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Virology

Doctor 2018 | Medicine | JU

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We will be discussing two families of viruses in this sheet: Poxviridae and Papillomaviridae.

Poxviridae

Poxviruses are a family of large, genetically complex viruses having no obvious symmetry. Therefore, they are not icosahedral nor helical in shape.

The agent of previous medical importance to humans, variola virus, was the cause of smallpox, the first infectious disease to be declared eradicated from earth. The last known case was in Somalia in 1977.

The eradication of smallpox was successful because of the efforts of WHO and the help of different countries. This was also helped by the fact that the smallpox vaccination was the first vaccine that was introduced into the human population in a scientific way by the English physician Edward Jenner in 1796. Remember that he inoculated individuals with cowpox allowing them to obtain immunity to smallpox.



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

Factors That Lead to the Successful Eradication of Smallpox:

It is important to know these factors because they can be used as a model for initiating other campaigns to eradicate other infectious diseases from the population.

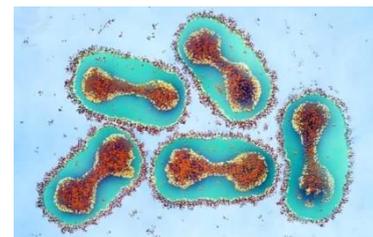
1. The availability of an effective, live attenuated vaccine.
2. Variola virus was antigenically stable and only a single antigenic type existed.
 - a. Recall that this is similar to Hepatitis A, which has only one known serotype. This makes it easier for a more effective vaccine to be created, because there is only one antigen for the immune system to have to target.
3. The absence of asymptomatic cases or persistent carriers. This helps to identify and isolate every single smallpox case and therefore makes it easier to break the chain of transmission of this infectious disease.
4. The absence of an animal reservoir.
5. The emotional effect of this highly lethal, disfiguring disease helped to gain public cooperation in the eradication efforts.

Structure & Classification

The genome is a single linear double-stranded DNA, encoding for more than 200 polypeptides. The virion is enveloped.

The different members of the poxviridae family each can infect different vertebrate species. What's common between these members is that they share a common nucleoprotein antigen. Otherwise, they are quite distinct.

Humans are the natural host for **variola** (causative agent of smallpox) and **molluscum contagiosum virus** (MCV) (agent of skin disease).



TEM of smallpox virus

Monkeypox, cowpox, and several other animal poxviruses can also cause human disease. However, the diseases they cause are less severe compared to the disease caused by variola virus.

Replication

The entire replication cycle takes place in the **cytoplasm**, which is an exception among DNA viruses. (for the rest of the DNA viruses, part of the replication cycle normally occurs in the nucleus)

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 shutoff of all cell macromolecular syntheses, causing the death of the cell.

Pathogenesis & Clinical Picture

Variola viruses are transmitted:

1. Aerogenically - through air (breath) and saliva
2. Through contact with the skin lesions of an infected person.

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 (caused by chicken pox), all develop together through the same stages.



Clinical Findings

- The incubation period was 10–14 days.
- The onset was usually sudden.
- One to five days of fever and malaise precede the appearance of the exanthems (an eruptive skin rash). These lesions begin as macules, then all develop together into papules, then vesicles, and finally pustules. These formed crusts then fall off after about 2 weeks, leaving pink scars that faded slowly.
- The case-fatality rate reached 40%. Deaths were related to bleeding, cardiovascular collapse, and secondary infections.

Epidemiology

- Transmission of smallpox occurred by contact between cases or inhalation of the airborne virus.
- Smallpox was highly contagious (very important point!).
- 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 a potentially devastating biologic weapon because it is highly contagious and has a high case fatality rate.

Molluscum contagiosum virus (MCV)

- This is the other member of the poxviridae family that infects humans.
- Molluscum contagiosum is a viral infection characterized by small, discrete, skin-colored, 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.
- The characteristic **punctum** is very typical of MCV infection.

Fomites are objects or materials which are likely to carry infection, such as clothes, utensils, and furniture.

A **punctum** is a slight depression in the center of a rounded body (see image C in the figure below)



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 Diagnosis (Dx) & Treatment (Rx)

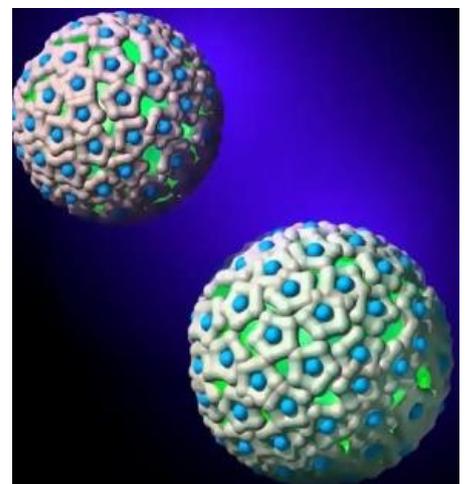
- The diagnosis of molluscum contagiosum is based on observation of the characteristic umbilicated papules. (umbilicated = punctums)
- Histopathology and molecular diagnosis (by PCR) from cytological smears and infected tissue can be used in clinically atypical cases.
- MC is benign and self-limiting.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

Papillomaviridae

Introduction

We will now discuss the next family of viruses: papillomaviridae. They are:

- Double-stranded DNA viruses
- Naked viruses
- Icosahedral
- Oncoviruses – Can cause cancer
- “It is known that HPV can establish latency”



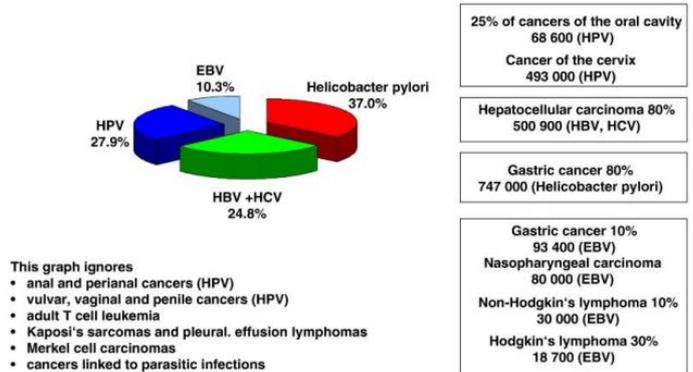
Estimated Annual Global Cancer Incidence Due to Infections

Human Papilloma Virus (HPV) is one of the most important infectious agents that result in cancer in the human population. It can cause cervical, anal, perianal, vulvar, and oropharyngeal cancers.

Examples of other infectious agents that can cause cancer in human populations:

1. Bacteria
 - a. Helicobacter Pylori
2. Viruses
 - a. Hepatitis B and C
 - b. Kaposi's Sarcoma Herpes Virus (Human Herpes Virus)
 - c. Merkel Cell Polyomavirus
 - d. Human T-Lymphotropic Virus (HTLV) Type I

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



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

Taxonomy

1. Family – Papillomaviridae
2. Genus – Alphapapillomavirus
3. Species – Human Papillomavirus - Members of this species share 60% to 70% genetic identity.
4. Type – Share 71% to 89% genetic identity.
5. Subtype – Share 90% to 98% genetic identity.
6. Variants – Share 99% to less than 100% genetic identity.

Important Features of Papillomaviridae

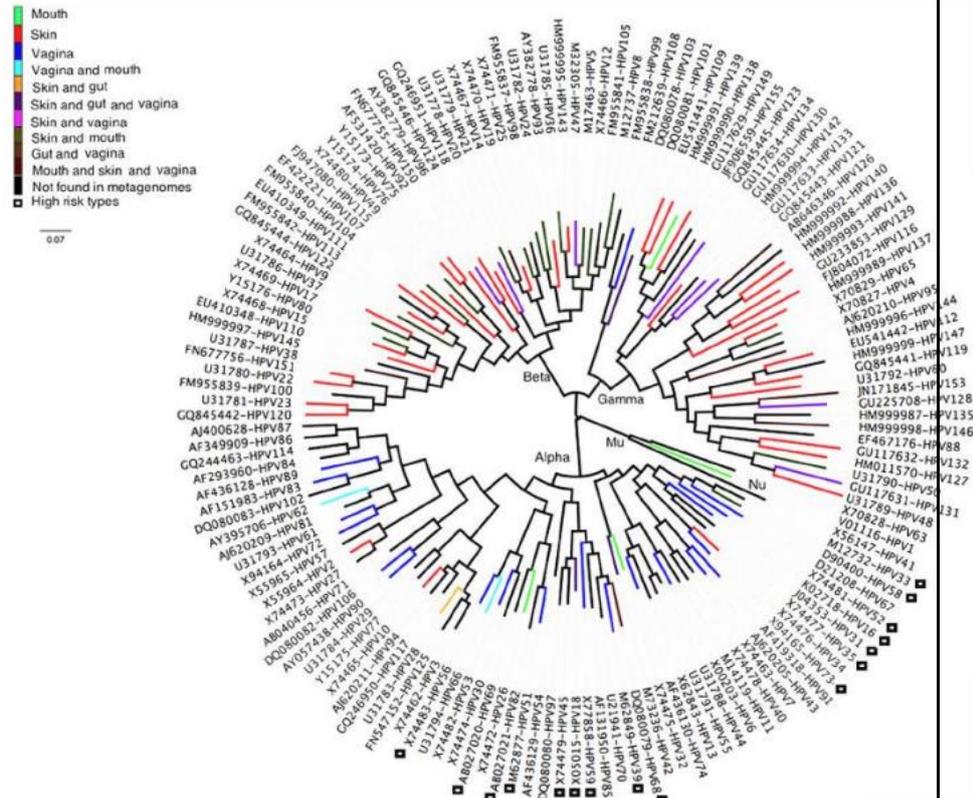
- Natural Host: Humans
- Tropism: Can infect epithelial cells of skin or mucous membranes
- Cellular Receptors: Heparan sulfate (among others)
- Transmission:
 - Direct and indirect contact with skin and mucous membranes
 - Sexual contact
- Geography: It is present globally with no specific geographic distribution.



Classification

By 2010, 120 different HPV types had been identified, based on differences in their DNA sequences in certain well-characterized virus genes.

The image to the right is a phylogenetic tree that shows the extensive variability of HPV types with certain types affecting specific areas of the human body.



HPV Types and Classification Based on Pathogenicity

- 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. High Risk - Virus types that produce lesions having a high risk of progression to malignancy, such as in cervical carcinoma.
 2. Low Risk - Types that produce mucosal lesions that progress to malignancy with lower frequency. For example, those causing anogenital warts and laryngeal papillomas.
 3. Benign - Other virus types are associated only with benign lesions. For example, those causing common, flat, and plantar warts of the skin.

HPV Replication

As we know, HPV infects epithelial cells of the skin or mucous membranes. Once the virus has infected the cell, it depends on the host cell to replicate its genome, synthesize viral proteins, and ultimately form new viruses. For HPV, this replicative cycle depends on how differentiated the cell is, and the specific factors that are present in these sequential states of epithelial cells. This means that the expression of genes does not occur all at once in one cell, but overtime as the epithelial cells differentiate.

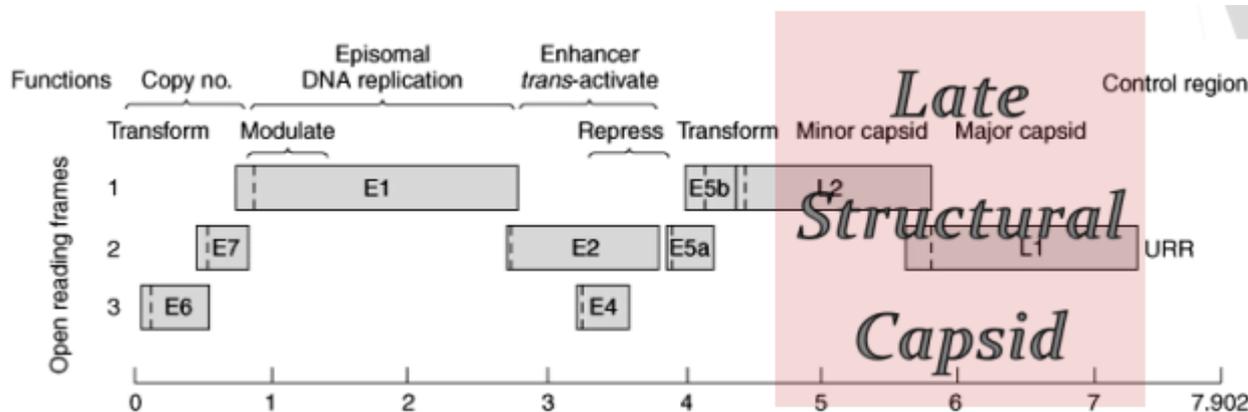
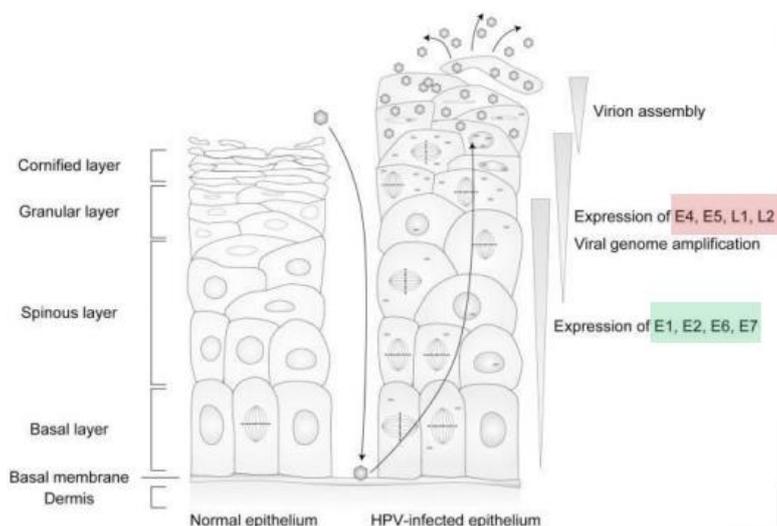
The epithelial cells are layered so that the basal layer (at the bottom) is least differentiated while the uppermost layer is most differentiated. Viral nucleic acid can be found in basal cells, but late gene expression is restricted to the uppermost layer of differentiated keratinocytes.

As we can see in the figure to the right:

The expression of early genes (such as E1 and E2) is close to the basal layer of the skin and mucous membranes.

As the epithelial cells differentiate, we see new early and late genes being expressed.

Finally, late structural genes are expressed exclusively in the uppermost layer of differentiated keratinocytes, and virion assembly can occur.



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. As discussed earlier, the viral replication cycle proceeds in parallel with the steps of keratinocyte differentiation, which will end with the terminally differentiated cornified layer of the growing wart.

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)

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

For the clinical manifestations its important to recognize that the majority of HPV infections are asymptomatic. Therefore, we should remember that the majority of these infections will not be detected clinically. For the cases we do detect, we can classify the manifestations based on where they occur.



HPV lesions in buccal mucosa

Clinical Manifestations: Oral Cavity

- Benign HPV infections of the oral cavity commonly occur.
- 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 (low risk types), and HPV16 (high risk type), have frequently been recovered from oral tissue.

1. Oral Squamous Papilloma

- Among the HPV lesions that may be found in the oral cavity, the oral squamous papilloma is the **most frequent** of all oral manifestations of HPV.
- The possibility of oral exposure to genital mucosa HPV (HPV6, HPV11, and HPV16) is through oral sex.



- Risk factors include:
 - Early sexual debut
 - Multiplicity of sexual partners
 - Frequent practice of oral sex

These pictures illustrate an example of oral squamous papilloma coming from the genital regions.



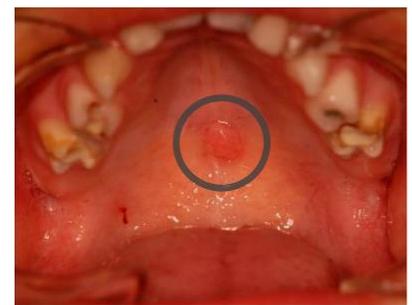
2. Oral Verruca Vulgaris (Common Wart)

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



3. Oral Condyloma Acuminatum

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



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 to predominantly infect the oral cavity.
- Treatment is usually unnecessary since most of the lesions are benign, regress spontaneously and there is no tendency to malignant transformation.



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

5. Oropharyngeal Cancer

- This is the most serious of all oral manifestations
- 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.
- The trend is that there is an increasing contribution of HPV to oral cancer.
- HPV16 accounts for about 90% of the HPV-positive tumors in the oral cavity.

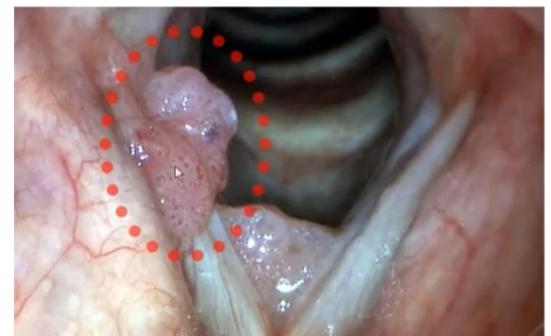
Clinical Manifestations: Skin

Warts may be classified as common (fingers and hands), plantar (sole of foot), or flat (arms, face, and knee). Most commonly caused by the benign HPV types 1, 2, 3, 4, and 7 among others.



Clinical Manifestations: Larynx

Laryngeal papillomatosis is a rare medical condition in which benign tumors (papillomas) occur and present with hoarse voice, shortness of breath, or coughing. The disease is mostly caused by HPV-6 or HPV-11 (low risk types).



Clinical Manifestations: Genital Tract

Genital HPV infection is considered the most common sexually transmitted viral infection in the world, with an estimated lifetime risk of at least 75% involving both females and males.

Infection with high-risk HPV types can end up in the development of vulvar, vaginal, penile or anal cancer. But the most common is cervical cancer.

1. Cervical Cancer

Among the most common cancers in women worldwide.

Pap smear screening has decreased the frequency of cervical cancer in industrialized countries. However, it is not able to detect all cases.

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.

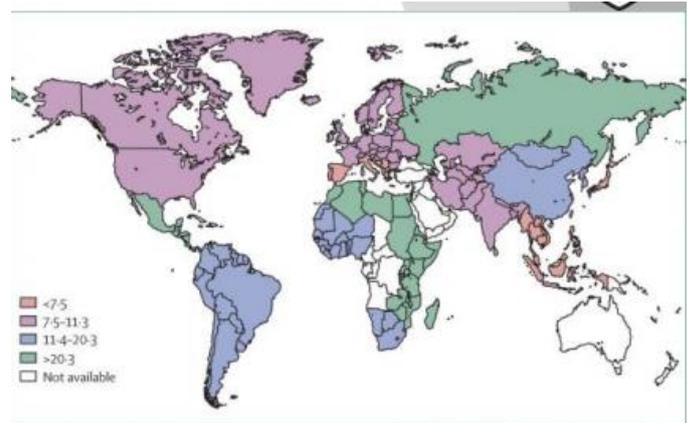
2. Anogenital Warts (Condylomas)

Condylomas are outgrowth lesions that are frequently multiple.

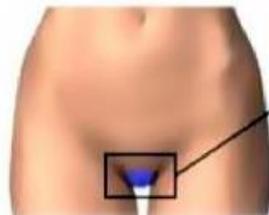
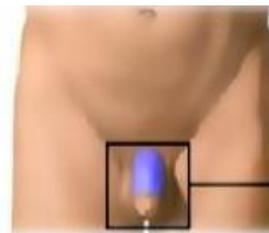
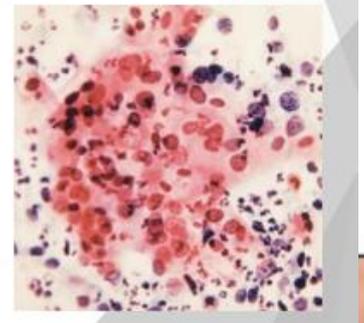
They can arise anywhere on the external genitalia and can be found simultaneously in multiple sites.

In men, they occur most commonly on the penis and anus, and in women on the perineum and anus.

About 90% of genital warts are caused by HPV6 or HPV11 (low risk types).



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



Condyloma acuminata can be found on vagina, vulva, cervix, around the anus and on penile shaft



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 15th most frequent cancer among women in Jordan and the 10th 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. In general, it is less common in Jordan compared to other regions in the world.

Diagnosis

- Visual inspection can give clues to diagnose HPV infection.
- Molecular detection can help in diagnosis as well. Typing has the potential to detect low and high risk types.
- 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:

- a) Liquid nitrogen
- b) Laser vaporization
- c) 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.