Human Papillomavirus Infections:

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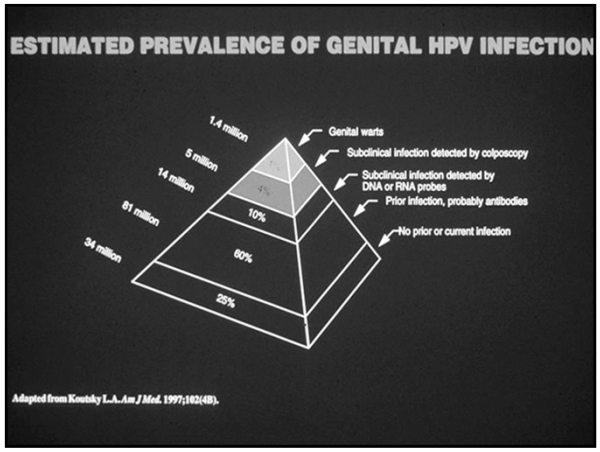
Human Papillomavirus Infection: Broad Overview

- More than 100 different serotypes
- Gaps in our knowledge about epidemiology and natural history
- Infection usually transient but may be lifelong
- Multiple infections are possible
- Limited to epidermal and dermal layers
- Certain types are oncogenic
- Pharmacologic therapy is not “curative”
- Vaccines relatively new protective

Global Incidence Rates of STDs: >330 Million New Infections Yearly

All HPV	200 million/yr?
Trichomonas	170 million/yr
Chlamydia	89 million/yr
Gonorrhea	62 million/yr
Genital Warts	30 million/yr
Herpes	20 million/yr
Syphilis	12 million/yr
HIV	5.5 million/yr
Hepatitis B	2.5 million/yr
Chancroid	2 million/yr



Introduction

- Genital HPV is one of the most common STDs.
- More than 30 HPV types can infect the genital tract.

Introduction

- HPV types are divided into 2 groups based on their association with cervical cancer:
  - Low-risk types associated with genital warts and mild Pap test abnormalities
  - High-risk types associated with mild to severe Pap test abnormalities and cervical cancer
- Most genital HPV infections are transient, asymptomatic, and have no clinical consequences.

National Rates of HPV Infection

- Estimated 20 million infections currently detectable
- Incidence rates approach 6.2 million new infections each year
  - 4.6 million of these in 15-24 age group

Total Costs of HPV Infection

- Recent estimates of total direct HPV-related costs in the United States: ~$3 billion per year[1]
  - Estimated total direct costs associated with anogenital warts: $167.4 million[1]

1. Chesson HW, Blandford JM, Gift TL, Tao G, Irwin KL. *Perspect Sexual Reprod Health.* 2004;36:11–19.

Prevalence in the U.S.

- It is estimated that **at least** 50% of sexually active men and women acquire genital HPV at some point in their lives.
- A recent estimate suggests 80% of women will have acquired genital HPV by the age of 50.

Incidence and Prevalence of Genital HPV-associated Diseases

- Genital warts
  - Incidence may be as high as 100/100,000.
  - An estimated 1.4 million are 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 8.3/100,000.

Genital warts — Initial visits to physicians' offices: United States, 1966–2007

Note: The relative standard error for genital warts estimates range from 17% to 29.3%.

SOURCE: National Disease and Therapeutic Index (IMS Health)

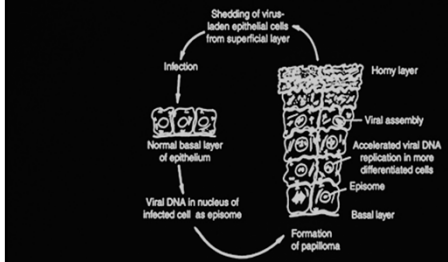
Epidemiologic Classification of Genital HPV Types and Disease

	HPV Types	Manifestations
Low Risk	**6, 11**, 40, 42, 43, 44, 53, 54, 55	•Low grade genital lesions •Condylomata acuminata •Recurrent respiratory papillomatosis
High Risk	**16, 18**, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82	• Low grade genital lesions • High grade genital lesions • Cervical cancer • other anogenital cancers

HPV Genotyping System

- Low-risk types
  - Most visible warts caused by HPV types 6 and 11
  - Recurrent respiratory papillomatosis associated with HPV types 6 and 11
- High-risk types
  - HPV types 16 and 18 found in more than half of anogenital cancers
  - Most women with high-risk HPV infection have normal Pap test results and never develop precancerous cell changes or cervical cancer

HPV REPLICATION AND CELL DIFFERENTIATION



Adapted from Ahmed et al. *Fields Virology*. 1990;1:241.

Pathology

- HPV infects stratified squamous epithelium and stimulates cellular proliferation.
- Affected cells display a broad spectrum of changes ranging from benign hyperplasia to dysplasia to invasive carcinoma.

Virology of HPV: Infection

- Once viral infection established, uses host cell to replicate and express viral proteins
- Requires cells actively dividing, so expresses proteins to inhibit cellular differentiation and stimulate continued cellular proliferation
- Unrestricted cell growth is **hallmark** of HPV infection

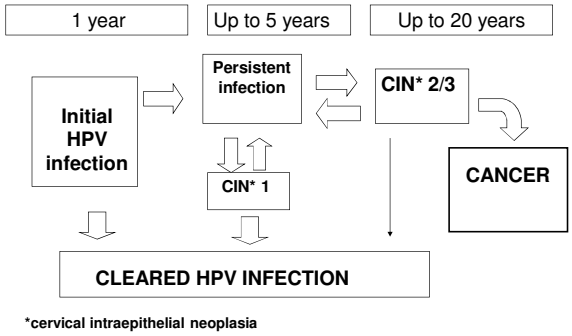
Transmission of Genital HPV

- Predominantly associated with sexual activity
- Can occur from asymptomatic and subclinical patients
- Infectivity after treatment of genital warts or cervical cell abnormalities is unknown

Transmission of HPV Infection

- Transmission may occur via:
  - Direct contact with lesions, or virus being shed in genital secretions, cells
    - May be sexual or nonsexual
  - Auto-inoculation
  - Fomites?

Natural History of HPV Infection and Cervical Cancer



*cervical intraepithelial neoplasia

Natural History of HPV

- Most genital HPV infections are transient, asymptomatic, or subclinical, and have no clinical consequences in immunocompetent individuals.
- The incubation period is unclear.
- The median duration of new cervical infections is 8 months but varies by type.
- Gradual development of an effective immune response is the likely mechanism for HPV DNA clearance.

Natural History of HPV (continued)

- **Persistent infection** is infection that is not cleared by the immune system and is characterized by persistently detectable HPV DNA.
  - HPV infection that persists is the most important factor for precancerous cervical cell changes and cervical cancer.
  - Most women with persistent HPV infection do not develop cervical cancer precursors or cervical cancer.

HPV Natural History cont

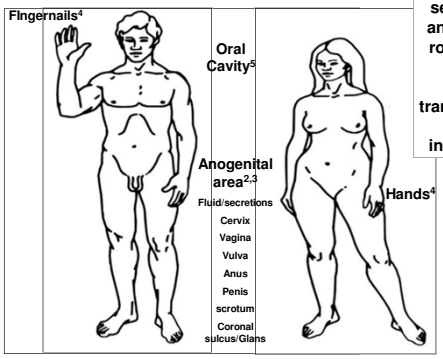
- Persistent infection with high-risk HPV types is associated with development of precancerous or cancerous cervical changes. Factors associated with persistence on the cervix are still being studied; so far, they include:
  - Older age,
  - Multiple partners,
  - High-risk HPV types,
  - Smoking, and
  - **HIV infection**

Natural History of HPV: Importance of Counseling Patients

- When patients have positive HPV DNA tests clinicians should explain:
  - Persistent, continuous infection as noted by positive tests over prolonged time is associated with high grade lesions
  - Incident infections that are cleared are not associated with disease
  - Overwhelming majority are latter

HPV and Cancer

Where HPVs are Found:



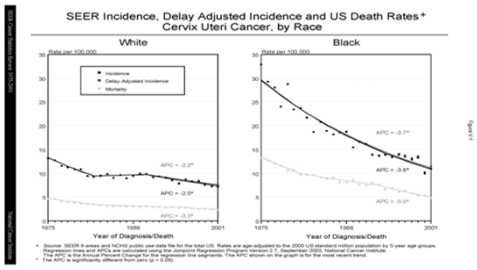
HPV can be spread via sexual contact and non-sexual routes such as vertical & horizontal transmission and auto-innoculation.[1,2]

1. Castellsague X et al. *BMC ID* 2009; 9:74. 2. Hernandez B et al. *EID* 2008;14(6):888-894. 3. Moscicki AB et al. *AIDS* 2003;17:311-20. 4. Sonnex C et al. *STI* 1999;75:317-319. 5. Sanchez-Vargas LO et al. *Infect Agent Cancer* 2010;5:25.

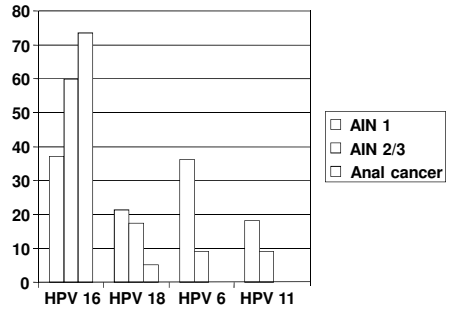
Cancers linked to HPV

• Cervical cancer	• 99.7%
• Vulvar cancer	• 50%
• Vaginal cancer	• 65%
• Penile cancer	• 35%
• Anal cancer	• 95%
• Oropharyngeal cancers	• 66%

Delay Adjusted Incidence and U.S. Death Rates of Cervical Cancer by Year of Diagnosis and Race: 1973-2001



Distribution of Certain HPV Types in AIN and Anal Cancer[1a]



[a]Meta-analysis of 29 studies

1.De Vuyst H et al. *Int J Cancer* 2009;124:1626-1636.

Anal Cancer
A Disease Affecting Both Men and Women

- Women account for 60% of the cases of anal cancer.[1]
  - Risk of anal cancer is elevated among women with cervical and vulvar cancers.[2]
  - Oncogenic HPV infections may spread to the anal canal from the cervix and vulva.[3]
- Although anal cancer occurs in both heterosexuals and men who have sex with men, MSM are at particularly high risk for anal HPV-associated disease.[3,4]

1.*Cancer Facts and Figures 2010.* American Cancer Society Web site. *http://www.cancer.org.* Accessed March 12, 2011. 2. Saleem AM et al. *Obstetrics and Gynecology* 2011;117:643-649. 3.Hoots BE et al. *Int J Cancer* 2009;124: 2375-2383. 4. Daling JR et al. *Cancer* 2004;101(2): 270-280.

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Anal Intercourse is Not Required for the Development of Anal Cancer

Percentages of men and women with anal cancer who reported **no** history of anal intercourse from selected studies[a].

Study	Females	Males (sexual orientation n/a)	Heterosexual males	Non-Heterosexual Males
Daling[1b] 2004	66% [83/127]	N/A	100% [54/54]	12.5% [6/48]
Daling[2c] 1987	83% [74/89]	74% [43/58]	N/A	N/A

[a]Studies included anal and rectal cancer cases.

[b]Between 1986 and 1998 in the Seattle area, men (*n* 119 patients) and women (*n* 187 patients) diagnosed with anal cancer were identified through the local Surveillance, Epidemiology, and End Results registry. Random-digit telephone dialing was used to ascertain control participants (n 1700) and identified participants were interviewed in person and provided blood samples. Archival tumor tissue was tested for human papillomavirus (HPV) DNA, and serum samples were tested for HPV type 16 (HPV-16).[1]

[c]Persons under 70 years of age were identified from records of population based cancer registries of 3 counties in whom anal cancer was diagnosed from Jan. 1978-Dec.1985. All histologic types of tumors were included. To elucidate risk factors for anal cancer, individuals were interviewed and blood specimens were obtained from 148 persons with anal cancer and from 166 controls with colon cancer. Interviewers were not blinded to the subjects' diagnoses or to hypotheses in general.

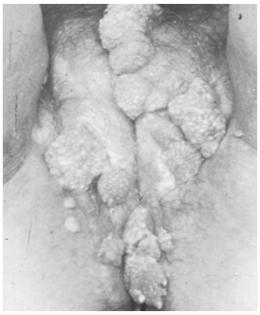
1. Daling JR et al. *Cancer* 2004;101:270-280. 2. Daling JR et al. *NEJM* 1987;317(16):973-977.

Oropharyngeal Squamous Cell Cancers (OSCC)

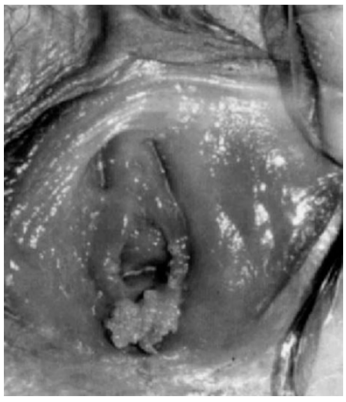
- HPV is a common and increasing cause of OSCC
  - Tonsilar and Tongue account for 90% of all OSCCs
  - 45%-100% associated with HPV
  - HPV 16 most prevalent

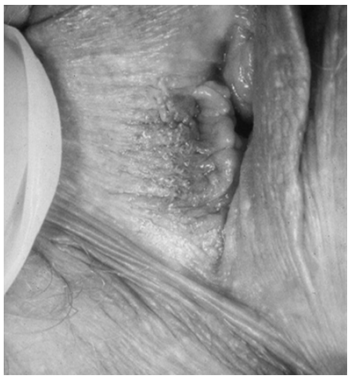
Warts

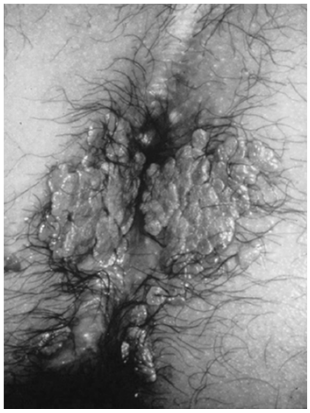
Female Genital Warts

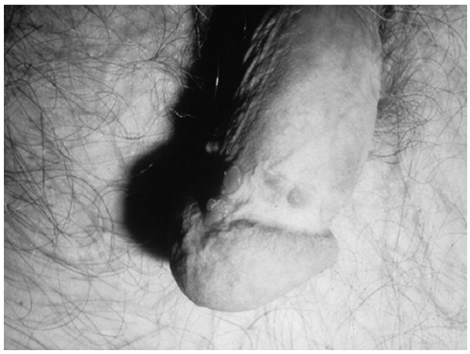


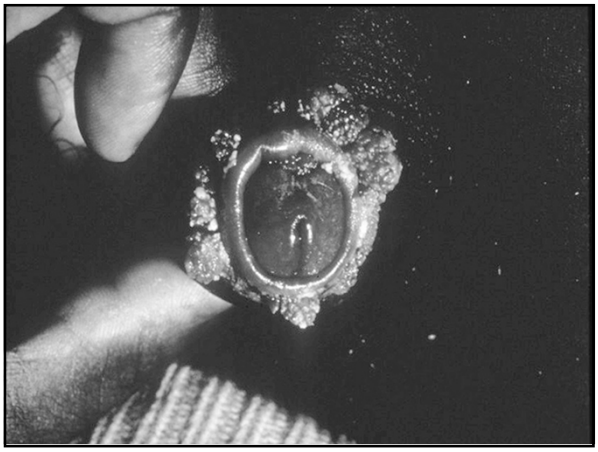
Source: CDC/NCHSTP/Division of STD, STD Clinical Slides





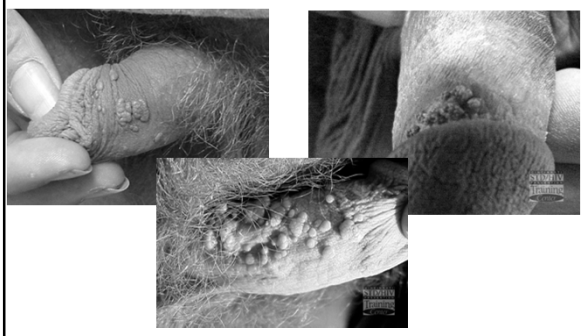






HPV

HPV Penile Warts

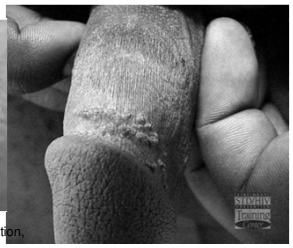


Source: Cincinnati STD/HIV Prevention Training Center

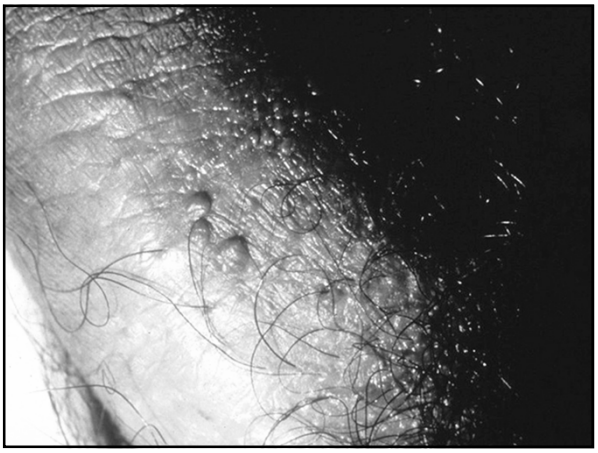
HPV

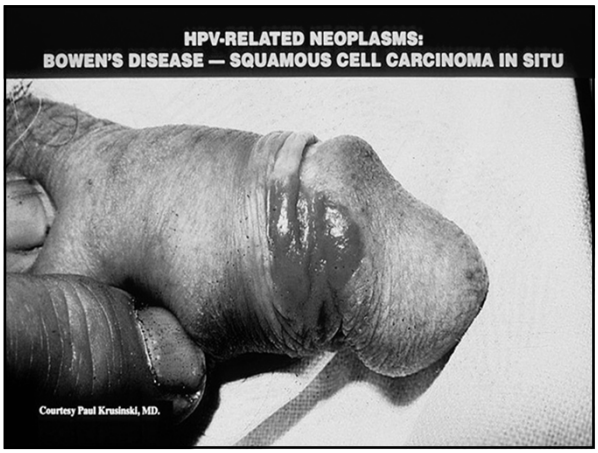
Genital Warts in a Male

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides



Source: Cincinnati STD/HIV Prevention Training C

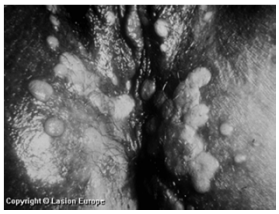


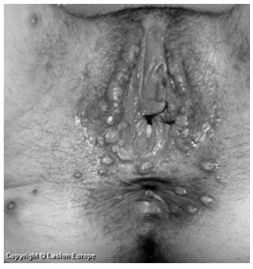


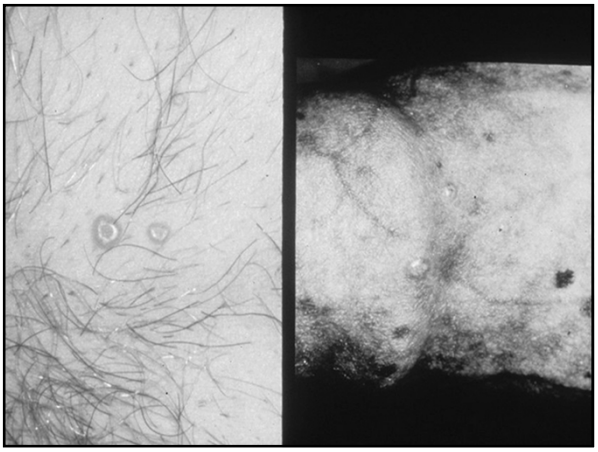
Differential Diagnosis of Genital Warts

- Infectious:
  - Condylomata lata
  - Molluscum contagiosum
- Seborrheic keratosis
- Nevi
- Normal Anatomic Structures:
  - Skin tags
  - Pearly penile papules
  - Sebaceous glands
  - Micropapillomatosis (exaggerated vulvar skin papillae)

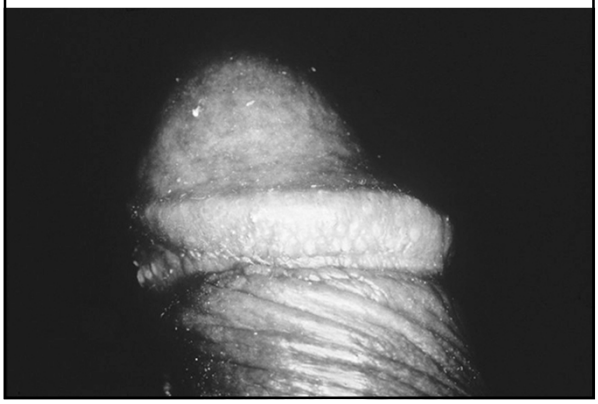
Condylomata lata (syphilis)







Benign Penile Papules



Diagnosis of Genital Warts

- Diagnosis is usually made by visual inspection with bright light.
- Diagnosis can be confirmed by biopsy when:
  - Diagnosis is uncertain
  - Concern for malignancy

General Treatment of Genital Warts

- Primary goal is removal of symptomatic warts.
- Untreated, genital warts may
  - regress spontaneously
  - persist with or without proliferation.
- In most patients, treatment can induce wart-free periods.
- Treatments may reduce but do not eradicate infectivity.
- Effect of current treatment on future transmission is unclear.

General Treatment of Genital Warts (continued)

- No evidence that presence of genital warts is associated with development of cervical cancer.
- Some patients may choose to forgo treatment and await spontaneous resolution.
- Screen persons with newly diagnosed genital warts for other STDs

Treatment of External Genital Warts

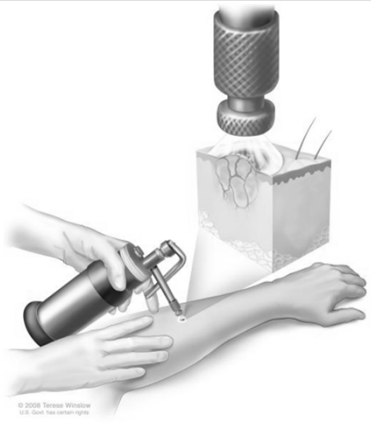
- Topical therapies may be:
  - Cytodestructive
  - Keratolytic
- No matter which topical therapy, response rates vary from 30-80% effectiveness
- Surgical treatments are more costly
- No therapy guarantees prevention of recurrences

Treatment Regimens

- Patient-applied and provider-administered therapies are available.
- Providers should be knowledgeable about and have available at least 1 patient-applied and 1 provider-administered treatment.
- Choice of treatment should be guided by:
  - The preference of the patient
  - The available resources
  - The experience of the healthcare provider

Treatment Regimens (continued)

- Factors influencing treatment selection:
  - Wart size
  - Number of warts
  - Anatomic site of wart
  - Wart morphology
  - Patient preference
  - Cost of treatment
  - Convenience
  - Adverse effects



Patient Applied Therapies

Treatment Response

- Affected by:
  - Number, size, duration, and location of warts, and immune status
- Many patients require a course of therapy rather than a single treatment.
- No evidence that any specific treatment is superior to any of the others.

Recurrence

- Up to 2/3 of patients will experience recurrences of warts within 6-12 weeks of therapy; after 6 months most patients have clearance.
  - If persistent after 3 months, or if there is poor response to treatment, consider biopsy to exclude a premalignant or neoplastic condition, especially in an immunocompromised person.
- Treatment modality should be changed if patient has not improved substantially after 3 provider-administered treatments or if warts do not completely clear after 6 treatments.

Complications

- Patients should be warned that persistent hypopigmentation or hyperpigmentation are common with ablative modalities.

Prevention

- Condoms
- Vaccine

HPV vaccines

- Gardasil (Merck)
  - Quadrivalent vaccine types 6/11/16/18
    - 6/11 associated with 90 % of genital warts
    - 16/18 associated with 75% of cervical cancers
  - FDA approved for use in girls and boy
- Cervarix (SK)
  - Bivalent vaccine types 16/18
  - FDA approved for use in girls

Human Papillomavirus Vaccines

- HPV4 vaccine is approved for
  - females 9 through 26 years of age for the prevention of cervical cancers, precancers and genital warts
  - males 9 through 26 years of age for the prevention of genital warts
- HPV2 vaccine is approved for
  - females 10 through 25 years of age for the prevention of cervical cancers and precancers
  - not approved for males or for the prevention of genital warts

HPV Vaccine Recommendations

- Recommended age for routine HPV vaccination is 11 or 12 years
- Vaccination is recommended for females 13 through 26 years of age not previously vaccinated or who have not completed the full 3-dose series
- HPV4 vaccination is recommended for males age 13-21 who have not completed the full 3-dose series

Vaccine Safety Concerns

- Much Media hype
- Review of all available data – from post marketing surveillance
  - Most side effects non-serious
    - arm pain and fainting
  - Of the serious events reported in VAERS (guillain Barre, DVT, death) none were more common than would be expected in general population. Several of the deaths following vaccine were from MVAs

Vaccine Safety Questions

5 Placebo controlled trials over 21,000 girls

- Post Marketing surveillance as of December 08
  - 11,916 VAERS reported possibly associated events
  - 94% non-serious/mostly fainting after vaccination
  - 6% serious events – Guillain Barre (no more that would be expected by chance), DVT/PE (most on BCP or other risk factor for DVT), deaths
- Experts found no common pattern to deaths including MVA's.
- Australia reported severe allergic reactions in 2.6/100,000 doses; greater than for meningococcal vaccine
- US reports an incidence of about 1.0/100,000 following any vaccine and no increased rate after Gardasil over unvaccinated girls

Pregnancy

- Vaccine is not to be given during pregnancy
- What about pregnancy safety?
  - About 800 inadvertent pregnancies reported to date
  - Rates of complications similar to reported for unvaccinated population

HPV Vaccine and Cervical Cancer Screening

- Cervical cancer screening recommendations NOT changed for vaccinated females
  - could subsequently be infected with a high-risk HPV type not in either vaccine
  - if sexually active prior to vaccination could have been infected with a vaccine-type HPV before vaccination

What can/should we do?

- Discuss the safety and efficacy of HPV vaccine.
- Educate on the potential seriousness of HPVrelated diseases.
- Clearly communicate your own recommendation for vaccination.
- Communicate the vaccination recommendations of medical organizations and societies.