Invited Paper

IAPSM's Position Paper on the Human Papilloma Virus (HPV) Vaccine for Adult Immunization in India

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Abstract

Cervical cancer ranks as the second most common cancer in women in India, primarily caused by persistent infection with the human papillomavirus (HPV). Given its long latent period, secondary prevention through screening and early detection is essential. However, fear and stigma associated with cancers and the costs involved in disease management are the prominent barriers to its uptake. HPV vaccination is one of the vital components of the World Health Organization's (WHO) Global Strategy to speed up the elimination of cervical cancer as a public health problem. In India, four prophylactic HPV vaccines are currently available. These vaccines are non-infective and highly immunogenic, safe, and effective when administered before HPV exposure. According to WHO recommendations, the primary target group for HPV vaccination consists of girls between the ages of 9 and 14 years. Further, studies have confirmed that both single-dose and two-dose schedules of the HPV vaccine offer comparable efficacy and protection. HPV vaccines are administered intramuscularly in the deltoid region, with 0.5 ml as the standard dose. These vaccines may cause local reactions, as well as mild systemic reactions, such as headache and myalgia, but they are transient. Implementing catch-up vaccination for adolescent girls aged between 9 and 14 years at the time of HPV vaccine introduction would be a cost-effective and sustainable strategy. This would serve as a crucial component of public health efforts to manage HPV infections and eliminate cervical cancer in India.

Keywords: Cervical cancer, HPV, immunogenicity, vaccine, virus-like-particle

Introduction

Cervical cancer ranks as the second most common cancer among Indian women with an annual incidence of 134,420 cases that accounts for about one-fourth of (25.9%) of all cancers detected in women.[1,2] The age-standardized incidence rate for cervical cancer in India is 17.3 per lakh women, which is higher than the global average of 13.1 per lakh women.[3] Cervical cancer occurs due to chronic infection with the human papillomavirus (HPV) and the risk increases by six times for women living with human immunodeficiency virus (HIV).[4] Cancers attributed to HPV infections are cervical cancers, anogenital cancers, and head and neck cancers though the majority are cervical cancers that could be prevented to a major extent with HPV vaccination and regular screening for cervical cancer. As per the GLOBOCAN report (2020), India contributed to 7% of the global cancer incidence and 24% of cancer related to HPV globally.[5,6] A multicentric study in the country reported 76% of cervical cancer cases being positive for HPV types 16/18.[7] Likewise, a study from Odisha reported an overall HPV prevalence of 60% among symptomatic women attending two apex referral hospitals and more than 90%

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of women with invasive cervical cancers (ICC) being HPV infected.[8] Various factors associated with HPV infections and thereby cervical cancer in the Indian context are summarized in Table 1.

Screening and treatment of cervical cancer in India

As cervical cancer has a long latent period, secondary prevention through screening and early detection is crucial in the prevention and control of this disease. In India the most frequently used screening modality is Pap smear test, followed by visual inspection with acetic acid (VIA) with or without artificial intelligence (AI) enabled devices.[17] HPV testing has gained importance recently and testing with self-sampled swabs shows a promising future.[18] Colposcopy, biopsy, and histopathological examinations are employed for further confirmation and to guide the need for treatment.[17,18] However, fear and stigma toward cancers and the costs involved in investigations and treatment are the prominent barriers to its uptake. A study in a tertiary care hospital in North India reported that health system costs for various cervical cancer treatment modalities ranged from INR 19,494 to 41,388 (USD 291 to 617) and additional INR 4,042 to 23,453 (USD 60 to 350) out-of-pocket expenditure. This was a subsidized cost of cancer treatment; however, no such data are available from private sectors in India.[19] Due to these existing barriers, the majority (>70%) of the cases in India present to the healthcare facilities in the final stage of the disease, which leads to poor prognosis hence, the pooled five-year survival rate for cervical cancer in India is only 51.7%.[20]

Table 1: Factors linked to HPV infection and cervical cancer

Domains	Factors
Sexual practices & education[9]	• Starting sexual activity at a younger age • Having multiple sexual partners • Lack of comprehensive sexual education in schools and communities
Health system[10,11]	• Poor access to healthcare facilities • Lack of organized cervical cancer screening programs • Lack of affordable treatment facilities
Vaccination programs[12]	• Poor vaccine coverage • High cost • Parental hesitancy
Socio-cultural[13]	• Stigma toward seeking sexual health • Fear toward cancer
HIV infection[14-16]	• High prevalence of HIV infection

The HPV vaccination program and its global impact

As part of the primary prevention strategies, various vaccines have been developed against the most prevalent oncogenic types of HPV (16,18) which have been proven safe and effective and recommended by the World Health Organization (WHO) since 2009.[4,21] Following this, approximately 60% of the WHO member states have launched the HPV vaccine in routine immunization programs though it is being done at a lower pace in low- and middle-income countries (LMICs) which contribute to the majority of cervical cancer incidence globally.[22] However only 15% of adolescent girls could be vaccinated with the second dose of the HPV vaccine by 2019.[23] The performance coverage was better for the first dose (67%) as compared to that for the final dose (53%) in the programs. The LMICs performed better than high-income countries for the first dose, but experienced higher drop-out rates, leading to lower performance for the final dose.[22]

The national HPV vaccination program implemented in England, UK in 2008 has led to a considerable decline in cervical cancer, as well as, cervical intraepithelial neoplasia (CIN) grade-3 incidence in young women born after Sept 1, 1995.[24] In contrast, presently less than 1% of girls have received the HPV vaccine and less than 2% of women have undergone screening for cervical cancer in India.[25] Current evidence shows that the HPV vaccine plays an important role in preventing high-risk HPV infections and thereby preventing cervical cancer. Hence, it is critical to have this vaccine in the national immunization schedule of India. This would help the country to align with the targets that need to be met by 2030 according to the cervical cancer elimination strategy recommended by WHO.[26]

HPV vaccines available in India

The following vaccines are available in India [Table 2]:

Table 2: HPV vaccines available in India

HPV Vaccine	Population	No. of doses	Schedule	Dose, route and site of administration
Bivalent vaccine (Cervarix)#[27]	9–14 years	2	0 and 5–13 months	0.5 (ml, intramuscularly, deltoid region)
	≥15 years	3	0, 1–2.5, and 5–12 months	
Quadrivalent vaccine (Gardasil)[27]	9–13 years	2	0 and 6 months	
	≥14 years	3	0, 1–2, and 4-6 months	
Quadrivalent vaccine (Cervavac)[27]	9–14 years	2	0 and 6 months	
	≥15 years	3	0, 2 and 6 months	
9-valent vaccine (Gardasil 9)[28]	9–14 years	2	0, 6–12 months*	
	15–45 years**	3	0, 1–2 and 6 months^	

#Discontinued in India since September 2022; *In a two-dose schedule, 5 months should be the minimum interval; ^In a three-dose schedule, 4 weeks should be the minimum intervals between the 1st and 2nd dose, 12 weeks between the 2nd and 3rd dose, and 5 months between the 1st and 3rd dose; ** 9-26 years for immunocompromised persons

As recommended by WHO, girls aged between 9 and 14 years should be the primary target for HPV vaccination, in whom, two doses are recommended, before they become sexually active.[29] In a multicentre trial that was later changed to a cohort study, following the suspension of trial by the government of India, Gardasil vaccine efficacy against chronic HPV 16 and 18 infection was reported to be 95·4% (95% CI: 85·0–99·9%), 93·1% (95%CI: 77·3–99·8%) and, 93·3% (95%CI: 77·5–99·7%) in one dose, two-dose and three-dose recipients respectively. It was also reported that equivalent protection was provided by a single dose, two doses, and three doses of Gardasil vaccine against the infection by HPV 16 and 18 when followed up for 9 years.[30] This fact is validated by the WHO position paper which affirms that a single-dose and two-dose schedule of HPV vaccine provides a comparable efficacy and durability of protection.[31]

Efficacy and immunogenicity of HPV vaccines available in India

HPV vaccines consist of 'virus-like' particles (VLP) with an adjuvant to boost the immune response. VLPs are self-assembled purified L1 structural proteins that are noninfective and non-pathogenic. These vaccines are for prophylactic use only and not for the treatment of HPV infections or HPV-related disease.[32] Following vaccination, VLPs are identified by the immune system of the host in the local lymph nodes and produce a strong antibody response (IgG), much higher levels than that induced by natural HPV infections, and provide cross-protection to some extent against non-vaccine-related serotypes. On subsequent exposure to HPV infection, IgG is produced by the plasma cells and memory B cells in circulation.[32,33]

Cervarix

It is a bivalent vaccine that was approved for use in 2009, for preventing cervical cancer, anal cancer, and premalignant anogenital lesions caused by some oncogenic HPV types (HPV 16 and 18) from age nine years onwards.[34] Cervarix vaccination has been reported to produce high and long-lasting HPV-18 and HPV-16 antibody levels for 9.4 years and additionally, it offers cross-protection as well.[34]

Gardasil

This quadrivalent vaccine was approved for use in 2006. A meta-analysis reported that the quadrivalent HPV vaccines show adequate efficacy against genital warts in young females and males. The vaccine efficacy, for CIN 2+ and CIN 3+ linked with HPV 6/11/16/18, was found to be almost 100%. These vaccines had cross-protection effect efficacy of 46%, 29%, 7%, 18%, and 6%, against HPV 31/33/45/52/58 respectively.[35-39]

Gardasil 9

In a randomized trial, a much lesser incidence (0.5 cases per 10,000 persons) of high-grade cervical, vaginal, and vulvar disease linked with HPV31/33/45/52/58 was reported among participants who received the Gardasil 9 vaccine in comparison to those who received the quadrivalent HPV vaccine (19 cases per 10,000 persons).[40]

Cervavac

Reports from Cervavac trials show that 100% seroconversion was achieved for all 4 HPV serotypes (6,11,16, and 18) in cohort 1 (9-14 years) among boys and girls and in cohort 2 (15-26 years) among men and women at the end of seven months follow-up period.[41] WHO International Agency for Research on Cancer (IARC) study in India has shown that even 2 to 4-fold higher antibody titers correlated well with high vaccine efficacy as observed with a single dose at 10 years.[42] Given this, the Cervavac vaccine has shown a > 1000-fold rise in antibody titer for all four HPV serotypes in the vaccine trial period which reassures long-term protection.

Duration of protection and repeat vaccination

As shown in Table 3, HPV vaccination has demonstrated long-lasting protection across multiple clinical trials, with no evidence of declining efficacy over time or the need for a booster dose following the primary vaccination.[31,43-46]

Safety of HPV vaccines

Allegations about vaccine safety issues have been one of the main barriers to receiving HPV vaccination by the target populations.[47] The Global Advisory Committee on Vaccine Safety (GACVS) reviewed HPV vaccine safety data in 2007 and later in 2008,2009,2013,2014, and 2015. The safety concerns were mainly anaphylaxis and syncope and the risk of anaphylaxis was reported to be approximately 1.7 cases per million doses, while syncope was recognized mainly as injection-related anxiety or stress. Though many population-based studies have reported Guillain–Barré syndrome (GBS) as a signal, the most recent study found no such increased risk for GBS with any of these vaccines.[48]

Adverse events reported with the HPV vaccines

Adverse events that have been reported in clinical trials of HPV vaccines in India are summarised below in Table 4.

Contraindications and precautions

Contraindications for the vaccine include hypersensitivity reactions to a previous dose of Gardasil, Cervarix, and Cervavac.[49,50]

After the vaccination, it is advised to observe the person for 15 minutes for any post-vaccination syncope. If syncope is associated with tonic–clonic movements, the individuals need to be maintained in a supine or Trendelenburg position which restores cerebral perfusion. It is recommended to postpone the vaccination during an acute severe febrile illness. Precautions must be taken while vaccinating individuals with any coagulation disorders as bleeding may occur after an intramuscular administration in such individuals.[51-53]

Recommendations for HPV vaccination among special populations have been summarized in Table 5.

Interference with concomitantly administered vaccines (if any)

A meta-analysis, which included over a dozen trials involving 9–25 years old healthy individuals found that when HPV vaccines were co-administered with other routine vaccines, there was no clinically significant interference with the induction of specific antibodies against HPV types 16, 18, 6, 11, 31, 33, 45, 52, and 58.[54] Co-administration with the hepatitis B vaccine may result in lower hepatitis B surface antibody titers.[55] However, HPV vaccines should not be administered concomitantly with other vaccines in the same syringe or vial.

Cost-effectiveness of HPV vaccination

The National Technical Advisory Group on Immunization (NTAGI) and its Standing Technical Subcommittee (STSC) have recommended the inclusion of the Quadrivalent HPV vaccine in the Universal Immunization Programme (UIP) since 2017.[53] In developing countries like India, HPV vaccination is impacted mainly by its cost, which is approximately about INR 2000 -3000 for each dose.[56] A study from south India that used the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model considered the incremental cost per disability-adjusted life year (DALY) averted as the main cost-effectiveness outcome and the number of cervical cancer cases prevented was considered as primary clinical endpoint. The total vaccine cost per fully immunized girl (FIG) was reported to be 24.2 US$ (vaccine price, as well as, vaccine delivery cost) while cancer treatment cost from a healthcare standpoint was 879.97 US$ and that from a societal standpoint (treatment cost + productivity loss) was projected to be 1229.97 US$. This study showed that vaccinating girls at 12 years with the HPV vaccine routinely in India is highly cost-effective.[53] This is further substantiated by a recent systematic review of the HPV vaccination cost-effectiveness in 11 LMICS including India which also showed that this is a cost-effective strategy.[57]

Table 3: Duration of protection offered by HPV vaccination

Vaccine	Follow-up	Vaccine efficacy against incident infection	Duration of antibody protection
Cervarix	9.4 years	95.6%	>20 years (modeling)
Gardasil	10 years	100%	14 years
Cervavac	10 years	100%	14 years

Table 4: Adverse events reported in clinical trials of HPV vaccines

System	Frequency of Adverse Events by HPV Vaccines		
	CERVARIX[49]	GARDASIL[50]	CERVAVAC®[51]
General disorders and administration site conditions	Pain/redness/swelling over the injection site and fatigue* Pyrexia# Induration^ Local paraesthesia^	Pain*/erythema ****/swelling over injection site* Pyrexia#	Pain */erythema#/swelling over injection site# Pyrexia#
Nervous system disorders	Headache * Dizziness #	Headache * Dizziness#	Headache * Dizziness#
Gastrointestinal disorders	Nausea, vomiting, diarrhea, and abdominal pain#	Nausea#	Nausea#
Skin and subcutaneous tissue disorders	Itching/pruritus, rash, urticarial#	Pruritus# Hematoma#	Injection site pruritus#
Musculoskeletal and connective tissue disorders	Myalgia* Arthralgia #	Pain in extremity#	Pain in extremity#
Respiratory disorders	Upper respiratory tract infection^	Bronchospasmα	
Trial participants' details	In 10-72 years old, girls and women N=16,142 (CERVARIX) N=13,811(Control)	In 9–45 years old girls and women *n*=6995 (GARDASIL) *n*=5692 (Placebo)	In 9–26 years old 1530 study participants

Frequencies are described as: *Very common (≥1/10); #Common (≥1/100-<1/10); ^Uncommon (≥1/1,000-<1/100); αrare (≥1/10,000-<1/1000) and ᵞvery rare (<1/10,000). Source: As submitted by Sponsors to Central Drugs Standard Control Organization (CDSCO), New Delhi

Table 5: HPV vaccination recommendations for special populations

Population	Pregnant women	Lactating mothers	Immunocompromised individuals	Paediatric Group (<9 years)
Vaccines				
CERVARIX[49]	Not to be used*	Not to be used during lactation due to lack of evidence	No data available	Safety and effectiveness not established
GARDASIL[50]	Not to be used*	It may be administered to lactating women^	Immunologic response may be diminished	Safety and effectiveness not established
CERVAVAC[51]	Not to be used*	Can be administered	May have reduced antibody response	Safety and effectiveness not established

*Postpone or interrupt vaccination until the completion of pregnancy; ^It is unknown whether antigens or antibodies induced are excreted in human milk

HPV vaccination program implementation issues

As recommended by WHO, girls aged between 9 and 14 years should be the primary target for HPV vaccination in all countries.[58] Globally, HPV vaccination has been introduced through different delivery platforms such as schools, health facilities, or community outreach.[59] India is expected to roll out the indigenously developed quadrivalent HPV vaccine shortly. The vaccine will be provided primarily through schools and school dropouts or the girls absent on the day of vaccination will be vaccinated at a health facility or by mobile teams.[51] As the burden of HPV-associated cancers is higher in North-Eastern states, vaccination can be prioritized in these states.[51]

To introduce the HPV vaccine at the country level following implementation issues like adequate vaccine supply, national/local level microplanning, intersectoral coordination between the Ministry of Education and the Ministry of Health, training/capacity building of the health staff/school teachers, proper communication and community sensitization about vaccination and working toward the sustainability of this program need to be considered.[52] Sikkim and Punjab states' experience of HPV vaccination programs for school girls could be used as a model to launch the vaccine at the national level.[60,61]

Future research priorities

India has developed its first indigenous quadrivalent HPV vaccine, the Cervavac of Serum Institute of India (SII) which will be available at a low cost (Rs 200-400), and the NTAGI has recommended for its introduction in the National Immunization Schedule as a two-dose regimen since data on a single dose of this vaccine is not yet available.[51] After introducing this vaccine in the National immunisation programme seroconversion rate and cost-effectiveness of the indigenous vaccine must be studied and compared with other vaccines available in India. Apart from HPV 16 and 18, the type 58 variant is also found in Indian Women, and in the future, there will be a need to cover this high-risk variant in the Indian vaccine.[62,63] Further studies are needed in the Indian context related to long-term immunogenicity, duration of protection of single-dose/two-dose HPV vaccine in different age groups, and cost-effectiveness of HPV vaccination.[64] Females who were already part of different vaccine trials like those done in Sikkim and Punjab could be part of long-term follow-up for the seroconversion and incidence of cervical cancer.[60,61] It is also crucial to conduct further research on seroconversion and the efficacy of a single versus two or three-dose HPV vaccine in people living with HIV/AIDS.

Implementation research to identify the different strategies for better uptake of the HPV vaccine, especially in high-risk populations should be carried out in the Indian setting.[65] Opportunities to integrate the HPV vaccination program with the Tetanus, Diphtheria (Td) vaccine at 10 or 15 years of age under the national immunization program could be explored.[66] The vaccine effectiveness can be checked by the prevalence of HPV infection and anogenital warts before and after the introduction of the vaccine. Population-based cancer registries for cervical cancer should also be used for analyzing the effectiveness of the vaccine over a longer period.[67]

IAPSM's position on the introduction of the HPV vaccine for the Indian population

India contributes a significant share of the global burden of cervical cancer amounting to one-quarter of the cases. The uptake of screening programs remains poor due to health system and socio-cultural barriers.[31,68] This emphasizes the need to prevent this disease through immunization of adolescent girls before they become sexually active. In India, currently, we have HPV vaccines that have a proven safety profile including the homegrown low-cost quadrivalent HPV vaccine, Cervavac. On reaching this milestone, India's journey toward cervical cancer prevention accords with the WHO's Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem which recommends the inclusion of HPV vaccine in all national immunization programs and targets reaching 90% of all girls by the age of 15 years by 2030. Further, studies have shown that a single dose is equivalent to two or three doses of HPV vaccine as endorsed by WHO for LMICs. Catch-up vaccination of 9- to 14-year-old adolescent girls at the time of HPV vaccine introduction would be a cost-effective approach and make the program sustainable. Various field trials have shown that in Indian settings, schools form an ideal platform for vaccinating adolescent girls. However, adequate planning, intersectoral collaboration, and necessary capacity building are critical for the success of the program. Fear and myths about the vaccine need to be alleviated among health workers and parents through proper communication. They also need to be educated about the HPV vaccination as a primary prevention measure and not a substitute for screening for cervical cancer in later years. This requires strengthening the cervical cancer screening programs further in parallel to vaccination programs.

IAPSM members have an essential role in planning, establishing intersectoral collaboration, dealing with HPV vaccine hesitancy, generating awareness among parents and community, and provide evidence by conducting community-based studies on long term effectiveness of the HPV vaccines.

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Conflicts of interest

There are no conflicts of interest.

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