CERVICAL CANCER PREVENTION

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Learning Objectives

Upon completion of this content, the learner will be able to

1. Describe the epidemiology of genital HPV infection in the U.S.;
2. Discuss the clinical manifestations of genital HPV infection;
3. Identify methods used to diagnose cervical cellular abnormalities;
4. Summarize Vaccine guidance for HPV vaccine

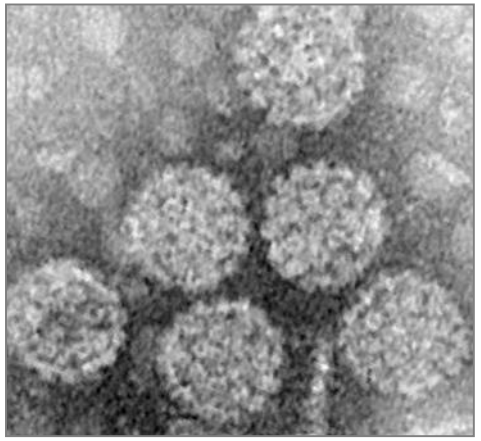
Incidence in the U.S.

- Estimated annual incidence of sexually- transmitted HPV infection is 14.1 million
- Estimated $1.7 billion spent annually in direct medical costs to treat conditions associated with genital HPV infection
- An estimated 79 million females aged 14–59 years are infected with HPV infection.

Incidence and Prevalence of HPV-associated Diseases

- Genital warts
  - Incidence may be as high as 100/100,000.
  - An estimated 1.4 million may be affected at any one time.
- Cervical cancer
  - Rates of cervical cancer have fallen by approximately 75% since the introduction of Pap screening programs.
  - Incidence is estimated at 8.1/100,000.

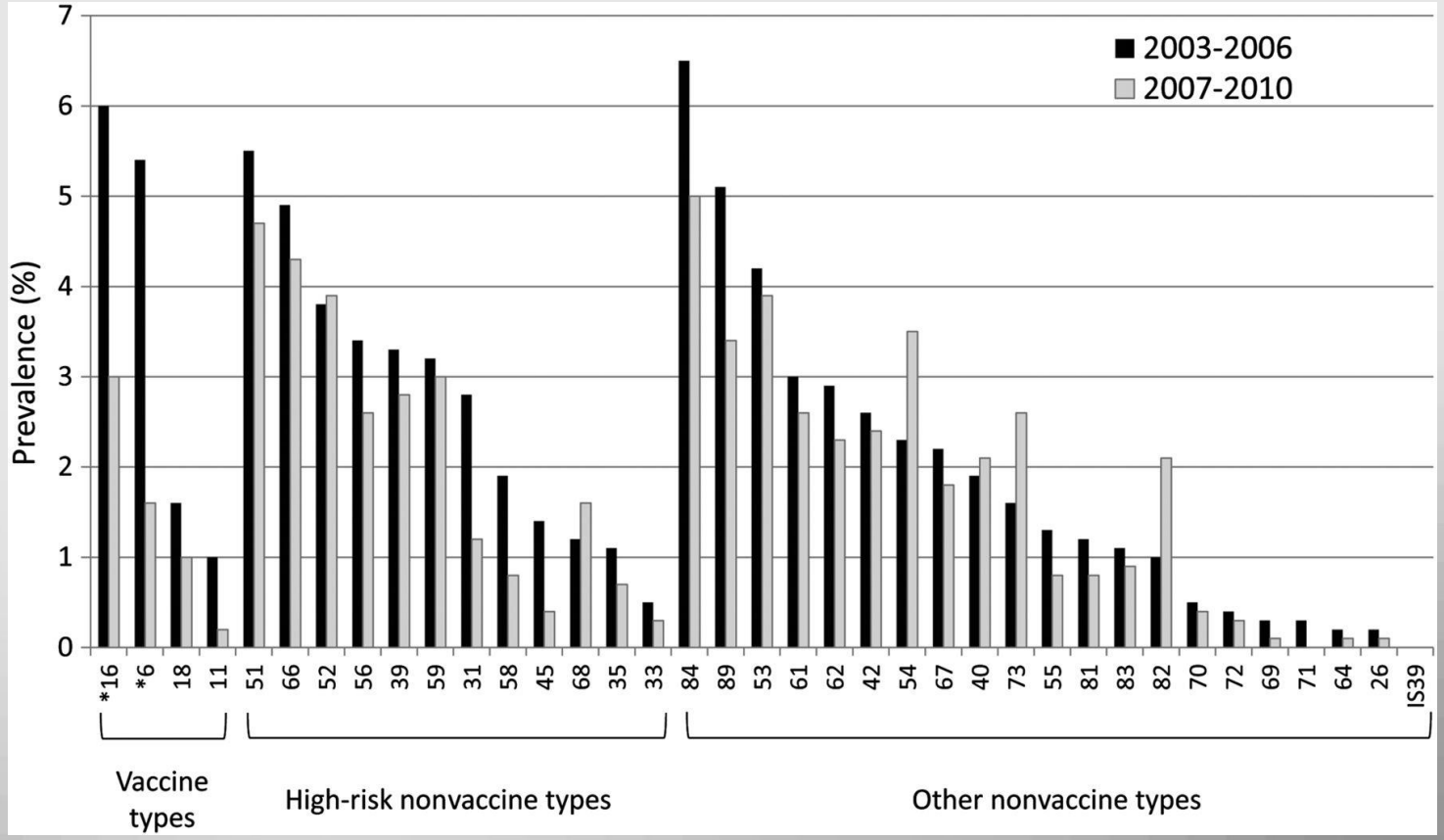
Human Papillomaviruses (HPV)



- Double stranded DNA virus
  - More than 130 closely related viruses
  - Types numbered in order of discovery (L1)
  - Classified as low risk (non-oncogenic) or high-risk (oncogenic)
- Almost all males and females will be infected at least once in their lifetime
  - Most people not aware when infected
  - Necessary but not sufficient for development of cancer
- Estimate 79 million Americans currently HPV infected
  - Most common sexually transmitted pathogen in males and females
  - 6.2 million new infections each year
  - 26,200 new HPV cancers each year

HPV Prevalence

Prevalence of human papillomavirus (HPV) types among females aged 14–19 years, 2003–2006 and 2007–2010.



Markowitz L E et al. J Infect Dis. 2013;208:385-393

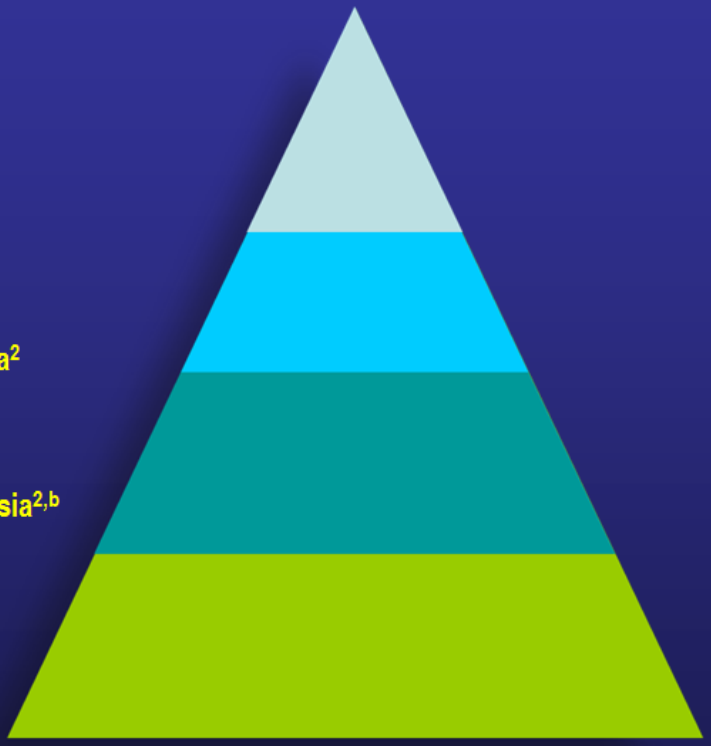
Estimated Annual Burden of HPV-Related Diagnoses in the United States, 2012[a]

WOMEN
~12,200 new cases of cervical cancer[1]
~4,500 new cases of vulvar cancer[1,b]
~2,700 new cases of vaginal cancer[1,b]
MEN and WOMEN
~6,200 new cases of anal cancer[1,b]

WOMEN
~330,000 new cases of high-grade cervical dysplasia[2]

WOMEN
~1.4 million new cases of low-grade cervical dysplasia[2,b]

MEN and WOMEN
~1 million new cases of genital warts[3]



Estimated new HPV infections per year (incidence): ~6.2 million[4]
Estimated active HPV infections (prevalence): ~20 million[4]

[a]Case counts for HPV-related diagnoses are not all related to HPV types 6, 11, 16 and 18.
[b]Not all cases are related to HPV infection.

HPV=human papillomavirus.

1. American Cancer Society (ACS) Cancer Facts & Figures 2012. cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf. Accessed January 3, 2013. **2.** Schiffman M et al. *Arch Pathol Lab Med*. 2003;127:946–949. **3.** Fleischer AB et al. *Sex Transm Dis*. 2001;28:643–647. **4.** Centers for Disease Control and Prevention (CDC). *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 12th ed. Chapter 10: Human papillomavirus. cdc.gov/vaccines/pubs/pinkbook/downloads/hpv.pdf. Accessed January 3, 2013.

HPV-associated cancers United States, 2004-2008

Anatomic Area	Average annual number of cases*	Estimated+ HPV attributable	Estimated+ HPV 16/18 attributable
Cervix	11,967	11,500	9,100
Vagina	729	500	400
Vulva	3,136	1,600	1,400
Anus (F)	3,089	2,900	2,700
Oropharynx (F)	2,370	1,500	1,400
Total (Females)	**21,291**	**18,000**	**15,000**
Penis	1,046	400	300
Anus (M)	1,678	1,600	1,500
Oropharynx (M)	9,356	5,900	5,600
Total (Males)	**12,080**	**7,900**	**7,400**

* Defined by histology and anatomic site; Watson M et al. Cancer 2008. Data source: National Program of Cancer Registries and SEER, covering 100% coverage of US population. + Gillison ML, et al. Cancer 2008 . Ref: Human Papillomavirus-Associated Cancers MMWR 2012;61(15):258-261.

Perianal Warts

Source: Seattle STD/HIV Prevention Training Center at the University of Washington/ UW HSCER Slide Bank

POPULATION	PAGE NUMBER	RECOMMENDED SCREENING METHOD[a]	MANAGEMENT OF SCREEN RESULTS	COMMENTS
Aged < 21 y	153	No screening		HPV testing should not be used for screening or management of ASC-US in this age group
Aged 21-29 y	154-155	Cytology alone every 3 y	HPV-positive ASC-US[b] or cytology of LSIL or more severe: Refer to ASCCP guidelines[2]	HPV testing should not be used for screening in this age group
			Cytology negative or HPV-negative ASC-US[b]: Rescreen with cytology in 3 y	
Aged 30-65 y	155-162	HPV and cytology "cotesting" every 5 y (preferred)	HPV-positive ASC-US or cytology of LSIL or more severe: Refer to ASCCP guidelines[2]	Screening by HPV testing alone is not recommended for most clinical settings
			HPV positive, cytology negative: Option 1: 12-mo follow-up with cotesting Option 2: Test for HPV16 or HPV16/18 genotypes • If HPV16 or HPV16/18 positive: refer to colposcopy • If HPV16 or HPV16/18 negative: 12-mo follow-up with cotesting	
			Cotest negative or HPV-negative ASC-US: Rescreen with cotesting in 5 y	
		Cytology alone every 3 y (acceptable)	HPV-positive ASC-US[b] or cytology of LSIL or more severe: Refer to ASCCP guidelines [2]	
			Cytology negative or HPV-negative ASC-US[b]: Rescreen with cytology in 3 y	
Aged > 65 y	162-163	No screening following adequate negative prior screening		Women with a history of CIN2 or a more severe diagnosis should continue routine screening for at least 20 y
After hysterectomy	163-164	No screening		Applies to women without a cervix and without a history of CIN2 or a more severe diagnosis in the past 20 y or cervical cancer ever
HPV vaccinated	164-165	Follow age-specific recommendations (same as unvaccinated women)		

ASCCP indicates American Society for Colposcopy and Cervical Pathology; ASC-US, atypical squamous cells of undetermined significance; CIN2, cervical intraepithelial neoplasia grade 2; HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion.

[a]Women should not be screened annually at any age by any method.

[b]ASC-US cytology with secondary HPV testing for management decisions.

Saslow, D., Solomon, D., Lawson, H. W., Killackey, M., Kulasingam, S. L., Cain, J., Garcia, F. A. R., Moriarty, A. T., Waxman, A. G., Wilbur, D. C., Wentzensen, Spitzer, M., Moscicki, A.-B., Franco, E. L., Stoler, M. H., Schiffman, M., Castle, P. E., Myers, E. R. and ACS-ASCCP-ASCP Cervical Cancer Guideline Committe American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the pr detection of cervical cancer. CA: A Cancer Journal for Clinicians, 62: 147–172. doi: 10.3322/caac.21139

Classification of Cervical Cellular Abnormalities

2001 Bethesda System

- Atypical Squamous Cells (ASC-US and ASC-H) are cells that do not appear to be completely normal
  - Atypical Squamous Cells of Undetermined Significance (ASC–US)
    - Changes are often caused by HPV infection.
    - Changes are usually mild.
  - Atypical Squamous Cells cannot exclude a High-Grade Squamous Intraepithelial Lesion (ASC–H).
    - Changes are more likely to be associated with precancerous abnormalities than ASC-US.

Classification of Cervical Cellular Abnormalities-continued

- Low-grade squamous intraepithelial lesion (LSIL)
  - Usually transient, caused by HPV infection
- High-grade squamous intraepithelial lesion (HSIL)
  - Generally changes due to persistent infection with a high-risk HPV type
  - Lesions associated with HSIL have a higher risk for progression to cervical cancer.

Diagnosis of Cervical Cellular Abnormalities-continued

- Colposcopy
  - Indication guided by physical exam or Pap test findings with or without HPV DNA test findings
- Cervical biopsy
  - May be indicated if there is/are
    - Visible exophytic lesions on cervix
    - Pap test with HSIL, ASC-H, or other findings
- The ASCCP has released the Updated Consensus Guidelines on the Management of Women with Abnormal Cervical Cancer Screening Tests and Cancer Precursors © 2013.http://www.asccp.org/Guidelines-2/Management-Guidelines-2

Current Therapeutics and Vaccines in the Field

Prevention versus Treatment

HPV vaccine (Prevention)

- Primary prevention in 13-17 year old girls and boys, Maryland NIS 2013

Gender	HPV > 1 Dose	HPV > 3 Doses
Girls	57.3%	37.6%
Boys	34.2%	13.9%

Aldara Cream

(Genital wart Treatment)

- Women
  - In clinical trials for Imiquimod vs LEEP for CIS, CIN 3, CIN, VulvarIN
- Male-male intercourse
  - Anal dysplasia application
- HIV positive persons
  - Anal HSIL

TOPICAL TERAMEPROCOL FOR THE TREATMENT OF EARLY HPV

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6329a4.htm#tab1

9-Valent HPV vaccine (9vHPV)

- Licensed by FDA December 10, 2014
  - Females 9-26 yrs, males 9-15 yrs
  - Trials conducted with 3-dose schedule
- L1 VLP vaccine, similar to quadrivalent HPV vaccine
- Targets 5 additional high risk types
  - 6,11,16,18, **31,33,45,52,58**
- Males 16-26 yrs - not part BLA submitted in 2013
  - Data presented to ACIP October 2014
  - sBLA submitted to FDA

BLA – Biologics License Application

Available HPV vaccines

	Bivalent (Cervarix)	Quadrivalent (Gardasil)	9-valent (Gardasil 9)
Manufacturer	GlaxoSmithKline	Merck	Merck
L1 VLP types	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45 ,52, 58
Adjuvant	AS04: 500 µg aluminum hydroxide 50 µg 3-*O*-desacyl-4'-monophosphoryl lipid A	AAHS: 225 µg amorphous aluminum hydroxyphosphate sulfate	AAHS: 500 µg amorphous aluminum hydroxyphosphate sulfate
Licensed	Females 9-25 years	Females 9-26 years Males 9-26 years	Females 9-26 years Males 9-15 years

L1 – Major capsid protein ; VLP – virus like particle

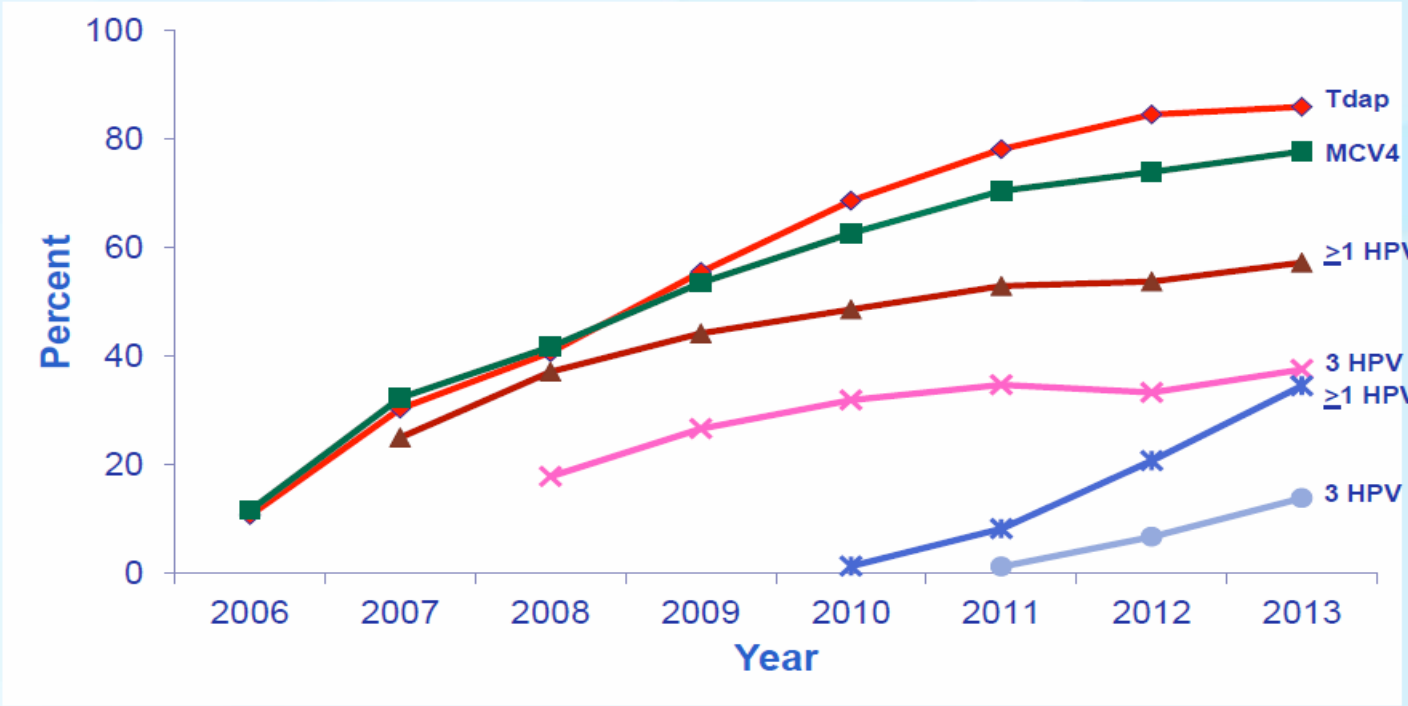
Current recommendations for HPV vaccination in the United States

- Routine vaccination at age 11 or 12 years*
- Vaccination recommended through age 26 for females and through age 21 for males not previously vaccinated
- Vaccination recommended for immunocompromised persons (including persons HIV-infected) and for men who have sex with men through age 26
- 3-dose schedule (0,1-2 and 6 months)

*The vaccination series can be started at age 9 years

Human papillomavirus vaccination. MMWR Recommendations and Reports 2014; 63

National estimated vaccination coverage levels among adolescents 13-17 years NIS-Teen, 2006-2013



NIS-Teen = National Immunization Survey-Teen
MMWR 2014:63;625-33

Total HPV doses distributed – Year-to-date (2012-2014)

Patient Counseling about HPV

- HPV infection is usually not detectable or harmful
- Almost everyone who has sex gets HPV infection at some point
- Positive HPV signals a sexually acquired infection but not an STD
- Positive HPV does not mean a cancer is present

QUESTIONS

Discussion?