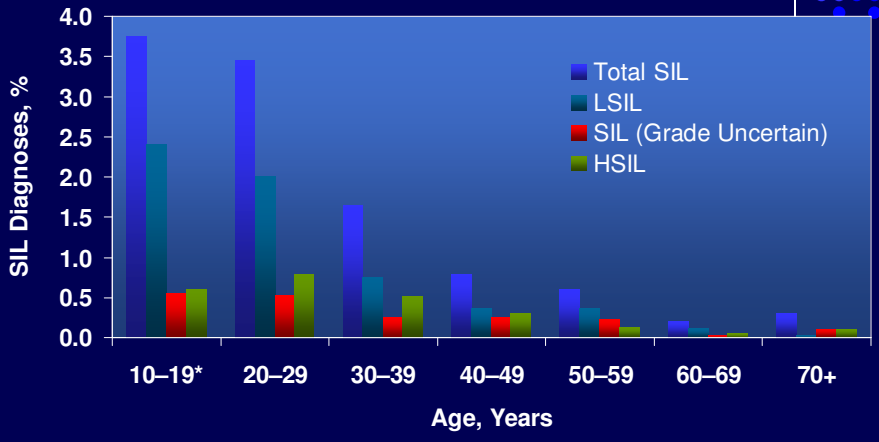
Cervical Intraepithelial Neoplasia (CIN)[1]

CIN 1 | CIN 2 | CIN 3

- CIN Stages[2]
  - CIN 1: Mild dysplasia
  - CIN 2: Moderate dysplasia
  - CIN 3: Severe dysplasia; includes carcinoma in situ (CIS)

1. Reprinted with permission from Dr. JW Sellors and Dr. R Sankaranarayanan. Sellors JW et al, eds. Lyon, France: International Agency for Research on Cancer; 2003. *Colposcopy and Treatment of Cervical Intraepithelial Neoplasia. A Beginner's Manual.* Reprinted with permission of the International Agency for Research on Cancer, World Health Organization. 2. Bonnez W et al. In: Richman DD et al, eds. *Clinical Virology.* 2nd ed. American Society for Microbiology, Washington, DC. 2002:569–611.

Prevalence of Abnormal Cervical Cytology is Highest at Younger Age

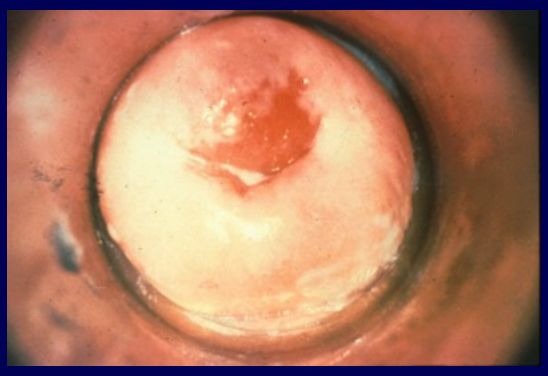


SIL = squamous intraepithelial lesions.
LSIL = low-grade squamous intraepithelial lesions.
HSIL = high-grade squamous intraepithelial lesions.
*N=10,296 Pap smear diagnoses.
From Mount SL, Papillo JL. *Pediatrics.* 1999;103:539–545. Reprinted with the permission of the American Academy of Pediatrics.

Risk factors for genital HPV infection: role of the immature cervix

- The squamo-columnar junction ("transformation zone") is relatively exposed on the cervix of young women
- Columnar cells are more vulnerable to infection by HPV and other STIs
- This area of actively dividing cells is vulnerable to HPV infection and viral replication

Normal cervix: transformation zone with squamous and columnar epithelia



Anal Cancer

- ~ 90% of cases are HPV-related
- Dramatic increase in prevalence over past 30 yrs
- More common in women than men
- Risk factors
  - Presence of HPV in the ano-genital area
  - # of sex partners
  - Receptive anal intercourse [strong risk factor but not required]
  - Smoking
  - Immunosuppression

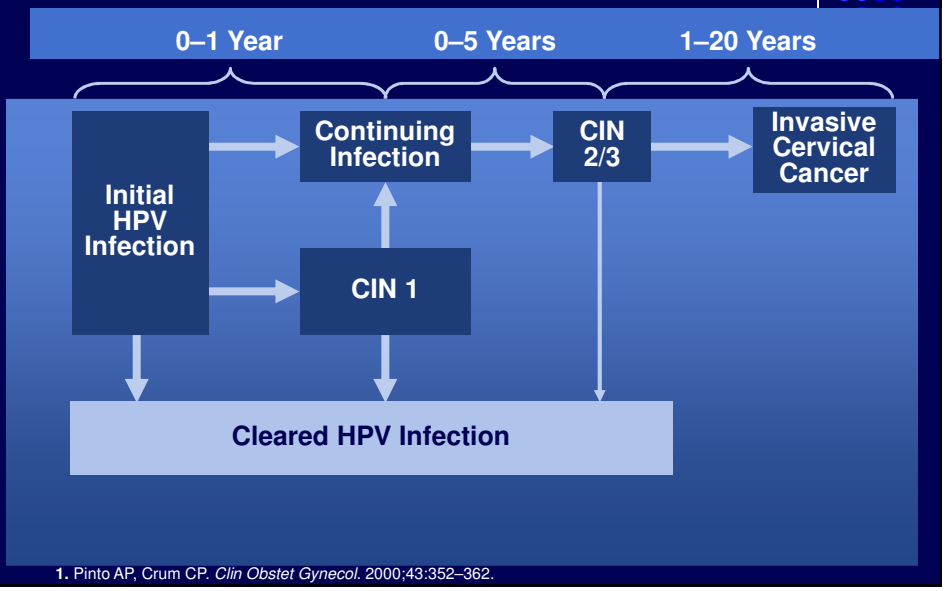
Natural history of HPV infection

- Most HPV infections are transient and asymptomatic, regressing as a result of host humoral and cellular immunity
  - Especially in adolescents
  - Especially for low-risk HPV type
- Approximately 70% of new infections clear within 1 year and 90% within 2 years

HPV Persistence

- Persistent infection: Detection of same HPV type two or more times over several months to 1 year
- Persistent infection with high-risk types of HPV (especially 16 and 18) is crucial for development of cervical pre-cancerous lesions and cancer
- Persons who are immunosuppressed are much more likely to have persistent infection and to progress to pre-cancerous lesions and cancer

Natural History of HPV Infection and Potential Progression to Cervical Cancer



1. Pinto AP, Crum CP. *Clin Obstet Gynecol.* 2000;43:352–362.

Diagnosing HPV Infection

- Clinical exam
- Cervical cytology (Pap) screening
- Swabs of ano-genital area (not recommended for routine clinical use)
- ?? Anal cytology
  - No national guidelines for routine screening
  - Unknown efficacy to decrease anal cancer

Diagnosing cervical dysplasia by Pap testing/cervical cytology

- Atypical squamous cells of undetermined significance (ASCUS) or cannot exclude high-grade SIL (ASC-H)
  - *Often related to HPV infection*
- Low-grade squamous intraepithelial lesion (LSIL) = mild dysplasia, CIN1
  - *~ always related to HPV infection*
- High-grade SIL (HSIL) = moderate and severe dysplasia, CIS, CIN 2-3
  - *~ always related to HPV infection*

Current Recommendations for Cervical Cytology (Pap) Screening

- Begin screening at age 21 years**
- Cytology screening every year if doing Pap smear/every 2 years if doing liquid based test
- Immunocompromised (HIV +, transplant, etc.) women need screening twice/year post diagnosis and then annually if results are normal

** *Still need to screen for other STIs*

Basis for these recommendations

- Most HPV infections in adolescents are transient
- Most LSIL resolves spontaneously
- LSIL takes several years to progress to HSIL (if at all)
- Risk of HSIL is low, even w/ with high risk HPV
- Pap smears on young women often lead to unnecessary testing, invasive procedures, etc.

Treatment of HPV Infection

- Genital warts
  - Destruction: podofilox; trichloroacetic acid; cryosurgery; electrosurgery; laser ablation
  - Surgical excision
  - Stimulate the immune system: imiquimod; interferon
  - ? No treatment—may resolve spontaneously
  - ***No one treatment is best; recurrence is common***
- Persistent abnormal cervical cytology
  - Remove/destroy the neoplastic cells by: cryocautery, electrocautery, laser cautery, loop electrical excision procedure (LEEP), or cervical conization
- Recurrent respiratory papillomatosis in infants

Prevention of HPV infection

- Behavioral strategies
  - Delay age of first intercourse
  - Limit number of sexual partners
  - Avoid use of cigarettes
  - Correct and consistent use of condoms
- Vaccination

HPV Vaccination

- Two FDA-licensed vaccines: Gardasil® and Cervarix®
- Both are made of the protein outer coat of HPV, combined into virus-like particles (VLP) [NO live virus or HPV DNA]
- Both produce a strong and lasting humoral immune response
- Given IM
- Dosing schedule: 0, (1)2, 6 months
- Should complete the series with the same vaccine

HPV Vaccines: GARDASIL®

- A quadrivalent vaccine containing HPV 6/11/16/18 virus-like particles
- Approved by FDA for use in 9-26 yo females (6/06) and for 9-26 yo males (10/09)
- Highly effective for the prevention of ano-genital cancers and pre-cancers
- Highly effective (99%) for the prevention of genital warts

Cervarix©

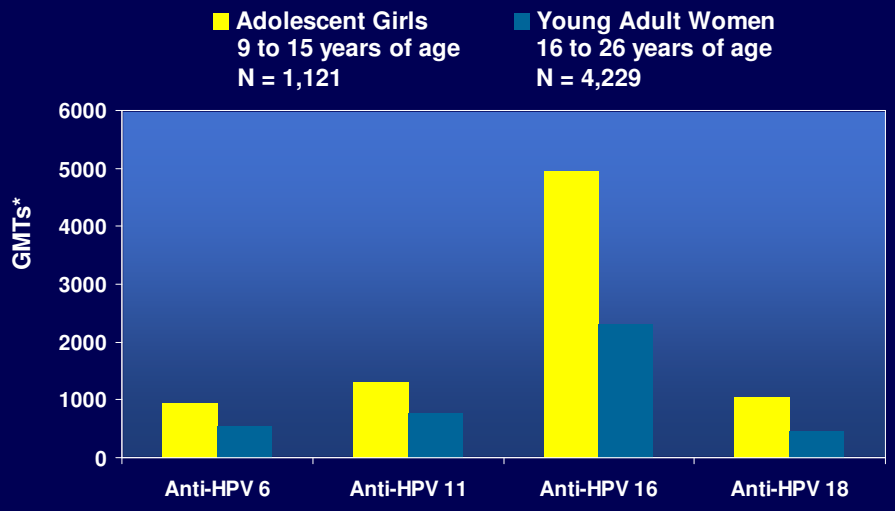
- Bivalent vaccine (types 16 and 18)
- Similar efficacy to quadrivalent vaccine against these two types
- Approved by FDA for use in for females age 9-25 (10/09); not approved for use in males
- Does not prevent infection with types 6 and 11 (genital warts)

ACIP (10/09) did not voice a preference for either vaccine to prevent cervical cancers and pre-cancers in females

Assessing efficacy of Gardasil in teens

- The end point used in the clinical trials in older teens and adults was cytologic abnormalities (pre-cancers and cancers), but these would not be expected in young adolescents or children
- Thus humoral immune response in pre-adolescents was used to "bridge" with efficacy data from 16-26 year olds

Bridging the Efficacy of GARDASIL® From Young Adult Women to Adolescent Girls

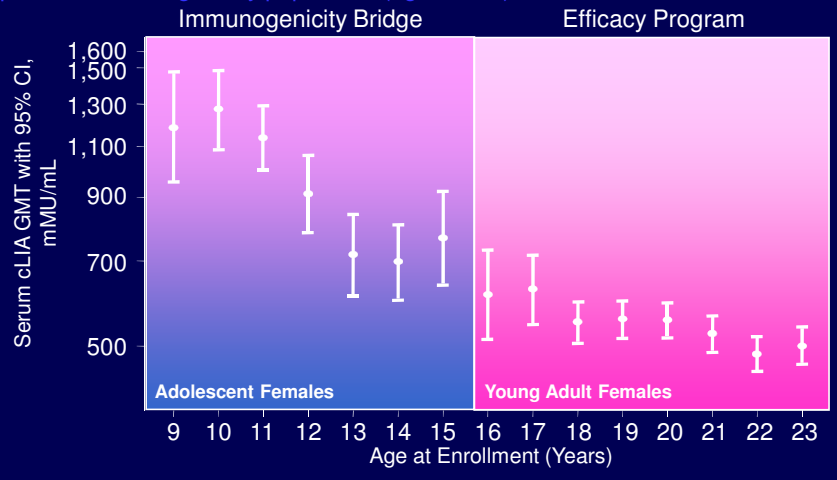


*GMT = Geometric mean titer in mMU/mL (mMU = milli-Merck units).

Neutralizing Antibodies by Age at Enrollment

Neutralizing anti-HPV 6 GMTs at Month 7

Per-protocol immunogenicity population (ages 9–26)



*Inclusive of 5 study protocols; all GMTs measured using cLIA.

Vaccine-Related Adverse Experiences*

- At injection site: pain, swelling, itching, bruising, and redness
- Systemic (sx usually mild): headache, fever, nausea, dizziness, vomiting
- Dizziness/fainting – most common in adolescents/young adults (observe for 15 min after giving)
- Post-licensure safety monitoring from 6/06 through 3/12 continued to show no new HPV vaccine safety concerns

*As of 7/12, approx. 46 million doses of quadrivalent HPV vaccine were distributed in the US

Interrupted vaccine schedules

(based on data from clinical trials)

	GARDASIL	CERVARIX
Minimum interval between dose 1 & 2	4 weeks	4 weeks
Minimum interval between dose 2 & 3	12 weeks	
Minimum interval between dose 1 & 3	24 weeks	20 weeks

If the series is interrupted, administer dose 2 as soon as possible and space dose 3 as noted above

Impact of HPV Vaccination

- These are prophylactic vaccines
- Those already infected with one or more vaccine-related HPV types
  - Are not protected against disease progression (no known therapeutic benefit)
  - Are protected from clinical disease caused by the remaining vaccine HPV types. *Thus, even if already evidence of HPV infection (genital warts, abnormal Pap, etc.), these patients will still benefit from vaccine*

Why target pre-adolescents?

- There are two other vaccines recommended for this age group, and the concept of a 11-12 year old "well visit" is more established
- Younger teens have higher antibody responses *(highest response < puberty)*
- Age-based strategies are much more effective at getting kids immunized than are risk-based strategies (compare to Hep B); no "risk factors" have been identified that accurately predict which patients will acquire HPV

ACIP Recommendations

FEMALES

- Routine vaccination at 11–12 years of age (can be started at 9)
- Catch-up vaccination for 13–26 year olds if not previously vaccinated or who have not completed the 3-dose series

MALES

- Routine vaccination with quadrivalent vaccine at 11-12 years of age (can be started at 9)
- Catch-up vaccination for 13-21 year olds if not previously vaccinated or who have not completed the 3-dose series; males aged 22 through 26 years may be vaccinated

ACIP Recommendations (*cont*)

- Ideally, vaccine should be administered before potential exposure to HPV.
- Each HPV vaccine is administered IM in a 3-dose schedule: dose #2 given (1)2 months later and dose #3 given 6 months after the first dose.
- HPV vaccine can be administered at the same visit at which other age-appropriate vaccines are provided, such as Tdap and MCV4.

ACIP Recommendations (*cont*)

- Current recommendations for cervical cancer screening have not changed for females who receive HPV vaccine.
- Immunocompromised females can receive HPV vaccine.
  - However, the immune response to vaccination and vaccine effectiveness might be less than in females who are immunocompetent.
- HPV vaccine is contraindicated in people with a history of immediate hypersensitivity to yeast or to any vaccine component.

ACIP Recommendations Endorsed by Other Organizations

- American Academy of Pediatrics
- American Academy of Family Physicians
- American College of Obstetricians and Gynecologists
- American College of Physicians
- Society for Adolescent Health & Medicine
- American Cancer Society (but said insufficient evidence to recommend for or against catch up vaccination for females 19-26 yrs]

Parental Concerns about HPV Vaccination

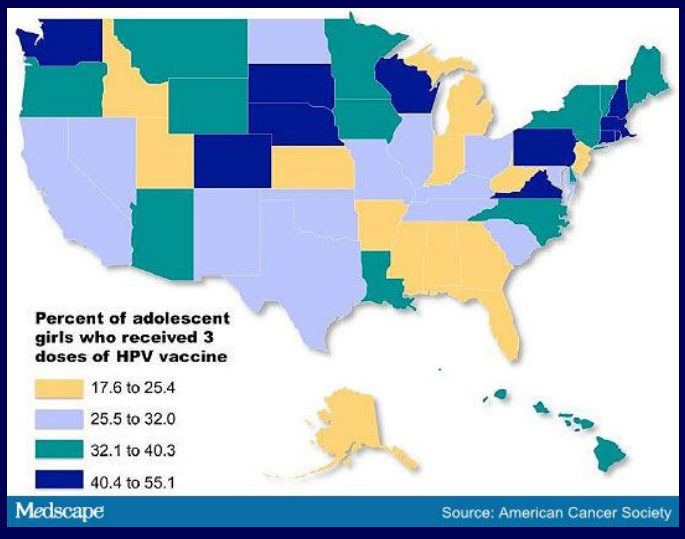
- Is immunizing against HPV "license" to be sexually active?
  - Prescribing OCPs or distributing condoms have not been shown to increase sexual activity
  - In general, concerns about acquiring a STI does not play a big role in teens' sexual behavior (thus no reason to think a vaccine against a STI will have much influence)
- Focus groups with parents have shown general acceptance of a STI-prevention vaccine, given the potential seriousness of the outcome (cancer) and the lack of effective treatments for infection

So How Successful Have We Been at Vaccinating Teens and Young Adults against HPV?

NOT!!

HPV Vaccination Coverage in the US (2010)

- 48.7% of 13-17 yo females had received ≥ one dose
  - Only 32% had completed the 3-dose series
- % vaccinated is even lower in some Southern states [states w/ high cervical CA incidence] and in uninsured girls
- Healthy People 2020 target = 80% coverage rate



Effectiveness of HPV Vaccine: a recent report*

- Denmark has provided quadrivalent HPV vaccine to all 12 yo females since 2009 and catch-up vaccine to those females up to age 15 since 2008 → 80-85% vaccine coverage
- The incidence of genital warts in young women has decreased 45.3% between 2007-2011, virtually eliminating genital warts in this group

*Sexually Transmitted Diseases 2013; 40:130-135

Resources

General info on HPV

http://www.cdc.gov/hpv/

CDC fact sheet

http://www.cdc.gov/std/hpv/STDFact-HPV-vaccine.htm

ACIP recommendations

http://www.cdc.gov/nip/vaccine/hpv

Immunization Action Coalition (handouts, FAQs, videos)

http://www.immunize.org/hpv/