



*Medical Virology for 2<sup>nd</sup> Year M.D. Students*



# **Poxviridae Papillomaviridae**

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## Poxviridae-Introduction



- ❖ Poxviruses are a family of large, genetically **complex** viruses having no obvious symmetry.
- ❖ The agent of previous medical importance to humans, **variola virus**, was the cause of **smallpox**, the first infectious disease to be declared eradicated from the earth.
- ❖ The last known case was in Somalia in 1977.

Ali Maow Maalin





## Smallpox Eradication



**Smallpox vaccination.**  
Application of Vaccinia vaccine to the skin with a **bifurcated needle**.



**Smallpox vaccination.**  
Historical cartoon (1802) by James Gillray, depicting smallpox vaccination. In 1796 **Edward Jenner**, an English doctor, coined the word vaccination to describe his use of cowpox inoculation to obtain immunity to smallpox.



**Smallpox eradication, Cameroon, 1969.**  
Young boy being vaccinated against smallpox and measles during the Smallpox Eradication and Measles Control Program.



# Poxviridae-Introduction





## The factors that led to successful eradication of smallpox



1. The availability of an effective, **live attenuated** vaccine.
2. Variola virus was antigenically stable and **only a single antigenic type** existed.
3. The absence of asymptomatic cases or persistent carriers.
4. The absence of an animal reservoir.
5. The emotional effect of this highly lethal, disfiguring disease helping to gain public cooperation in the eradication efforts.



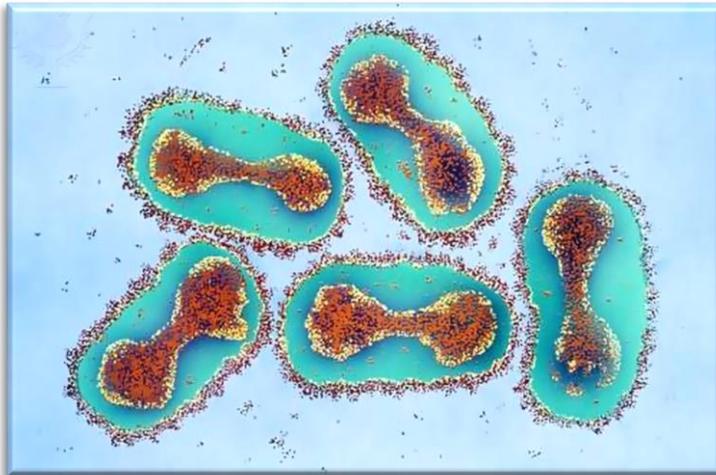
## Structure & Classification



- ▶ The genome is a single linear **double-stranded DNA**, encoding more than 200 polypeptides. The virion is **enveloped**.
- ▶ The vertebrate poxviruses are related by a common nucleoprotein antigen, but are otherwise quite distinct.
- ▶ Humans are the natural host for variola and molluscum contagiosum virus (MCV), however, monkeypox, cowpox, and several other animal poxviruses can also cause human disease.



## Structure & Classification



Color enhanced transmission electron micrograph (TEM) of the Smallpox virus (Poxviridae). Magnification: 42,000 $\times$ .



## Replication



- ▶ The entire replication cycle takes place in the **cytoplasm**.
- ▶ The virus genome encodes all of the enzymes (including a viral DNA-dependent RNA polymerase) necessary for DNA replication and gene expression.
- ▶ The replication cycle is rapid and results in early shut-off of all cell macromolecular syntheses, causing the death of the cell.



## Pathogenesis & Clinical Picture



- ▶ Variola viruses are transmitted aerogenically.
- ▶ The mucosa of the upper respiratory tract provides the portal of entry.
- ▶ From there, the pathogens enter the lymphoid organs and finally penetrate to the skin, where typical eruptions form and, unlike varicella pustules, **all develop together** through the same stages.





## Clinical Findings



- ▶ The incubation period was 10–14 days.
- ▶ The onset was usually sudden.
- ▶ One to 5 days of fever and malaise preceded the appearance of the exanthems, which began as macules, then papules, then vesicles, and finally pustules. These formed crusts that fell off after about 2 weeks, leaving **pink scars** that faded slowly.
- ▶ The case-fatality rate reached 40%. Deaths were related bleeding, cardiovascular collapse, and secondary infections.





## Epidemiology



- ❖ Transmission of smallpox occurred by contact between cases or inhalation of airborne virus.
- ❖ Smallpox was **highly contagious**.
- ❖ The virus was stable in the extracellular environment but was most commonly transmitted by respiratory spread.
- ❖ The dried virus in crusts from skin lesions could survive on clothes or other materials and result in infections.
- ❖ Smallpox is potentially a devastating biologic weapon because it is highly contagious and has a high case fatality rate.





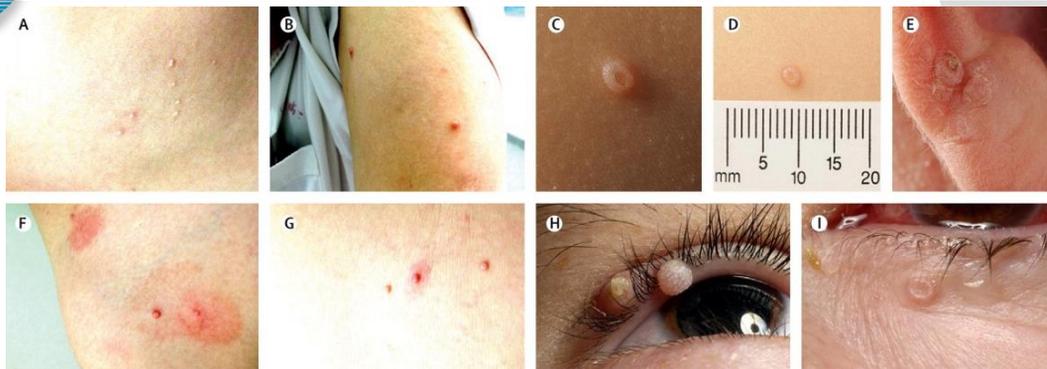
## Molluscum contagiosum virus (MCV)



- ▶ Molluscum contagiosum is a viral infection characterised by small, discrete, skin-coloured, dome-shaped papules.
- ▶ The number of individual lesions is generally fewer than 20.
- ▶ Rarely, molluscum contagiosum causes lesions on the palms and soles, or mucous membranes such as the lip, buccal mucosa or conjunctivae.
- ▶ MCV transmission occurs by direct contact, through contaminated fomites, or sexual activity.



## Molluscum contagiosum virus (MCV)



MC lesions on back of a 3-year-old patient (A). Lesions on arm of a 60-year-old patient (B). Single, non-inflamed lesion showing the characteristic **punctum** (C). Typical, non-inflamed lesion (D). MC on ear showing a haemorrhagic punctum (E). Inflamed lesions on shoulder of an 11-year-old patient (F,G). Two lesions on upper eyelid margin (H); Lower eyelid in a patient with MCV conjunctivitis (I)



## MC Dx & Rx



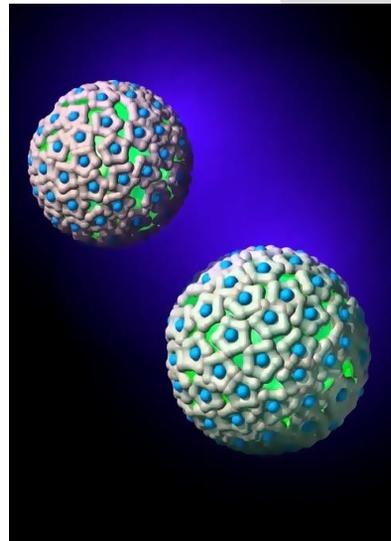
- ▶ The diagnosis of molluscum contagiosum is based on observation of the characteristic umbilicated papules.
- ▶ Histopathology, molecular diagnosis by PCR from cytological smears and infected tissue can be used in clinically atypical cases.
- ▶ MC is benign and self-limiting. The average duration of a single lesion is about 2 months.
- ▶ Physical therapy (curettage, cryotherapy), chemical agents or antiviral therapy (Cidofovir; DNA polymerase inhibitor).



## *Papillomaviridae*-Introduction



- Double-stranded DNA viruses.
- Naked.
- Icosahedral.
- Oncovirus.
- “It is known that HPV can establish latency”

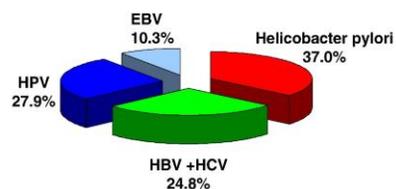




## Estimated annual global cancer incidence due to infections



Cancers due to 5 infections correspond to 18.6% of total cancer incidence



This graph ignores

- anal and perianal cancers (HPV)
- vulvar, vaginal and penile cancers (HPV)
- adult T cell leukemia
- Kaposi's sarcomas and pleural. effusion lymphomas
- Merkel cell carcinomas
- cancers linked to parasitic infections

25% of cancers of the oral cavity  
68 600 (HPV)

Cancer of the cervix  
493 000 (HPV)

Hepatocellular carcinoma 80%  
500 900 (HBV, HCV)

Gastric cancer 80%  
747 000 (Helicobacter pylori)

Gastric cancer 10%  
93 400 (EBV)  
Nasopharyngeal carcinoma  
80 000 (EBV)  
Non-Hodgkin's lymphoma 10%  
30 000 (EBV)  
Hodgkin's lymphoma 30%  
18 700 (EBV)

Source: Parkin et al., 2002, modified from zur Hausen, 2006).



## *Papillomaviridae*-Taxonomy



- Family (*Papillomaviridae*)
  - Genus (*Alphapapillomavirus*)
    - Species (*Human papillomavirus HPV*)  
[share 60% to 70% identity]
      - Type [share 71% to 89% identity]
        - Subtype [share 90% to 98% identity]
          - Variant



## Papillomaviridae-Important Features



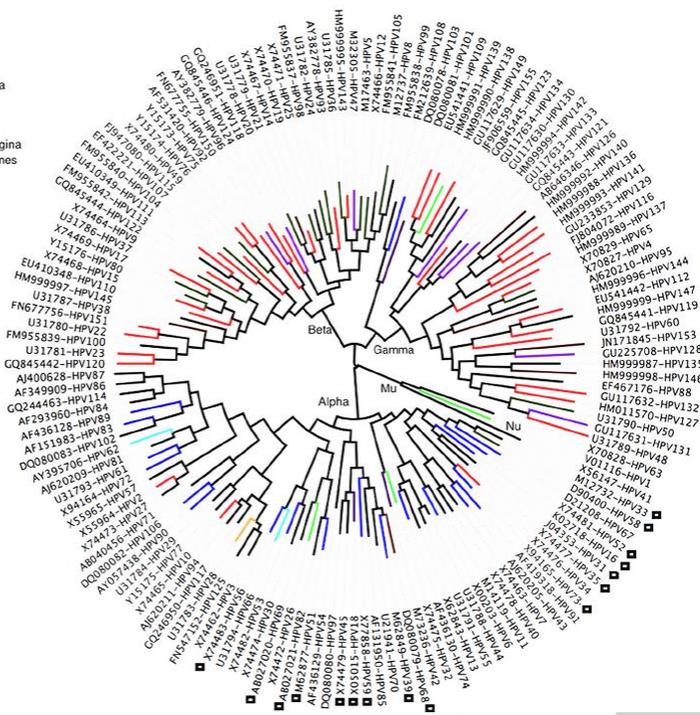
- ❖ *Natural Host:* Human.
- ❖ *Tropism:* Epithelial cells of skin, mucous membranes
- ❖ *Cellular receptors:* Heparan sulfate.
- ❖ *Transmission:* Sexual, indirect & direct contact.
- ❖ *Geography:* Worldwide.





- Mouth
- Skin
- Vagina
- Vagina and mouth
- Skin and gut
- Skin and gut and vagina
- Skin and vagina
- Skin and mouth
- Gut and vagina
- Mouth and skin and vagina
- Not found in metagenomes
- High risk types

0.07





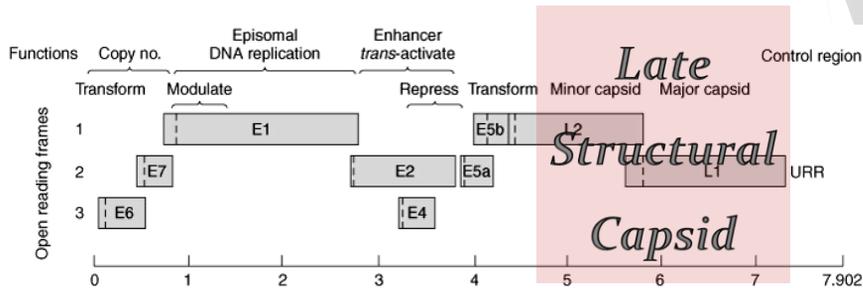
## Pathogenesis



- ▶ HPVs exhibit great tissue and cell specificity, **infecting only surface epithelia of skin and mucous membranes.**
- ▶ The HPVs within each of these tissue-specific **types** have varying potentials for causing malignancies:
  - 1) Virus types that produce lesions having a **high risk** of progression to malignancy, such as in cervical carcinoma.
  - 2) Types that produce mucosal lesions that progress to malignancy with lower frequency, causing, anogenital warts and laryngeal papillomas.
  - 3) Other virus types that are associated only with **benign lesions** (for example, common, flat, and plantar warts).



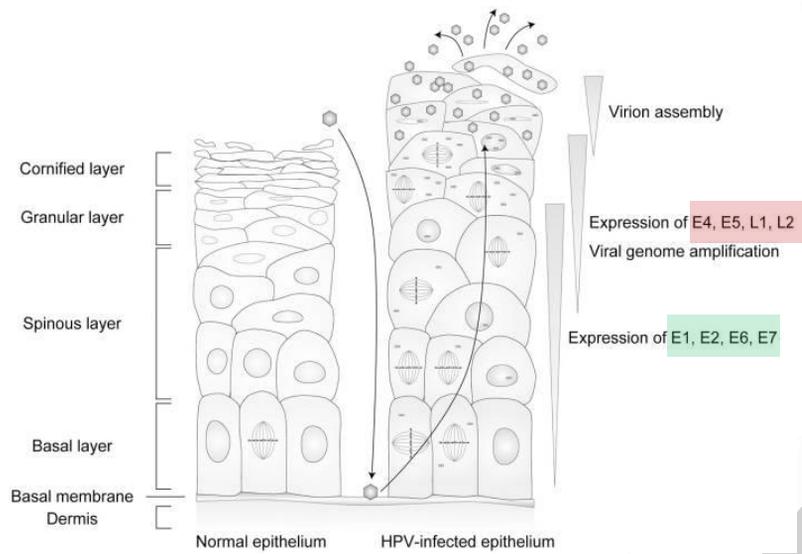
## HPV Replication



- ▶ Viral nucleic acid can be found in **basal cells**, but **late gene expression is restricted to the uppermost layer of differentiated keratinocytes**.
- ▶ Stages in the viral replicative cycle are dependent on specific factors that are present in sequential differentiated states of epithelial cells.



## HPV Replication





## Pathogenesis



- ▶ The development of a typical wart results from **cell multiplication** and **delayed differentiation** induced by certain HPV early proteins.
- ▶ The infected cells leave the basal layer and migrate toward the surface of the skin. **The virus replication cycle proceeds in parallel with the steps of keratinocyte differentiation**, which end with the terminally differentiated cornified layer of the growing wart.



## Pathogenesis



- ▶ **Early (E)** viral proteins activate the host cells, causing them to divide.
- ▶ This activation involves interaction between these viral proteins and cellular proteins (anti-oncoproteins) that normally function to regulate the cell cycle.
- ▶ Two of these cellular proteins are **p53** (cellular growth suppressor protein) and **pRb** (retinoblastoma gene product).



## Pathogenesis



- ▶ Progression to malignancy occurs particularly in the mucosa of the genital tract, and is associated with **a limited number of papillomavirus types** (high-risk).
- ▶ The affinity of binding between virus early proteins (**E6 and E7**) and cellular anti-oncoproteins correlates with a high risk for malignant progression.
- ▶ This interaction is only the first step in **a multistep process** involving alterations in expression of other cell oncoproteins and anti-oncoproteins and including, at some point, the non-site-specific **integration** of part of the viral genome into a host cell chromosome.



## Clinical Manifestations (Oral Cavity)



- ▶ Benign HPV infections of the oral cavity occur commonly.
- ▶ They may be **asymptomatic** or associated with single or multiple lesions in any part of the oral cavity.
- ▶ Genital-mucosal HPV types, especially **HPV6, HPV11, and HPV16**, have frequently been recovered from oral tissue.



HPV lesions in buccal mucosa



## Clinical Manifestations (Oral Cavity)

### ① Oral Squamous Papilloma

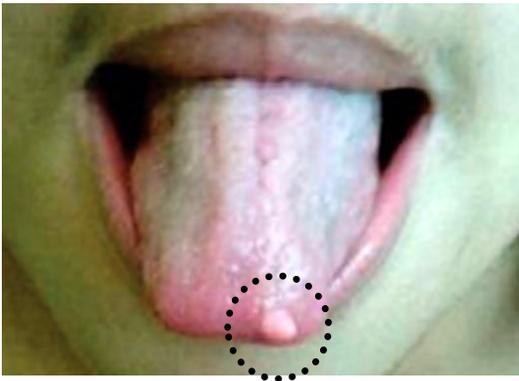


- ▶ Among the HPV lesions that may be found in the oral cavity, the oral squamous papilloma is **the most frequent**.
- ▶ The possibility of oral exposure to HPV (**HPV6, HPV11, and HPV16**) is through oral sex.
- ▶ Risk factors include:
  - Early sexual debut.
  - Multiplicity of sexual partners.
  - Frequent practice of oral sex.





## Clinical Manifestations (Oral Cavity) Oral Squamous Papilloma





## Clinical Manifestations (Oral Cavity)

### ② Oral Verruca Vulgaris (Common Wart)



- ▶ Oral verruca vulgaris lesions are caused by **HPV types 1, 2, 4 and 7**.
- ▶ The lesions are usually caused by **autoinoculation from lesions on the fingers and hands mainly in the children**.
- ▶ It tends to have pointed (verruciform) projections, to have a very narrow stalk and to be white from considerable surface keratin.

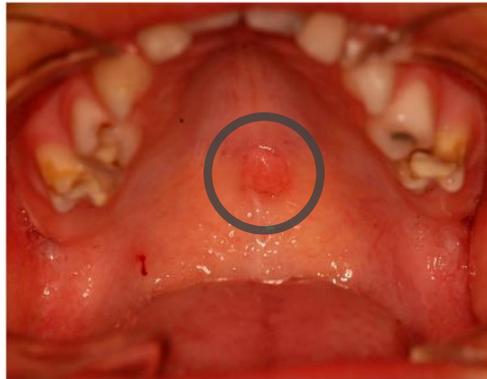


## Clinical Manifestations (Oral Cavity)

### 3 Oral Condyloma Acuminatum



- ▶ Oral condylomas are associated with **HPV 2, 6, and 11**.
- ▶ Condylomas resembles papillomas clinically, but are usually larger in size.





## Clinical Manifestations (Oral Cavity)

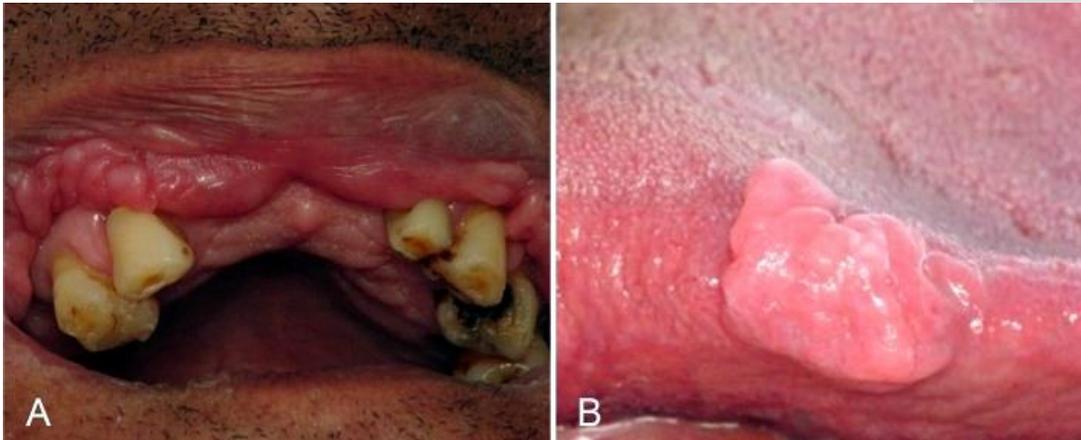


### ④ Focal epithelial hyperplasia (heck disease):

- A well-defined **benign** clinical entity that occurs only in the oral mucosa.
- Its distribution is worldwide, but it is most prevalent in the indigenous populations of Central and South America and of Alaska and Greenland.
- Most infection is attributed to HPV13 or HPV32, two types that appear predominantly to infect the oral cavity.
- Treatment is usually unnecessary since most of lesions regress spontaneously and there is no tendency to malignant transformation.



## Focal epithelial hyperplasia (heck disease):



Multiple lesions on the upper lip mucosa (A). Solitary tongue lesion (B).



## Clinical Manifestations (Oral Cavity)



### 5 Oropharyngeal cancer:

- Cigarette smoking and alcohol consumption are two well known risk factors for head and neck cancer.
- Although HPV does not appear to be involved in most cancers in the oral cavity, consistent data from developed countries indicate that a subset of head and neck cancers are attributable to HPV infection.
- **HPV16** accounts for about 90% of the HPV-positive tumors.



## Clinical Manifestations (Skin)



Warts may be classified as common (fingers and hands), plantar (sole of foot), or flat (arms, face, and knee). HPV types: **1, 2, 3, 4, 7** among others.





## Clinical Manifestations (Larynx)



Laryngeal papillomas (papillomas) are benign tumors (papillomas) that can cause hoarseness, shortness of breath or difficulty breathing.



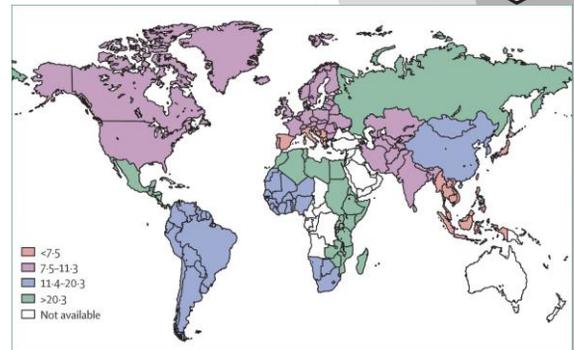
which benign tumors (papillomas) can cause hoarseness, shortness of breath or difficulty breathing. 6 or HPV-1



## Clinical Manifestations (the Genital Tract)



- Genital HPV infection is considered **the most common sexually transmitted viral infection**, with an estimated life-time risk of at least 75% and involving females and males.
- Infection with high-risk HPV types can end up in the development of vulvar, vaginal, penile or anal cancer.



Estimated HPV DNA prevalence in the world regions based on a 78 studies including 157,879 women with normal cytology.

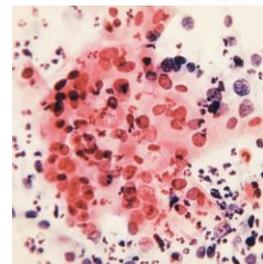


## Clinical Manifestations (the Genital Tract)



### ① Cervical Cancer:

- Among the most common cancers in women worldwide.
- **Pap smear** screening has decreased the frequency of cervical cancer in industrialized countries.
- **HPV-16 or HPV-18** is found most frequently in cervical carcinomas, though some cancers contain DNA from other types, such as **HPV-31 or HPV-33**.



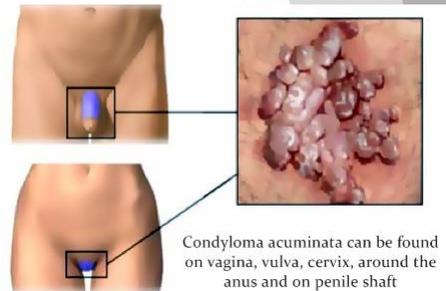


## Clinical Manifestations (the Genital Tract)



### ② Anogenital Warts (Condylomas):

- Condylomas are outgrowth lesions that are frequently multiple.
- They can arise anywhere on the external genitalia and can be found simultaneously in multiple sites.
- In men, they occur most commonly on the penis and anus, and in women on the perineum and anus.





## Clinical Manifestations (the Genital Tract)



### ② Anogenital Warts (Condylomas):

- About 90% of genital warts are caused by **HPV6** or **HPV11**.





## Epidemiology



- ▶ HPV infection represents **the most common sexually transmitted disease** in the United States.
- ▶ Cervical cancer is the second most common cancer in women living in less developed regions with an estimated 445,000 new cases in 2012 (WHO, 2016).
- ▶ Cervical cancer ranks as the 15<sup>th</sup> most frequent cancer among women in **Jordan** and the 10<sup>th</sup> most frequent cancer among women between 15 and 44 years of age. Data is not yet available on the HPV burden in the general population of Jordan. (source: [www.hpvcentre.net/statistics/reports/JOR.pdf](http://www.hpvcentre.net/statistics/reports/JOR.pdf)).



## Diagnosis



- Visual inspection.
- Molecular detection, typing?
- Cervical cancer screening (cytologic screening with **Pap smears** introduced in 1950s, the main goal of which is to prevent cancer by identifying premalignant lesions that can then be treated).





## Treatment



- ▶ Treatment of warts generally involves **surgical removal** or **mechanical destruction** of the wart tissue with:
- Liquid nitrogen.
  - Laser vaporization.
  - Cytotoxic chemicals such as podophyllin or trichloroacetic acid.





## Prevention



- ▶ A **quadrivalent** HPV vaccine (HPV types 6, 11, 16, and 18) was approved in the United States in 2006 and a **bivalent** vaccine (types 16 and 18) in 2007.
- ▶ Both are non-infectious recombinant vaccines containing virus-like particles composed of HPV L1 **proteins**.
- ▶ It is not known how long vaccine-induced immunity lasts, but it appears to extend for at least 5 years.





Thanks for listening!