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Review Article

A View on Prevention of Cervical Cancer by Human Papillomavirus Vaccination

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ABSTRACT

Cervical cancer, the fourth leading cause of death in women is mainly caused by sexually transmitted Human Papillomavirus (HPV). HPV consists of over 200 serotypes, out of which 12 types of HPV are considered high-risk, especially type 16 and 18 being the most oncogenic types. To prevent the incidence and prevalence of cervical cancer, administration of HPV vaccination is recommended. There are 3 types of vaccines approved by FDA, namely Bivalent, Quadrivalent, and Nonavalent HPV vaccines consisting of 0.5ml in each dose scheduled to 2 doses for children between 9 to 14 years, and humans above 15 years are recommended with 3 doses with few months apart. Although the vaccine is beneficial, it is noted that many were unable to get it due to various barriers in which the cost of the vaccine plays a key role, and lack of awareness on both disease, vaccine, and dose schedules plays another role. In order to make the vaccine available for everyone worldwide, single-dose administration is taken into consideration

INTRODUCTION

1.1 CERVICAL CANCER

Cervical cancer is the fourth most common cancer in women after colorectal cancer, lung cancer, and breast cancer. In India, every year, a hundred thousand women are prone to cervical cancer, half of whom defer to the cancer.

According to the National Family Health Survey (NFHS-4) for every 5 years women aged between 30-65 years, cervical cancer screening is done routinely in India and only 22.3% was found that women aged between 15 and 49 years had undergone the screening of cervical cancer. [1] According to the survey, cervical cancer ranked fourth most prevalent cause of cancer-related

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death among women to receive a diagnosis globally. [2] As screening and treatment facilities are scarce, cancer is primarily a health issue in low-resource nations [3]. Because there is less access to programs for screening, prevention, and treatment, cervical cancer is more common in developing nations.[4]

Cervical cancer is categorized into two types: about 75% of squamous cell carcinoma, which initiates at the transformation zone of the ectocervix, and about 25% of adenocarcinoma, which appears in the glandular columnar layer of the endocervix. The main cause of the development of cervical neoplasia is human papillomavirus (HPV) and 99.7% of cervical cancer can be detected. The subtypes of Human Papilloma Virus (HPV) 16 and 18 are the high-risk strains that cause cervical cancer. The adenocarcinoma is different from the squamous cancer of HPV subtypes.[5]

1.2 HUMAN PAPILLOMAVIRUS (HPV)

Human papillomaviruses (HPV), a double standard DNA virus with many serotypes belong to the family *Papillomaviridae*. While there are more than 100 distinct viral genotypes (as of 2020) in the HPV family, HPV 16 and 18 have been linked to over 70% of instances of cervical cancer, and HPV 6 and 11 can cause genital warts. There are two forms of HPV: high-risk (HR) varieties, which are linked to the development of cervical cancer and its precursor, high-grade cervical intraepithelial neoplasia, and low-risk (LR) variants, which can also generate harmless epithelial lesions like genital warts.[3]

HPV infection is a sexually transmitted infection (STI), and most of the risk factors for cervical cancer occur due to the high risk of sexually transmitted infection. Factors that increase the transmission and produce the carcinogenic effect of the virus are:

- Early sexual intercourse (i.e., before age 15 or 16 years), early marriage
- a multiple number of sexual partners,
- marriage,
- a sexual partner who has sexual intercourse with multiple partners,
- unprotected sexual intercourse (e.g., non-use of condoms, diaphragms, or gels),
- a past history of sexually transmitted infections or diseases of the partner,
- inadequate education about STDs
- non-exposure to cervical cancer screening.

Human papillomavirus (HPV), multiple sex partners, smoking, immunocompromised status (e.g., AIDS), chlamydia infection, long-term use of oral contraceptives, multiple full-term pregnancies, early age at first full-term pregnancy, low economic status, and low fruit and vegetable consumption are the main preventable risk factors for cervical cancer. Few of the more than 100 serotypes (of 2020) of the human papillomavirus are oncogenic, whereas in the high-risk strains, 40–60% of cervical cancer precursors and 70–75% of cases are caused by HPV-16 and HPV-18. Oncogenic subtypes may also cause other cancers, such as anal, vulvar, vaginal, penile, and oropharyngeal cancers.

2. EPIDEMIOLOGY:

Considering that, 10 years ago, cervical cancer was the third most recurrent cancer in women, although it was the most prevalent cancer in women in 42 low-resource nations, the understanding that the primary factor contributing to the development of cervical cancer is ongoing infection with oncogenic human papillomavirus (HPV) strains. In India, the incidence of cervical cancer has declined in urban regions but remained

the same in rural areas. Every year, cervical cancer affirms the lives of about 300,000 women and affects almost 600,000 and more, mostly middle-aged and low-income women. Multiple sexual partners and poor genital hygiene are associated with a higher HPV prevalence of the 100 HPV strains; 18 are considered to be high-risk forms for cervical cancer. In 2020, 24% of cancer incidence are from India of all cancer incidence globally that was linked to HPV and 7% of all cancer incidence globally. HPV high-risk strains 16 and 18 were considered to be in four of every five cervical cancer cases reported in India.[10]

According to May 2023 study, there are six approved human papillomavirus (HPV) vaccinations namely, three bivalent vaccines, two quadrivalent vaccines, and one nonavalent vaccine. 70%+ of cancer cases are caused by high-risk HPV 16/18 genotypes, which are prevented from recurring by the use of quadrivalent and bivalent HPV vaccinations. 18.5% more HPV-positive cervical malignancies are caused by high-risk HPV types 31/33/45/52/58, which are further persistently infected when left untreated and they are being prevented thanks to the nonavalent vaccine. Women under the age of 25 had the highest incidence of HPV infection. Women's deaths due to cervical cancer can be avoided by HPV-based cancer screening and advanced vaccination.[7]

3. RELATION BETWEEN HPV AND CERVICAL CANCER:

Human papillomavirus (HPV), a common viral infection related to a wide range of diseases in women and male reproductive tracts, involving the progression of potential precancerous lesions to cancer.[12] The virions of HPV are non-enveloped, containing a double-standard DNA (dsDNA) genome. The genetic material of HPV is enclosed by an icosahedral capsid composed of major and minor, respectively L1 and L2 structural proteins.

The main mode of transmission of HPV infection is through sexual intercourse, including oral sex, HPV infection also spreads through infected genital skin, mucous membranes contact, or body fluids.[12] HPV viruses can infect both cutaneous and mucosal and epithelium, being extremely tissue-specific. More than 200 types of HPV have been identified and distinguished. Classification of HPV types is based on various parameters, including their cancer-inducing potential, i.e. high-risk (Oncogenic) and low-risk types.

As of now, 12 types of HPV are considered as high-risk, causing cancer in both women and men. Type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 are cancer-causing HPV types, meanwhile, type 68 is categorized under probably cancer-causing. In general, HPV-infected patients (70-90%) mostly have no symptoms, and the infection resolves on its own within 1-2 years. The leading cause of HPV-associated cancer is High-risk type HPV infections compared to Low-risk type HPV infections.

Chronic infection of HPV in women proceeds to Cervical intraepithelial neoplasia grade 2/3 (CIN 2/3). 8-28% of high-grade cervical neoplasia occurrence is based on the type of HPV, development to neoplasia takes between months to years. 3-5% of neoplasia lesions in intraepithelium progress to invasive cervical cancer without any treatment that is when left the infection is left untreated. For women with a normal immune system, typically it takes 15-20 years of persistent HPV infection to progress into cervical cancer.[11]

The oncogenic types risk for cancer is based on serotypes, i.e. type-specific, in which HPV type 16 is the most oncogenic. The presence of HPV DNA

on repeated clinical biological samples (typically six months) indicates cervical cancer due to persistent HPV infection left untreated. Globally, HPV types 16 and 18 were the most prevalent types, with HPV type 16 being the most common in all areas. Women already infected with one HPV type are prone to be reinfected with the same HPV type and get co-infected with other HPV types later.[12]

HPV high-risk oncogenic types are is associated with most cancers of the cervical, vulvar, and vaginal cancer in women, penile cancer in men, anal, and oropharyngeal cancer in both men and women. Vaccination of HPV promotes the prevention of six different types of cancers, respectively the vaginal, vulvar, and cervical in women, along with penile cancer in men, prevents anal, and oropharyngeal cancer in both genders.[13] The recommended age group for vaccination is 9-14 years for both males and females and 15-26 years for women and men. Giuliano claims that vaccination is more productive when administered at an early age since the immune system responds better and that most children are not exposed to the virus.[14]

4. PREVENTION OF CERVICAL CANCER BY HPV VACCINATION:

Three vaccinations against HPV infection have been approved by the US Food and Drug Administration as a primary prevention for HPV cancers. Depending on the vaccination, 2v, 4v, or 9vHPV serotypes are covered. People from the ages of 9 to 26 are eligible for the bivalent and quadrivalent vaccines, while those between the ages of 9 and 45 are eligible for the 9-valent vaccine.[15]

4.1 HPV VACCINE OBJECTIVES

The main objective of the human papillomavirus (HPV) vaccine is to prevent infection with the primary oncogenic strains of HPV, which in turn prevents the development of invasive cervical cancer.1. A total of 124 nations and territories had national HPV vaccination programs in place as of December 2019.2. Since its approval in 2006, HPV vaccination has been virtually completely used in Sweden.[16]

The fact that 9vHPV only affects humans raises questions about its precise mode of action and presents research obstacles. Nonetheless, scientists think that the vaccination works by inducing the humoral reaction. In order to manage and prevent HPV infection and related disorders, this exercise thoroughly looks at the indications, actions, and contraindications of the 9vHPV vaccination.

4.2 FDA APPROVED VACCINES

The following lists the three FDA-approved vaccinations that are intended to guard against infection from varying strains of HPV.

- Bivalent (2vHPV) vaccine: Bivalent HPV vaccine, or 2vHPV, guards against HPV types 16 and 18. This vaccination is still in use in other nations even though it is not available in the US.
- Quadrivalent (4vHPV) vaccine: The 4vHPV vaccine delivers protection against HPV type 6,11, 16, and 18.
- Nonavalent (9vHPV) Vaccine: 9-valent HPV vaccine protects against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. This is the one and only HPV inoculation that offers protection against these specific HPV strains and is the one that is advertised in the US.

For both genders, ages between 9 and 45, the 9vHPV vaccine is usually advised in order to avoid

many illnesses and dysplastic lesions brought on by HPV, including the following: vulvar, cervical, oropharyngeal, and anal.

4.3 DOSAGE

The standard fixated dosage for bivalent, quadrivalent, and nonavalent HPV vaccine is a 0.5 ml single-dose prefilled syringe, administered in deltoid muscle i.e. given intramuscularly. Gardasil 9, the nonavalent vaccine contains 9 serotypes including Type 6 L1 (30mcg), 11 L1 (40mcg), 16 L1 (60mcg), 18 L1 (40mcg), 31 L1 (20mcg), 33 L1 (20mcg), 45 L1 (20mcg), 52 L1 (20mcg) & 58 L1 (20mcg), Vaccine is made up of virus-like particles (VLPs) that is a purified L1 structural protein resembling HPV-type specific empty shells obtained using recombinant DNA and cell culture technology.

4.4 SCHEDULING OF THE VACCINE

A three-dose vaccination schedule has been recommended for the quadrivalent HPV vaccine since 2006, however, school-based immunization programs adopted a two-dose schedule for vaccination since 2015. Girls and women were deemed vaccinated if they received at least one dose of the quadrivalent HPV vaccine. Vaccines against HPV are quite immunogenic. The current vaccines are administered intramuscularly, which allows for quick access to draining lymph nodes. They are also adjuvanted to create an inflammatory environment that is favorable for triggering a potent humoral response with a long half-life.

Antibody titers remain high with a multidose schedule for a minimum of 12 years for the quadrivalent (Gardasil) vaccine52, 93, 95, and bivalent (Cervarix) vaccine53, and for a minimum of 6 years for the nonavalent vaccine that was just licensed. Evidence does not support the necessity for a booster shot several years following the initial HPV immunization. Still, statistics are being assessed.[12]

Table 1: Vaccines, their doses based on age and schedules varying in months

Sr. No.	DRUG	AGE GROUP	DOSE SCHEDULE
1	Cervarix (Bivalent)	9-14 years	2-doses (5-13 months apart)
		15 years and above	3-doses (0, 1-2.5 months and 5-12 months)
2	Cecolin (Bivalent)	9-14 years	2-doses (6 months apart)
		15 years and above	3-doses (0, 1-2 months and 5-8 months)
3	Walrinvax (Bivalent)	9-14 years	2-doses (5-6 months apart)
		From 15 years	3-doses (0, 2-3 months and 6-7 months)
4	Gardasil (Quadrivalent)	9-13 years	2-doses (6 months apart)
		From 14 years	3-doses (0, 1-2 months and 4-6 months)
5	Cervavax (Quadrivalent)	9-14 years	2-doses (6 months apart)
		15 years and above	3-doses (0, 2 months and 4-6 months)
6	Gardasil9 (Nonavalent)	9-14 years	2-doses (5-13 months apart)
		15 years and above	3-doses (0, 1-2 months and 4-6 months)

4.5 SIDE EFFECTS OF THE VACCINE

Side effects associated with vaccination include both local and systemic reactions

- Local effects: Pain at the site of injection, redness and swelling
- Systemic effects: Headache, fatigue, myalgia, arthralgia, and gastrointestinal discomfort such as nausea, vomiting and abdominal pain.

5. BARRIERS AFFECTING THE VACCINATION PROGRAMME

The success of the vaccine project faced two major barriers: one was the lack of information on HPV vaccination, and the other was poor accessibility of the region (16%), compounded by pupil absenteeism (4%) and concerns about side effects (8%). The less prominent barriers include negative attitudes towards the vaccine by some populations, in this some girls and their parents have poor planning and inadequate transport so expected vaccination dates are delayed.[18]

The analysis of logistical challenges was applied to investigate the correlation in between HPV vaccination with demographic factors and cervical cancer, and health towards cervical cancer. The study found a significant correlation between education levels and attitudes toward cervical cancer with acceptance of HPV vaccination.

Improving awareness about HPV, parental acceptance, and vaccination rate, also dealing with the cost barrier. In addition to the resource-related barriers and low reproductive-aged women, inadequate healthcare providers have been trained in high-quality screening. Limited information on cancer risk, prevention, experience with fear, sexually transmitted infections, and also limited access to health care providers and preventive care accounts under barriers.

Barriers that affect the prevention of cervical cancer with the HPV vaccine include

- lack of knowledge about the disease and awareness of the vaccine
- The cost of the vaccine is a challenge in rural areas and
- Cultural factors such as lack of spousal support for gynecological healthcare.
- Little to no knowledge regarding the schedule, safety, and efficacy of vaccines by a healthcare provider.[21]

6. STRATEGY TO OVERCOME BARRIERS

HPV prevention strategies are difficult to talk about because HPV vaccination is effectively communicated and accepted within age ranges, especially given to young girls (9-12 years old), young women (13-26 years old), and adult women (27-45 years old). A greater barrier occurs at multiple levels needed to guide the development of interventions that will affect vaccine uptake in rural areas. The organized barriers and facilitators mentioned:

(1) Factors at the individual level, including knowledge, attitudes, and behavior are important considerations;
(2) social network interactions;
(3) organizational processes which include institutional factors for vaccination services;
(4) community factors and availability of the vaccine.[20]

To educate the community that HPV is a sexually transmitted infection, that affects both and needs to address vaccine safety.[18] In the community factors such as low vaccine cost, policies, and programs that increase vaccine access and availability, may also promote vaccination.[20] The strategies of community mobilization such as targeting audiences and also use of mass media to information on the HPV vaccine and cervical cancer to successful implementation.[18]

7. EFFECT OF VACCINE IN PUBLIC

The vaccine prevents the incidence of cervical and other HPV-related cancers when taken prior to the HPV-infection transmission. Over 95% of HPV

infection is caused by HPV type 16,18 and the cross-protection against other less-common HPV types which cause cervical cancer.[5]

CONCLUSION:

To prevent cervical cancer and other HPV-infected cancers in both women and men, it is recommended to take up a primary prevention method by taking the HPV vaccine under proper guidance from a healthcare provider without missing the dosing schedules. Gardasil9, a nonavalent vaccine prevents HPV-related cancers by protecting an individual from 9 types of high-risk serotypes types 6, 11, 31, 33, 45, 52, 58 along with type 16 and type 18. The Bivalent HPV vaccine protects against type 16 and type 18 and the Quadrivalent HPV vaccine protects from type 6, type 11, type 16, and type 18.

Lack of awareness among the public regarding the disease and vaccine, high cost of the vaccine, and poor knowledge among healthcare professionals about the scheduling, safety, and efficacy of the vaccine are the key barriers to the HPV vaccine administration, particularly in rural areas. Further studies are to be conducted on the single-dose administration for its effects, efficacy, and duration of protection in both females and males. to multiply the supply of vaccines worldwide, with lower costs.

Educational campaigns for the public on the disease and vaccine, and screening of cervical cancer with regular Pap smear tests help in the prevention of cervical cancer.

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