Human Papillomavirus

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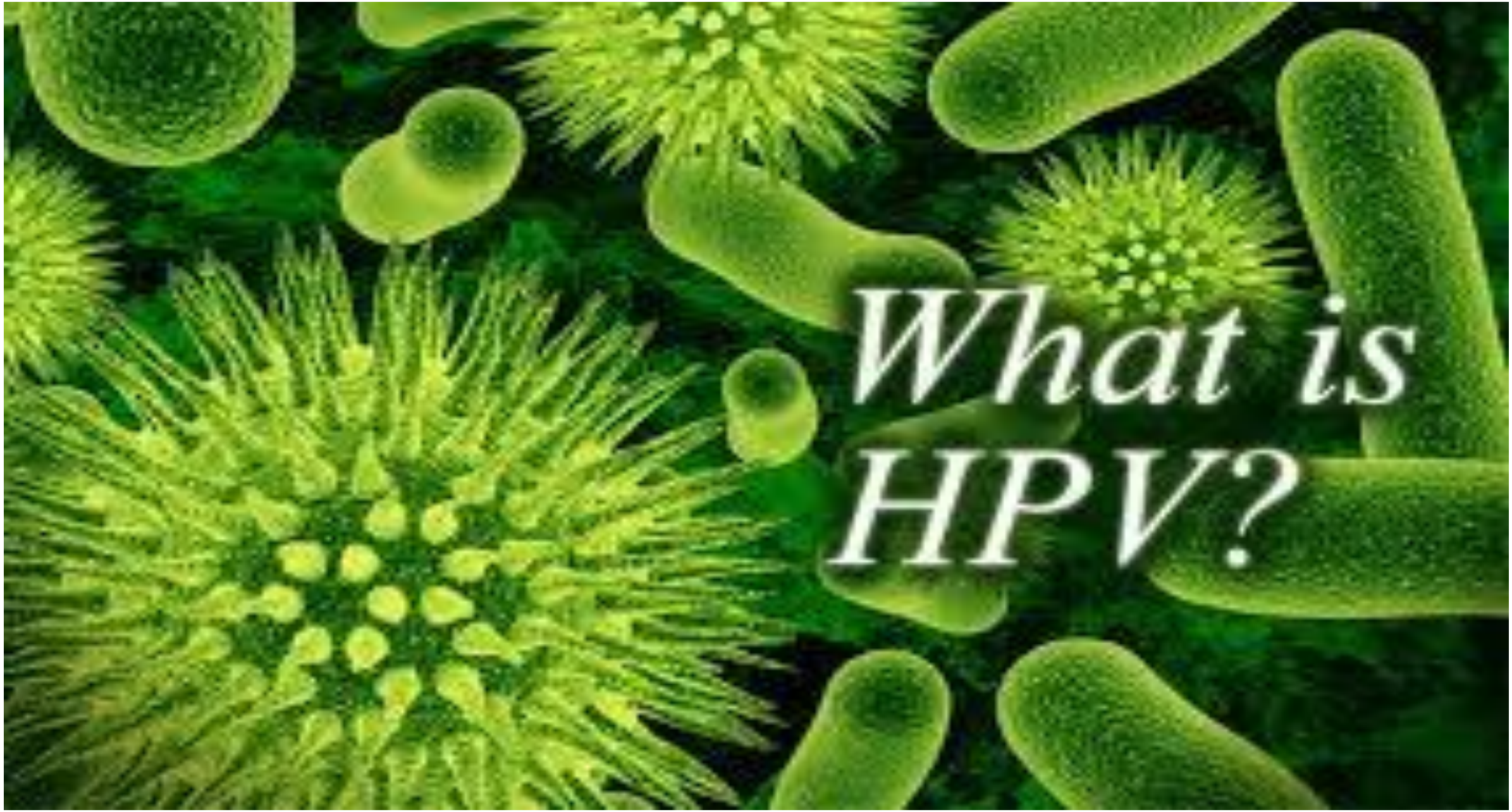

What is
HPV?

INTRODUCTION

- Papillomaviruses are double-stranded DNA viruses.
- These viruses are highly species specific; human papillomaviruses (HPV) infect only humans.

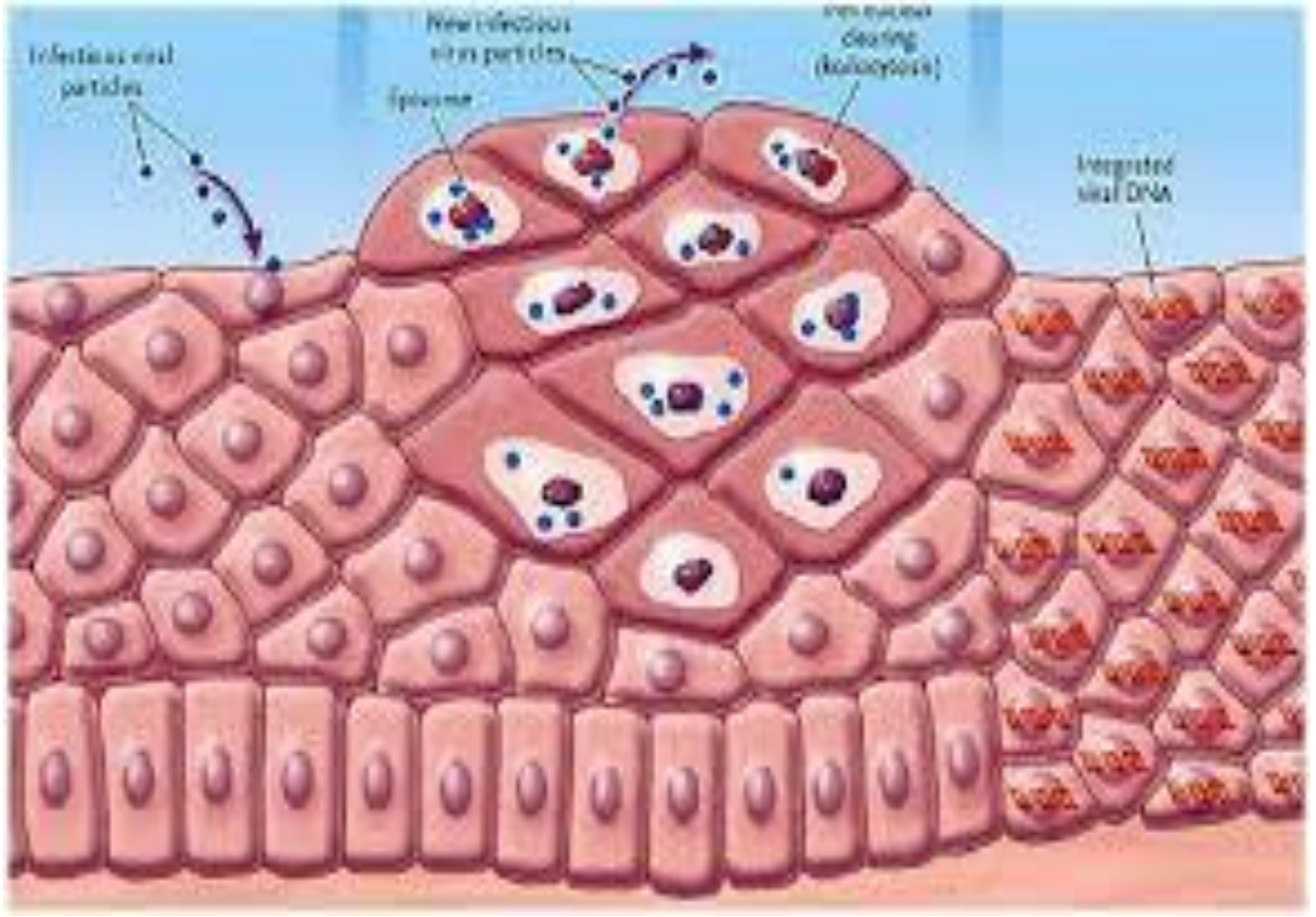
- There are more than 200 types can be subdivided into , near 40 types cause infection of anogenital tracts

  - cutaneous
  - mucosal
- Oncogenic potential:
  - Low risk oncogene 6, 11, 40, 42, 43, 44, 53, 54, 61, 72, 73, and 81
  - high risk oncogene 15 type: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 ,73 , 82

HPV Lifecycle cont.

- Like other viruses , HPV must deliver its genome to the host cell and subsequently exploit the cellular machinery for its own purposes.

- HPV infects the host at sites of epithelial **microtrauma** , where the HPV particle can gain access to the actively proliferating basal cells of the epithelium .



Oncogenic proteins

- The oncogenic potential of high – risk HPV is primarily attributed to the E6 and E7 proteins differ in high – risk and low – risk types .

- Malignant transformation requires the expression of E6 and E7 oncoproteins produced by HPV.

Viral integration and Transformation to Malignancy

- HPV genomes infect the cell via circular extra – chromosomal copies; however , over time , its viral genome can become inserted into host cell DNA , a process called integration .

- Thus , once integration has occurred , disruptions in the E2 ORF lead to increased production of E6 and E7 , thereby promoting immortalization and the oncogenic potential of the cell .

Viral integration and Transformation to Malignancy

cont.

- In LSIL: HPV DNA is not integrated.
- In most HSIL and cancers : HPV DNA becomes integrated

- HPV Integration has been found:
  - 83% of invasive cervical cancers
  - 8% of low – grade CIN

- Integration is highly associated with the transition of low – grade to high – grade lesion.

RISK FACTORS

RISK FACTORS

Genital HPV infections are almost exclusively acquired during sexual exposure

Micro trauma within the skin and mucosal surfaces are the likely sites of initial infection.

cutaneous warts :

- skin to skin spread
- close personal contacts for cutaneous warts.

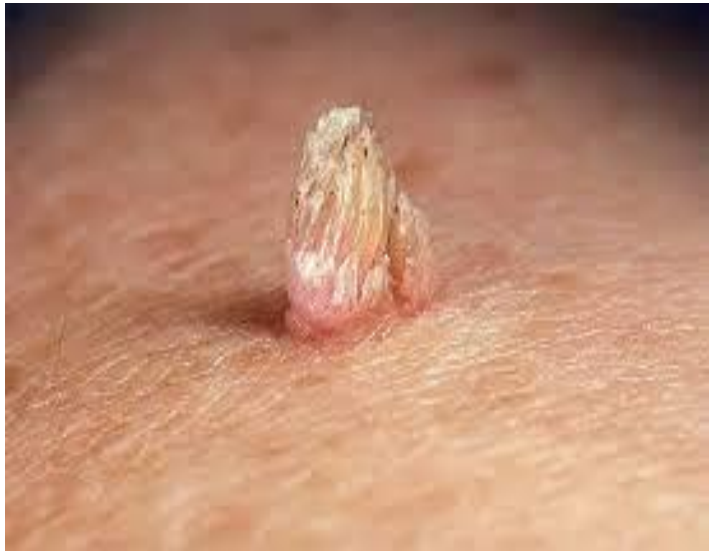
Anogenital warts and HPV cervix are transmitted by:

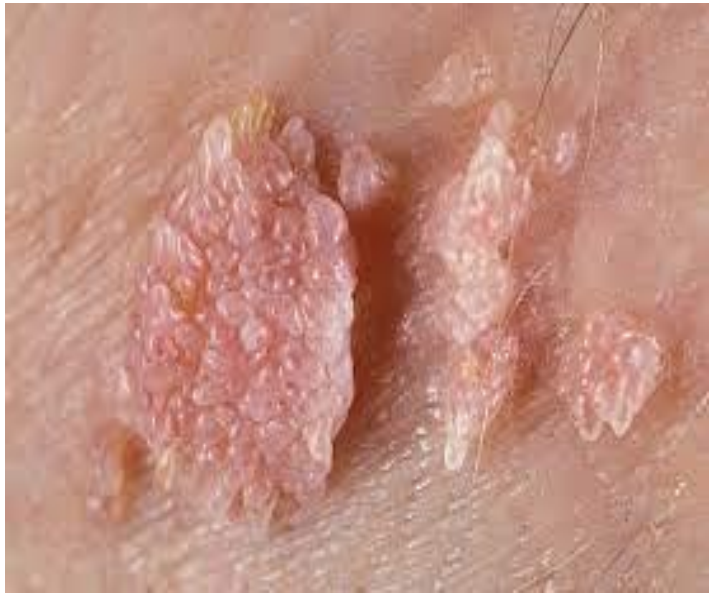
- genital-genital,
- oral-genital,
- anal-genital,
- oral-anal

Risk Factors cont.

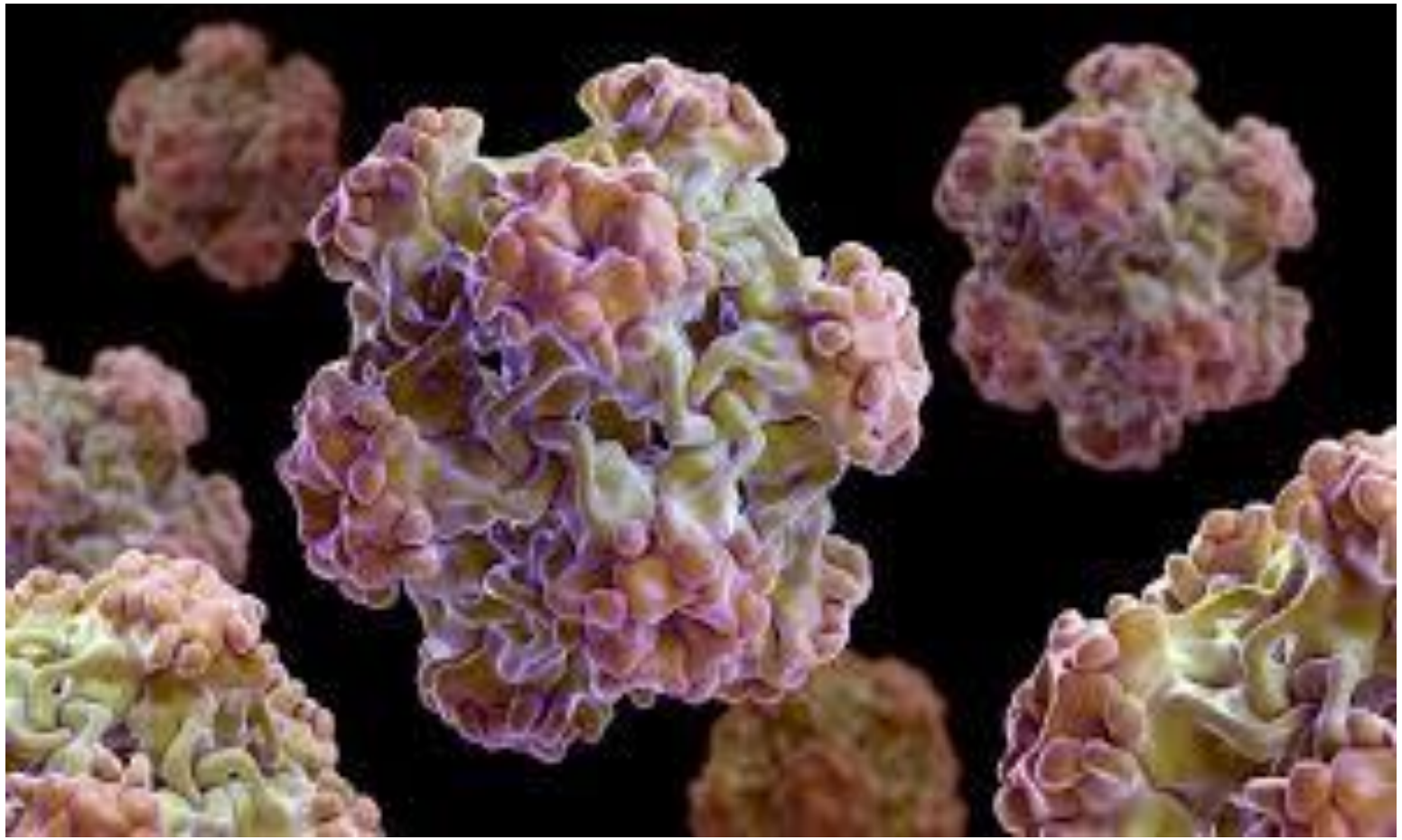
- number of male sex partners
- number of female sex partners
- sex with a new partner.

  the relative hazard was 10.1 per new partner per month .
- Both vaginal and anal intercourse are major risk factors
- penetrating vaginal intercourse is not required for transmission ,the prevalence of HPV infection is much lower among virgins
- other types of contact:
- fingers or toys, or from other genital organs infected with HPV .

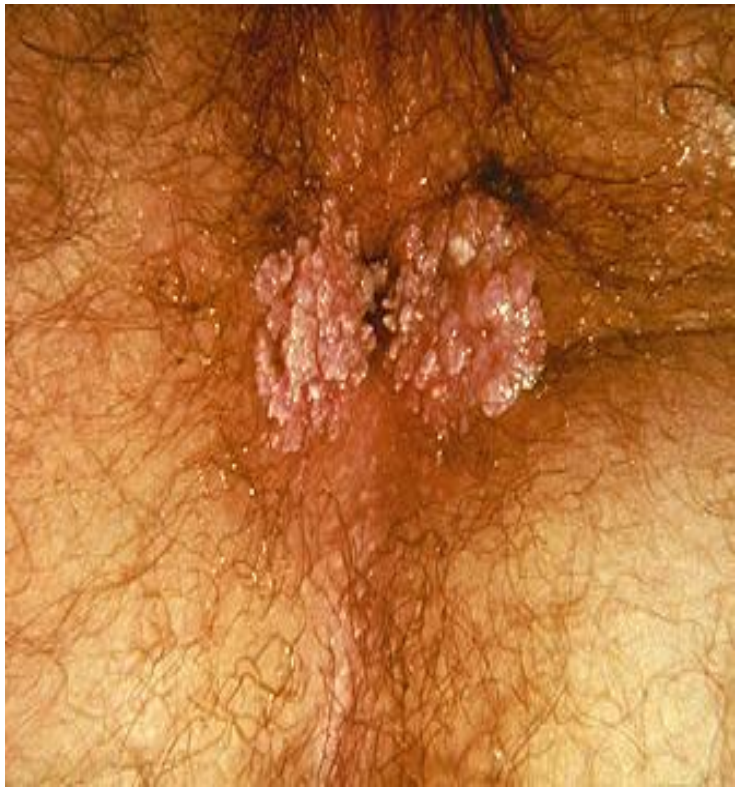




EPIDEMIOLOGY



EPIDEMIOLOGY



- (HPV) is a sexually transmitted pathogen that causes:
  - anogenital
  - oropharyngeal disease in males and females.

The high-risk HPV 16 and 18 cause: 70 % of all cervical cancers types 31, 33, 45, 52, and 58 cause : additional 20 %.

HPV types 16 and 18 also cause:
- nearly 90 % of anal cancers and a
- significant proportion of oropharyngeal cancer,
- vulvar and
- vaginal cancer, and
- penile cancer.

HPV types 6 and 11 cause: approximately 90 % anogenital warts.

EPIDEMIOLOGY

- Most HPV infections, including carcinogenic resolve within 12 months.

- low-grade cytological abnormalities are usually transient .

- carcinogenic HPV infections that persist beyond 12 months increase the likelihood of precancerous or cancerous lesions, although not all persistent infections progress.

- Median age of cytologically detected precancerous cervical lesions occurs approximately 10 years after the median age of sexual debut .

EPIDEMIOLOGY

- The prevalence of cervical HPV infection decreases sharply in women after the age of 25 .

- HPV can enter a latent state .
- cervical viral reactivation in :
  - HIV-infected
  - older women

- it is unknown whether all or only a subset of HPV infections become latent and whether re-emergent HPV infections carry a significant cancer risk.

Vaccines

AVAILABLE VACCINES cont.

- All prophylactic for prevent HPV infection and subsequent HPV-associated lesions.

- Therapeutic vaccines, to stimulate cell-mediated immunity and
- kill the infected cells ,regression of existing HPV-associated lesions, are in development but are not clinically available .

- HPV 12-based prophylactic vaccines are currently undergoing preclinical or clinical trials.

AVAILABLE VACCINES cont.

- Cervarix, a bivalent vaccine, targets HPV types 16 and 18 .
- Gardasil, a quadrivalent HPV vaccine, targets HPV types 6, 11, 16, 18 .

- Gardasil 9, a 9-valent vaccine, targets the same HPV types as the quadrivalent vaccine 6, 11, 16, and 18 as well as types 31, 33, 45, 52, and 58 .
- 9-valent vaccine is recommended for its greater HPV type coverage than the others for females.


1 x 0.5 mL Single-Dose Syringe
Sterile
DIN 02437058
GARDASIL® 9
[Human Papillomavirus 9-valent
Vaccine, Recombinant]
Suspension for injection
Each 0.5 mL dose contains 30/40/60/40/20/20/20/20/20 mcg
of HPV Types 6/11/16/18/31/33/45/52/58 L1 proteins.
MERCK
GARDASIL® 9


GARDASIL™
GARDASIL™
[Quadrivalent Human Papillomavirus
(Types 6, 11, 16, 18) Recombinant Vaccine]
MSD


GARDASIL®


Papilloguard®
Human Papillomavirus Bivalent Vaccine (Types 16 and 18), Recombinant
1 Dose (0.5 mL) contains:
HPV type 16 L1 protein 20 micrograms
HPV type 18 L1 protein 20 micrograms
Suspension for injection in a pre-filled syringe + 2 Needles
intramuscular injection
NOYA
Biopharma

Rational

- **Females**: Three types of Vaccins provide against cancers that can result from persistent HPV infection.
- This preventive effect is most notable and best studied with cervical cancer, which is one of the most common female cancers worldwide.

- Vaccination with the quadrivalent or 9-valent HPV vaccine also protects against anogenital warts (90 percent of which are caused by HPV types 6 and 11); although they are benign lesions, they are associated with physical and psychological morbidity and have a high rate of treatment failure.

Rational

- **Males**: HPV vaccination protects against cancers that can result from persistent HPV infection.

- HPV types 16 and 18 cause nearly 90% of anal cancers and substantial proportion of oropharyngeal and penile cancers.

- 9-valent or quadrivalent vaccine protects anogenital warts (90 % of which are caused by HPV types 6 and 11).

- The overall burden of HPV-associated cancers and precancers among males is less than females.

- Nevertheless, despite a smaller benefit in males compared with females, the overall benefit of vaccinating males outweighs its potential risks because of additional population benefits from herd immunity and the documented safety of HPV vaccines.

- Various models have indicated that vaccinating both males and females is more beneficial in reducing HPV infection and disease than by vaccinating only females

EFFICACY AND IMMUNOGENICITY

- Excellent antibody responses reported following immunization with 9-valent, quadrivalent, and bivalent vaccines.
- seroconversion rates :
  - 93 to 100 percent in females
  - 99 to 100 percent in males
- **Cervical, vaginal, and vulvar disease** :
  - All HPV vaccination is effective in preventing CIN2 or 3 and adenocarcinoma in situ .
  - quadrivalent and 9-valent HPV vaccines reduce the incidence of vaginal and vulvar intraepithelial neoplasia (VAIN and VIN 1- 3) .

efficacy of
Quadrivalent HPV vaccine

- preventing CIN2 or more severe disease:
  - 97 to 100% among HPV-naïve populations,
  - 44% among the overall population

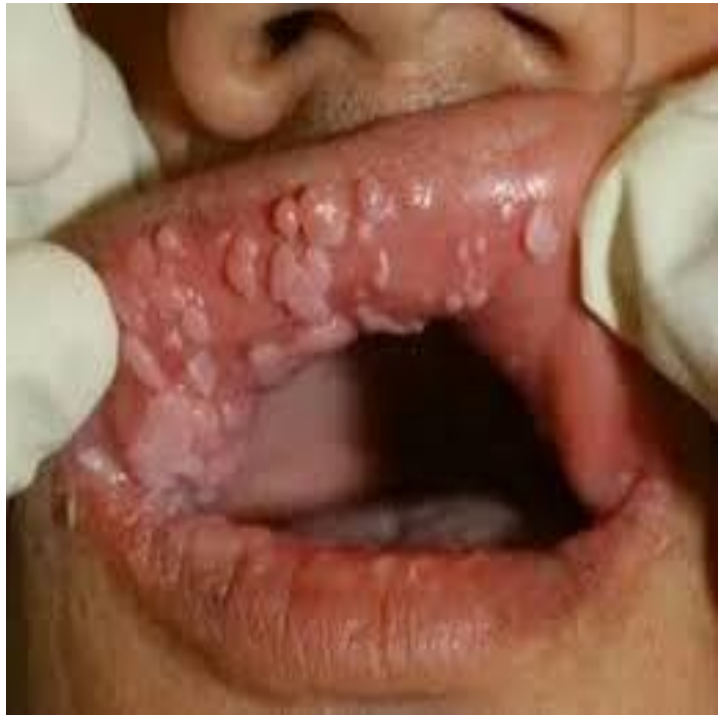
- preventing VIN 2 or 3 and VAIN 2 or 3 :
  - 100 % among HPV-naïve
  - 62 % among the overall population

Efficacy in Anal disease

- Since the majority of anal cancers in females and males are related to HPV 16 and HPV 18, a beneficial impact of vaccination to prevent anal intraepithelial neoplasia and anal cancer in females is anticipated.

Efficacy in Oral Disease

- Vaccine efficacy for the prevention of oral HPV was estimated to be 93%.
- Whether HPV vaccination can prevent the development of HPV-related oropharyngeal cancer has not yet been evaluated.



Efficacy in anogenital warts

- Clinical trials in females and males have demonstrated the efficacy of quadrivalent and 9-valent HPV vaccine for preventing anogenital warts (condylomata acuminata) which are most often caused by HPV types 6 and 11.
- The bivalent HPV vaccine does not target these HPV types and thus does not prevent anogenital warts.
- Gardasil efficacy among females aged 16 to 24 years,in preventing of vulvar and vaginal condylomata :
  - 100 % among HPV-naïve
  - 70 to 78 % among the overall population

Age range Vaccination

- 11 to 12
- as young as age 9

- Catch-up vaccination is also recommended for adolescents and adults aged 13 to 26 years who have not been previously vaccinated or who have not completed their vaccine series.

What should we do with adults 27 years and older?

- For adults 27 years and older, catch-up vaccination is not routinely recommended; the ACIP notes that the decision to vaccinate people in this age group should be made on an individual basis.

Why vaccination is not recommended for adults 27 years and older?

- Increased likelihood of prior exposure to HPV vaccine types with age, which reduces the potential individual benefit and thus the cost-effectiveness of HPV vaccination.

- However, it is recommended for :
  1 - with no prior sexual experience
  2 - limited number of prior sexual partners
  3 - health care workers who may be at risk for occupational exposure to HPV, even if they are older than 26 years

- Studies have suggested that HPV vaccination in women >25 years is immunogenic, efficacious, and safe.

- In the USA the HPV vaccine is approved through age 45. It is possible that some individuals over the age of 45 years may also benefit from vaccination, but the benefit has not been well studied.

Timing of immunization

- Clinical trial data of vaccine efficacy in males and females suggest that immunization with HPV vaccine is most effective among individuals who have not been infected with HPV .

- Thus, the optimal time for HPV immunization is prior to an individual's sexual debut.

- Neither vaccine treats or accelerates the clearance of pre-existing vaccine-type HPV infections or related disease.
- HPV vaccination is associated with a reduction in the incidence of cervical cancer, and vaccination prior to age 17 years compared with later was associated with an even lower incidence.

Choice of vaccine

Not all HPV vaccines are available in all locations. If cost and availability are not an issue, we recommend the human papillomavirus 9-valent vaccine. In the United States only the 9-valent vaccine is available (since 2017).

Question?

- Your patient has not completed her vaccination :

  She does not know vaccine formulation

  Or

  She knows but it is not available

What should you suggest to her?

In general, the same formulation should be used to complete the series, if possible.

if the 9-valent vaccine is being introduced into the formulary, a different HPV vaccine formulation can be used to complete the series

vaccination before 15 years of age

- Two doses of HPV vaccine should be given at 0 and at 6 to 12 months.

- If the second dose was administered less than five months after the first, the dose should be repeated a minimum of 12 weeks after the second dose and a minimum of five months after the first.

Vaccination at 15 years of age or older

- Three doses should be given at :

  0, 1 to 2 (typically 2), and 6 months.
- Minimum intervals between:
  - first two doses: four weeks (1 month)
  - second and third doses : 12 weeks (3 months)
  - first and third dose : five months

- If a dose was administered at a shorter interval, it should be repeated once the minimum recommended interval since the most recent dose has passed.
- if the vaccination series is interrupted for any length of time, it can be resumed without restarting the series.

Vaccination at Immunocompromised patients

- Three doses of HPV vaccine should be given at:

  0, 1 to 2, and 6 months regardless of age

Vaccination In pregnancy and lactation

- Is not recommended during pregnancy , although none of the approved HPV vaccines contain live virus.

- If a woman receives the HPV vaccine before she knows that she is pregnant she should be reassured that there is no evidence that this vaccine will harm the pregnancy, may resume the series in postpartum.

- Lactating females can receive the immunization series since subunit vaccines do not affect the safety of infant breastfeeding.

Pre-existing HPV-associated disease

Question

What should we do with a patient with an abnormal cytology test (cervical, vaginal, vulvar or anal), or genital warts, or positive HPV DNA test in regard of vaccination for HPV?

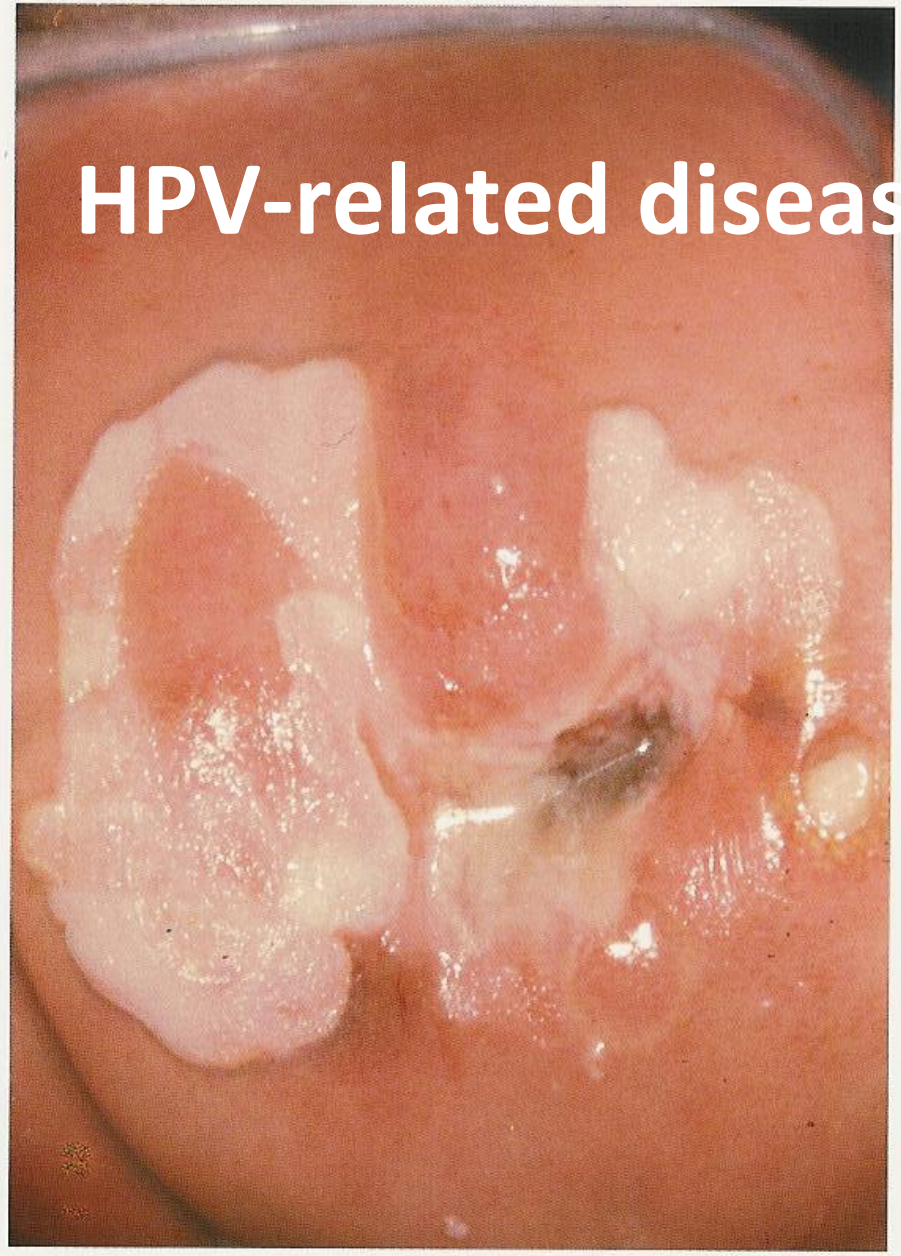
- Is NOT a contraindication to HPV immunization.
  However, immunization is less beneficial for females who have already been infected with one of more of the HPV vaccine types.

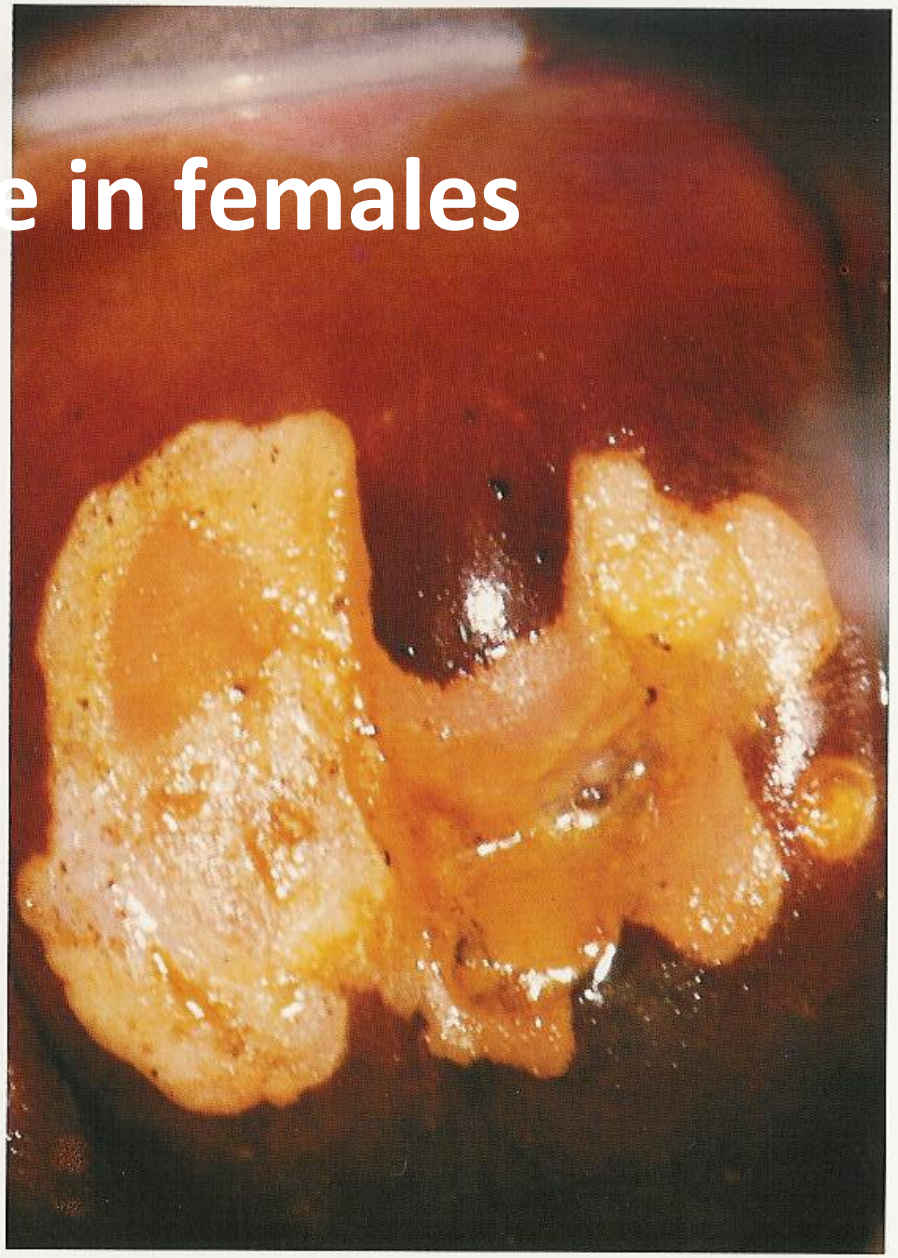
Health care workers at risk for occupational exposure

- Upper aerodigestive (nasal and oropharyngeal) HPV infection may be transmitted through exposure to HPV in vapors generated during surgical excision or ablation of HPV-associated lesions .

Health care workers who may be routinely exposed to HPV in this way receive HPV vaccination.

HPV-related disease in females





Concurrent vaccination

- HPV vaccine can be safely administered at the same time:

  - tetanus, acellular pertussis, and diphtheria vaccine and inactivated poliovirus vaccine

  - different anatomic site

- Recent studies found that two vaccine doses in young individuals have similar or greater immunogenicity compared with three doses in older females with reductions in cervical neoplasia .

- Three doses of HPV vaccine are still recommended for individuals 15 and older because of the lower immunologic response to HPV vaccination in this population.

Vaccine Dose and Administration

- Gardasil and Gardasil 9:

  three doses at time zero, and at

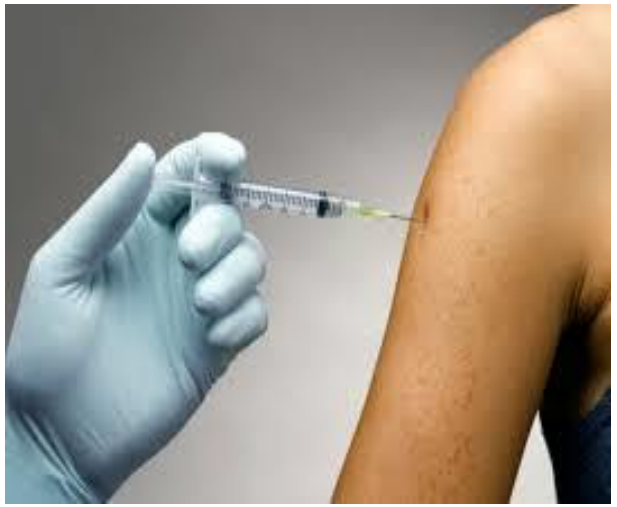
  two and six months

- Cervarix :

  three doses at time zero, and at

  one and six months

- In some countries, two doses of HPV vaccine are recommended for comparable imunogenicity and efficacy after two versus three doses.



Unnecessary evaluation

- **Prevaccination assessment** is not necessary.
  - Serologic testing
  - HPV DNA testing
  - Pregnancy testing is also

- **Postvaccination serology** is not necessary :
  measurement of antibody titers to monitor immunity postvaccination

- **Limited benefit of revaccination** :
  - HPV vaccines have demonstrated durable protection from HPV associated diseases, and so revaccination is not necessary.
  - For patients with already completed HPV vaccine series with the bivalent or quadrivalent vaccine, revaccination with 9-valent vaccine is not suggested.

Duration of protection

- Persistent antibody levels and protection against HPV infection have been reported up to 10 years following vaccination .

- precise level of antibody needed for protection against infection is unknown.

- Further data will become available in the future as female and male participants in vaccine studies are followed over time.

Side Effects of Vaccines

- mild injection site reactions,
- syncopal events. a routine 15-minute waiting period is need to decrease the risk of syncope .
- headache,
- nausea,
- vomiting,
- fatigue,
- dizziness, and
- generalized weakness
- no increased risk of Guillain-Barré Syndrome compared with other vaccines in similar age groups

92 percent are considered mild

Key messages

- HPV is a STD.
- Genital HPV is acquired by sexual intercourse.
- Penetrating vaginal or anal intercourse are not necessary for HPV infection.
- Vaccination is contraindicated in pregnancy
- Vaccination is not contraindicated in individuals with genital warts , positive HPV DNA test , abnormal cytology and lactation period.
- Pap smear, HPV DNA test, pregnancy and serologic tests pre and post vaccination are not need.
- Optimal time for HPV immunization is prior to an individual’s sexual debut , before HPV exposure.

Key messages

- Minimum intervals between:
  - first two doses: four weeks (1 month)
  - second and third doses : 12 weeks (3 months)
  - first and third dose : five months
- Neither vaccine treats or accelerates the clearance of pre-existing vaccine- type HPV infections or related disease.
- HPV vaccination is associated with a reduction in the incidence of HPV related Cancers


With Thanks