HUMAN PAPILLOMA VIRUS VACCINE

Introduction

Human Papilloma Viruses (HPVs) are highly species specific and widespread throughout the general population. It is known to produce epithelial tumours of the skin and mucous membranes.

Human Papilloma Virus (HPV) genital infection is a common sexually transmitted infection but asymptomatic and sub clinical. Most sexually active men and women will acquire an HPV infection at some time in their lives. Most HPV infections are transient but persistent genital infection with certain HPV genotypes can lead to the development of anogenital warts, anogenital precancers and cancers.

Diseases caused by HPVs include cancers of the cervix, vagina, vulva, penis and anus; a subset of head and neck cancers; anogenital warts; and recurrent respiratory papillomatosis.

Cervical cancer is the second most common cancer in women. Virtually all cervical cancer cases are linked to genital infection with HPVs, which is the most common viral infection of the reproductive tract.

Virology

HPVs are non-enveloped, double-stranded deoxyribonucleic acid (DNA) viruses in the family of *Papilloma-viridae*. The HPV genome is enclosed in a capsid shell comprising major (L1) and minor (L2) structural proteins.

Epitheliotrophic nature of the virus favours cutaneous and mucosal epithelial transmission involving skin and ano-genital tract. The virus enters the basal layer of the epithelium via minor trauma, abrasion and skin to skin contact during sexual intercourse. Some gene products in the HPV virus act as onco proteins and are responsible for inactivation of human tumour suppressor gene products of P53 and PRb which cause uncontrolled cellular proliferation and cytological changes in cervical epithelial cells leading to pre malignant and malignant lesions.

Nearly 40 distinct HPV genotypes are sexually transmitted. But almost 15 genotypes (e.g.16,18,31,33,35,39,45,51,52,56,58,59,68,73 & 82) are designated as "high risk" considering the causal association with cervical cancer. Out of this, genotypes, type 16 and 18 are identified to contribute nearly 70% of all cervical cancers worldwide. Genital infection with carcinogenic or high risk HPV is also implicated with a spectrum of other anogenital conditions described as malignancies and pre malignant conditions in vulva, vagina, anus, and penis.

The category of HPV designated as "low risk" for cervical cancer (geno types 6,11,42,43,44,54,61,72 and 81) is associated with the development of viral warts.

Of which genotypes 6 and 11 are associated with 90% of genital warts and 100% of recurrent respiratory papillomatosis (RRP) cases.

Clinical Features

Human Papilloma Virus infection usually does not cause any symptoms. Condylomata accuminatum (genital warts) may appear within several weeks or months after contact with genital infection of low risk geno types (6 and 11). Majority of the HPV infections are transient infections and persistent HPV genital infection with certain viral genotypes (16 and 18) can lead to the development of anogenital precancers and cancers.

Old age, genital infection with multiple HPV types and infection with high risk or virulent HPV geno-types, poor nutrition and poor immunity are factors associated with persistence of infection.

Genital infection with high-risk HPVgenotypes are associated with a spectrum of anogenital diseases, including cervical, vulval, vaginal, penile and anal cancers, and their precursors. In addition, genital HPV genotypes are associated with extragenital diseases, including some squamous cell carcinomas of the head and neck.

Epidemiology

Global Situation

Worldwide differences are observed in genital prevalence rates of HPV infection among women at risk (sexually active>15 years). Cervico-vaginal HPV prevalence rates in the general population ranging from 6 – 46% have been reported from different countries. A pooled analysis by WHO, has described a prevalence of cervico-vaginal infection as 6.6% for the South Asian region. The different prevalence rates are described to be closely related to the corresponding risk of cervical cancer relevant to the region.

In 2005, there were about 500 000 cases of cervical cancer and 260 000 related deaths worldwide. Cervical cancer incidence rates vary from 1–50 per 100 000 females; rates are highest in Latin America and the Caribbean, sub-Saharan Africa, Melanesia, and South-Central and South-East Asia. Most cases of cervical cancer are diagnosed in women aged >40 years.

Countries with well-organized programmes to detect and treat precancerous abnormalities and early stage cervical cancer can prevent up to 80% of these cancers. However, effective screening programmes and follow-up of women with abnormal screening tests have been difficult to implement in low-resource and middle-resource settings. Mortality rates from cervical cancer are therefore much higher in the developing world.

Situation in Sri Lankan

In Sri Lanka a community based HPV prevalence study done in 2008 at the district of Gampaha among 2000 women of 20-59 years revealed an overall cervical HPV prevalence of 3.3% and a prevalence of geno type 16 and 18 as 1.2%.
Hospital based cervical cancer data reveals that cervical cancer ranks as the 2nd most frequent cancer among women.

According to the Globocan cancer fact sheet, for year 2008 the estimated age standardized cervical cancer incidence rate for Sri Lanka was 11.8 per 100,000 women and age standardized estimated cervical cancer mortality was 6.9 per 100,000 women.

HPV vaccine

A new hope for prevention of cervical cancer and genital warts have evoked with the development of new vaccines against HPV geno types 16, 18 of high risk and 6,11 of low risk. Currently available vaccines are mainly prophylactic vaccines for HPV-naïve women and not a therapeutic vaccine for those who are already infected.

Vaccines are commercially available for use since 2006. Most of the developed countries have initiated vaccinating adolescents in prevention of HPV genital infection with the ultimate goal of preventing cervical cancer.

WHO recognizes the importance of cervical cancer and other HPV-related diseases as global public health problems and recommends that routine HPV vaccination may be included in the national immunization programmes, provided that: prevention of cervical cancer or other HPV-related diseases, or both, constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost effectiveness of vaccination strategies in the country or region is considered.

Characteristics of the HPV vaccine

Currently, 2 HPV vaccines are available internationally. Using recombinant technology, both are prepared from purified L1 structural proteins that self assemble to form HPV type-specific empty shells or virus-like particles (VLPs). Neither vaccine contains live biological products or viral DNA, so they are non-infectious. HPV vaccines are designed for prophylactic use only; they do not prevent the progress of the existing HPV infection or treat HPV-related diseases. Therefore it is important to immunize the target populations before they get exposed to the HPV infection.
Both vaccines are generally safe, well tolerated with high efficacy and immunogenicity.

Types of vaccine

Two types of prophylactic vaccines namely quadrivalent and bivalent are available.

Quadrivalent vaccine consists of a mixture of four HPV geno type specific L1 virus like particles (VLP) of geno type 6, 11, 16 and 18. The substrate of the vaccine is based on recombinant yeast technology (*Saccharomyces cerevisiae).* Each 0.5 ml dose of quadrivalent vaccine (Gardasil) contains 20μg HPV 6 L1 protein, 40 μg HPV 11 L1 protein, 40 μg HPV 16 L1 protein and 20 μg HPV 18 L1 protein with 225 μg Aluminum hydroxyl phosphate sulphate as an adjuvant.

Bivalent vaccine includes L1 VLPs of HPV geno types16 and 18. This is produced using a baculovirus technology that uses Hi-5 Rix4446 insect cells with an adjuvant known as ASO4 that contains Aluminium hydroxide plus 3-o-desacylated mono phosphoryl lipids (Alum and MPL).

Efficacy

Overall sero conversion observed is 99-100%. Exact duration of immunity after vaccination is yet to be explored but observed of at least 5 years duration. Trial showed efficacy of 100% against HPV type 16/18 related persistent infection and CIN 2/3.

Both vaccines appear to have partial efficacy against infection caused by HPV type 31 and 45, which are genetically related to type 16 and 18.

Limited clinical trial data indicates lower sero conversion and lower vaccine efficacy among immuno compromised as a result of disease condition or medication compared to immunocompetent.

Indication

Vaccines are indicated for use in females 9- 26 years of age for prevention of:

- cervical precancers and cancers,
- vulvar vaginal and anal precancers and cancers,
- ano-genital warts(Condylomata acuminate).

HPV vaccines are designed for prophylactic use only; they do not clear existing HPV infection or treat HPV related diseases.

Both vaccines are intended to be administered to females before the onset of

sexual activity – that is, before first exposure to HPV infection. Most countries that have licensed these vaccines, recommend their use in girls aged 10–14 years.

Dosage & Administration

Both bivalent and quadrivalent vaccines, 0.5 ml (each dose) of vaccine is administered intramuscularly (IM) as 3 doses.

The quadrivalent vaccine is given at baseline and again after 2 months and 6 months.

The bivalent vaccine is given at baseline and again after 1 month and 6 months.

Restarting the 3-dose series is not necessary if the programme has been interrupted, but remaining vaccine doses should be administered as close to the recommended schedule as possible. Currently, the manufacturers do not recommend a booster dose following completion of the primary series.

Both HPV vaccines are non-live and non-infectious and can be co-administered with other non-live and live vaccines using separate syringes and different injection sites.

Storage

Storage is recommended at $+2^0$C to $+8^0$C, and should not be frozen. Recommended protection from light.

Cautions and contraindications

The following conditions are considered as contraindications for the use of HPV vaccines.

- Presence of one of the general contraindications for any vaccine
- People with known hypersensitivity to any component of the vaccine.
- History of severe allergic reaction following a preceding dose of HPV vaccine

Adverse Events

Mild and transient local reactions at the site of injection (erythema, pain or swell ing) were reported following HPV vaccination and usually resolve within 3-4 days.

Systemic adverse events (fatigue, headache, and myalgia) are other symptoms observed. Severe reactions are not observed with HPV vaccination.

Usage of vaccine in specific circumstances

Use in pregnancy
Vaccines are not recommended to be given during pregnancy even though teratogenicity is not observed in animal studies. Vaccines can be administered to lactating mothers but antigen or antibody excretion in breast milk has not yet been observed.

Sources

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