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INVITED MINI REVIEW

HPV Vaccine: How Far have We Achieved?

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Abstract Globally, cervical cancer is the second most common cancer, and in India, it is the most common cancer in women. Human Papilloma virus (HPV) is the main cause of it. Although there are several methods for preventing cervical cancer, primary prevention by vaccination is the most effective option. HPV vaccine is safe and effective. It is expensive and is not a replacement for periodic cervical screening procedures. In developing countries, the cost effectiveness of vaccine and that of effective screening program with broader coverage is questionable. Today, HPV vaccine with regular cervical cancer screening program is the best possible tool to prevent cervical cancer.

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Introduction

The development of Human papilloma virus (HPV) vaccine has created an opportunity to protect women against cervical cancer. HPV viruses are most often the cause of cervical cancer. Vaccination against HPV 16 and 18 has potential to reduce cervical cancer by approximately 70 %. It also reduces overall burden of HPV-related cervical diseases [1]. Thus, HPV vaccine is predicted to have major impact by saving lives and reducing emotional and physical stress on patients and their lives. It is truly a revolution in cervical cancer prevention. The advent of vaccine against HPV has stirred much excitement as well as debate.

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. In developing countries, it is the commonest cause of death in women from cancer. Death in reproductive years has devastating effect on well-being of their families. WHO study shows 1.3 lakh women in India are diagnosed with cervical cancer and approximately 74,000 die every year [2, 3].

HPV: Cause of Cervical Cancer

Cervical cancer is caused by HPV viruses which are "oncogenic" or "high risk types." They are 15 in number. Globally, HPV 16, 18, 31, 33, and 45 are the commonest oncogenic HPV types, of 16 and 18 account for 70 % and 31, 33, and 45 account for 12 % of cervical cancer (Figure 1). Phylogenetically, HPV 16 is closely related to 31 and 18 to 45. Together, they are responsible for 82 % of squamous cell and 93.2 % of adenocarcinoma of cervix [4].

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 cervical Intraepithelial Neoplasia (CIN) grades 1–3. HPV infections and CIN 1 are referred as "low grade," whereas CIN 2 and 3 as "high grade squamous intraepithelial lesions". CIN 2 and 3 are "pre-cancerous" and can progress to cervical cancer [5]. It takes 10–20 years from initial HPV infection to invasive cervical cancer, though there are reports of progression within 1–2 years.

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

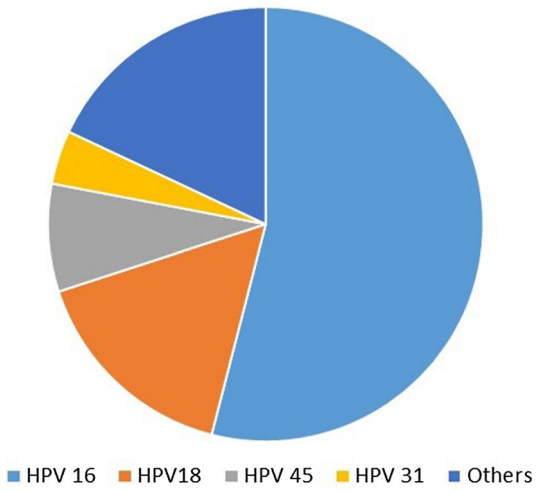

Fig. 1 Decreasing order of frequency–HPV 16, 18, 45, 31

Risk of Infection

Every sexually active women is at the risk of HPV infection. It is estimated that 50–80 % of women acquire HPV infection in their lifetime, of which up to 50 % is with oncogenic type [2]. Young women between 16–25 years are at greater risk but older women are likely to have persistent HPV infection due to "immune evasion" and "immune senescence" progressing to cervical cancer. It 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. Studies are unclear about mother-to-child HPV infection [7].

In 1991, the idea of HPV as a leading cause of cervical cancer was accepted and development of HPV vaccine started [8].

Primary Prevention

Cervical cancer screening is the means of detecting existing cervical disease and HPV DNA test for 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. [9].

In developing countries, effectiveness of implementation of screening program is limited due to finances and other organizational short comings. In low resource setting, single or two screens in lifetime with "see and treat" may be only feasible approach [10]. Vaccination may prove to be the best option to reduce incidence of cervical cancer provided if it is cost effective.

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

HPV Vaccine

HPV vaccine is prophylactic 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 associated diseases like CIN 1–3, cervical cancer, and adenocarcinoma in situ. Vaccine formulated with innovative adjuvant system provides optimal response. Following systemic vaccination,

high levels of antibodies are 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 years [11]. Mathematical modeling suggests persistence of these antibodies for at least 20 years. Hence at present booster dose is not recommended. This vaccine provides 100 % protection against CIN 2 lesions caused by HPV 16 and 18 for 6.5–9.5 years with additional protection against HPV 45 and 31.

Age

It can be given to all women between 10 and 45 years.

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

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

Types

Both bivalent and quadrivalent vaccines offer protection against HPV 16 and 18 with extra protection against 31 and 45. Quadrivalent protects against genital warts, vulval, and vaginal cancers caused by HPV 6 and 11.

Schedule/Administration

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

It is recommended that subjects who receive first dose complete all 3 doses. If flexibility is necessary, second dose can be administered between 1 and 2.5 months after first dose.

It is given by intra-muscular (IM) route, preferably in deltoid region. It can be given with other vaccines but at different injection sites.

Vaccine is available as pre-filled syringe of 0.5 ml suspension (white turbid). It is to be stored in refrigerator between 2 and 8 °C (Though stable at room temperature for 1 week).

Precaution/Warning

Clinical history and examination are 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 in milder febrile illness like cold.

It is not recommended during pregnancy due to insufficient data and hence best given after pregnancy. It can be given during lactational period only if possible advantage outweighs risks [12].

Currently, no data are available for its usage in immunocompromised subjects as adequate immune response may not be elicited.

Side Effects

Injection site reaction, headache, fever, arthralgia, and mild GI symptoms 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 low cost in short term, a mass screening program may cost substantially. HPV vaccine is considered to be "Primary Prevention," thereby reducing likelihood of persistent HPV infection to cancer. The economic and social cost of cervical cancer far exceeds that of vaccination. In countries like US and Australia, this vaccine has been mandatory, which shows its importance. It is preferable to give in adolescent age group (before sexual activity begins). Decision regarding vaccination is taken by parents primarily with adolescent having some role and hence they need to be educated. Studies have shown no increase in risky sexual behaviors and altered risk perception following vaccination [13]. This vaccine does not cover all carcinogenic HPV types and it has no therapeutic effect if received after exposure to HPV. Hence cervical cancer screening needs to be continued whether women have or have not received HPV vaccination.

Currently available vaccine is safe and effective. Pap test, screening for HPV DNA, or HPV antibody test is not recommended before vaccination. The primary concern is the cost and hence affordability and accessibility. Distrust due to "newness" of vaccine and altered sexual risk perception may also be some of the short comings. If the vaccine can be made more affordable with support from International/National organizations or NGOs, then it can be given to the poorest of poor [14].

Conclusion

HPV vaccine is recommended as it is powered for lasting longest multivalent protection by producing antibodies against five types of oncogenic HPV–16, 18, 31, 33, and 45

responsible for cervical cancer. The cost effective vaccine is needed for developing countries, as this vaccine has potential to save many lives. Till such time, secondary prevention method of screening should continue with existing infrastructure. Screening combined with vaccination can substantially reduce worldwide cervical cancer mortality.

Compliance with ethical requirements and Conflict of interest The Author declares that there is no conflict of interest/financial disclosure.

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