HPV Vaccines: Making Primary Prevention a Reality

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The development of human papilloma virus (HPV) vaccine has created the opportunity to protect women against Cervical cancer. HPV viruses are most often the cause of cervical cancer.[1] Vaccination against HPV 16 and 18 has potential to reduce Cervical cancer by approximately 70%. It also reduces the overall burden of HPV related cervical disease.[2] Thus, HPV vaccine is predicted to have major impact by saving lives and reducing emotional and physical stress on patients and their families. HPV vaccination is truly a revolution in Cervical cancer prevention.

Globally, cervical cancer is second most common cancer in women after breast cancer. In India, it is the most common cancer in women, contributing to one fourth of global burden. It is the commonest cause of death in women from any other form of cancer in developing countries. WHO study shows 1.3 lakh women in India are diagnosed with cervical cancer and approximately 74,000 die every year.[3]

HPV: Cause of cervical cancer

Cervical cancer is caused by Human Papillomavirus (HPV) which are "oncogenic" or "high risk types". These are 15 in number. Globally, HPV 16, 18, 31, 33 and 45 are the common oncogenic HPV types, of which HPV 16 and 18 account for 70% of Cervical cancer and HPV 31,33 and 45 account for 12%. (Fig. 1) Phylogenetically, HPV 16 is closely related to 31 and HPV 18 to 45. Together they are responsible for 82% of Squamous cell carcinoma and 93.2% of Adenocarcinoma of cervix.

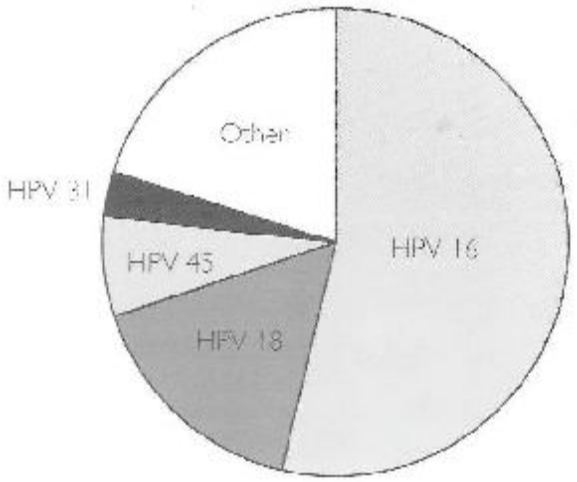

Fig 1: In decreasing order of frequency: HPV 16, 18, 45, 31

Most HPV infections usually resolve within 7 months to 2 years. When natural immunity fails, infection becomes persistent, which is "necessary cause" of Cervical cancer. Persistent HPV infection can bring about cellular changes in cervical epithelial cells called lesions. These are classified as CIN (Cervical Intraepithelial Neoplasia) grades 1 – 3. CIN 2 and 3 are "pre - cancerous" and can progress to Cervical cancer. HPV infections and CIN 1 lesions are referred to as "Low Grade squamous intraepithelial lesions "whereas CIN 2 and 3 are known as "High Grade". It takes 10 – 20 years from initial HPV infection to invasive cervical cancer, though there are reports of progression within 1 – 2 yrs.

Genital warts are benign, self limiting and are managed with local treatment. They are caused by HPV 6 and 11 which are 'low risk" or "non-oncogenic".

RISK OF INFECTION:

Every sexually active woman is at risk of HPV infection. It is estimated that 50-80% women acquire HPV infection in their lifetime of which up to 50% is oncogenic type. Young women between 16-25 years art at greater risk but older women are likely to have persistent HPV infection due to "immune evasion" and "immune senescence" leading to Cervical cancer. HPV transmission can also occur with skin to skin genital contact, hence an effective "HPV vaccine" that provides strong, sustained immune response is necessary for women against oncogenic HPV types.

In 1991, the idea of HPV as a leading cause of cervical cancer was accepted and development of HPV vaccine started.

PRIMARY PREVENTION:

Cervical cancer screening is the means of detecting existing cervical disease and HPV DNA test is used for detecting existing HPV infection. Vaccination against HPV is the only means of protecting women against Cervical cancer and a New Management option in Primary Prevention of Cervical Cancer. It is demonstrated that HPV vaccination with cervical cancer screening program is the most effective approach for Prevention of Cervical Cancer.

In developing countries, effectiveness of implementation of screening program is limited due to finances. Vaccination may prove to be the best option to reduce the incidence of Cervical cancer, provided it is cost effective.

Other benefits of HPV vaccines would be decrease in number of pre malignant cervical lesions and its associated morbidity, emotional stress and anxiety. Vaccines have significant social and economic value as it prevents illness and disability and reduce overall health expenditure.

HPV VACCINE:

HPV vaccine is prophylactic Cervical cancer vaccine with antigens based on proteins of HPV assembled into purified virus like particles (VLPs) which are highly immunogenic. This vaccine by preventing infection with HPV also protects against cytological abnormalities and disease associated with these infections like CIN grade 1 – 3, Cervical cancer and Adenocarcinoma in situ. Vaccine formulated with innovative adjuvant system provides optimal response. Following systemic vaccination, high level of antibodies is developed in serum, which transude through cervical mucosa to remain in cervix. When new HPV infection occurs, these antibodies neutralize the virus and prevent infection.

The antibody levels are 11 fold higher than natural response up to 9.5 yrs. Mathematical modeling suggests persistence of these antibodies for at least 20 yrs. Hence, at present booster dose is not recommended. This vaccine provides nearly 100 % protection against CIN 2 lesions caused by HPV 16 and 18 for 6.5 to 9.5 yrs with additional protection against HPV 45 and 31. [4]

Age / Vaccine:

It can be given to all the women from age group of 10 – 45 years.

Every sexually active woman continue to remain at risk of oncogenic HPV infection and vaccination will protect them from acquiring any new HPV infection which in future might lead to Cervical cancer. It is not recommended for age group of under 10 years.

Efficacy and cost effectiveness of vaccinating males is yet to be established.

Vaccine Types:

Cervarix (Glaxosmithkline) bivalent vaccine offers protection against HPV 16 and 18 with extra protection against HPV 31 and 45 – multivalent and better Immune response due to innovative adjuvant system.

Gardasil (MSD) quadrivalent vaccine offers protection against HPV 16 and 18, 6 and 11 so protects against Genital warts, vulval and vaginal cancers due to HPV.

Schedule / Administration:

Recommended schedule for bivalent vaccine is 0, 1 and 6 months; and for quadrivalent vaccine is 0, 2 and 6 months.

Recommended that subjects who receive first dose completes all three doses. If flexibility is necessary, second dose can be administered between 1 and 2.5 months after the first dose.

HPV vaccine is for Intramuscular (IM) injection only, in deltoid region.

It can be given with other vaccines but at different injection sites.

Available as pre filled syringe of 0.5 ml suspension (white turbid). To be shaken before use as upon storage, fine white deposit with clear supernatant is seen. To be stored in refrigerator between $2^{o}c$ – $8^{o}c$. (Though Vaccine is stable at room temp. of $37^{o}c$ for 1 week)

Precaution / Warning:

Clinical history and examination is recommended. Information that other oncogenic HPV infections not covered by HPV vaccine may not be prevented needs to be given.

Vaccination should be temporarily postponed in subjects with acute febrile illness, however it can be given with milder febrile illness like cold.

It can be given in women with usage of Hormonal contraception.

It is contraindicated in subjects with Known Hypersensitivity to any vaccines. To be administered with caution in subjects with thrombocytopenia/coagulation disorders.

Not recommended during pregnancy due to insufficient data and hence best given after pregnancy. To be used during breast feeding when possible advantage outweighs risks.

Currently no data is available for usage in immune-compromised subjects as adequate immune response may not be elicited.

Side Effects:

Headache, myalgia and injection site reactions like pain, redness and swelling are common side effects. Fever, arthralgia, GI symptoms like nausea, vomiting, diarrhea, itching, pruritus and rash can also be seen. Rarely giddiness or upper respiratory tract infection may be seen.

Overall HPV vaccine is SAFE and WELL TOLERATED.

Indian Scenario:

Screening is "secondary prevention". In India, vast majority of women remain unscreened and present with invasive cancer at a very late stage. Although individual screening may involve lower cost

in short term, a mass screening program may cost substantially. HPV vaccination is considered to be "PRIMARY PREVENTION" there by reducing likelihood of persistent HPV infection to cancer. The economic and social cost of CERVICALCANCER far exceeds those of vaccination. In countries like US and Australia this vaccine has been mandatory that shows its importance.

HPV vaccine is recommended as it is powered for lasting longest multivalent protection by producing higher antibody against 5 types of oncogenic HPV – 16, 18, 31, 33, 45 responsible for Cervical Cancer.

References

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