

# Cervical cancer in India and HPV vaccination

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## ABSTRACT

Cervical cancer, mainly caused by Human Papillomavirus infection, is the leading cancer in Indian women and the second most common cancer in women worldwide. Though there are several methods of prevention of cervical cancer, prevention by vaccination is emerging as the most effective option, with the availability of two vaccines. Several studies have been published examining the vaccine's efficacy, immunogenicity and safety. Questions and controversy remain regarding mandatory vaccination, need for booster doses and cost-effectiveness, particularly in the Indian context.

**Key words:** *Cancer, cervix, human papillomavirus, vaccine*

## INTRODUCTION

Cervical cancer is the fifth most common cancer in humans, the second most common cancer in women worldwide and the most common cancer cause of death in the developing countries. Sexually transmitted human papilloma virus (HPV) infection is the most important risk factor for cervical intraepithelial neoplasia and invasive cervical cancer.<sup>[1]</sup> The worldwide incidence of cervical cancer is approximately 510,000 new cases annually, with approximately 288,000 deaths worldwide.<sup>[2]</sup> Unlike many other cancers, cervical cancer occurs early and strikes at the productive period of a woman's life. The incidence rises in 30–34 years of age and peaks at 55–65 years, with a median age of 38 years (age 21–67 years). Estimates suggest that more than 80% of the sexually active women acquire genital HPV by 50 years of age.<sup>[3]</sup> Hence, the advent of a vaccine against HPV has stirred much excitement as well as debate.

## INDIAN SCENARIO OF HPV INFECTION

Cervical cancer is ranked as the most frequent cancer in women in India. India has a population of approximately 365.71 million women above 15 years of age, who are at risk of developing cervical cancer. The current estimates indicate approximately 132,000 new cases diagnosed and

74,000 deaths annually in India, accounting to nearly 1/3<sup>rd</sup> of the global cervical cancer deaths.<sup>[4]</sup> Indian women face a 2.5% cumulative lifetime risk and 1.4% cumulative death risk from cervical cancer. At any given time, about 6.6% of women in the general population are estimated to harbor cervical HPV infection. HPV serotypes 16 and 18 account for nearly 76.7% of cervical cancer in India. Warts have been reported in 2–25% of sexually transmitted disease clinic attendees in India; however, there is no data on the burden of anogenital warts in the general community.<sup>[4]</sup> There are currently several cervical cancer research programmes in India. The National cancer registry programme, established by the Indian council of medical research, acts as a surveillance system for cancer in India. It collects data in an “active” manner, visiting government and private sector hospitals, specialized cancer hospitals and pathology laboratories to get information on the types and magnitude of cancer cases. The cancer registry in India does not cover the entire country actively but collects information only from a few urban and rural registries established in the country.

## HUMAN PAPILLOMA VIRUS DISEASE SPECTRUM

HPV is a member of the family Papillomaviridae.<sup>[5]</sup> They are small, non-enveloped deoxyribonucleic acid (DNA) viruses.<sup>[6]</sup> They are classified according to DNA sequence using the L1 open reading frame of the genome. Over 100 serotypes of HPV have been discovered, of which 15–20 are oncogenic. The lag period between the oncogenic HPV infection and the invasive cervical cancer is 15–20 years. Based on the association with cervical cancer, genital HPVs are further grouped into high-risk types, probable high-risk types and low-risk types.<sup>[7]</sup> Worldwide, high-risk

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type HPV-16 and 18 contribute over 70% of all cervical cancer cases (the most prevalent being HPV-16 in at least 50–60% and HPV-18 in at least 10–12%). Similarly, in Indian women, the most common prevalent genotypes are HPV-16 and 18.<sup>[11]</sup> Non-oncogenic HPV serotypes-6 and 11 contribute over 90% of benign genital infections such as genital warts.<sup>[8]</sup> Oncogenic HPV serotypes have also been implicated in the causation of anal, vulvar, vaginal, penile and oropharyngeal cancers.<sup>[9]</sup>

HPVs infect the basal epithelium and are grouped as cutaneous and mucosal types.<sup>[10]</sup> HPV cervical infection results in cervical morphological lesions ranging from normal (cytologically normal women) to development of different stages of high-grade precancerous lesions (cervical intraepithelial neoplasia: Cervical intraepithelial neoplasia (CIN)-1, CIN-2, CIN-3/Carcinoma *in-situ*) and, subsequently, invasive cervical cancer (ICC).<sup>[11]</sup> HPV infection is measured by means of HPV DNA detection in cervical cells (fresh tissue, paraffin-embedded or exfoliated cells). The relative frequency of HPV-16/18 increases with the severity of the lesion.<sup>[10]</sup>

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## PREVENTIVE METHODS

HPV transmission is influenced by sexual activity and age. Almost 75% of all sexually active adults are likely to be infected with at least one HPV type. However, vast majority of the infections resolve spontaneously and only a minority (<1%) of the HPV infections progress to cancer. The lifetime risk for genital HPV is 50–80% and genital warts is approximately 5%.<sup>[11]</sup> In women who undergo routine screening, the risk of having an abnormal Papanicolaou (Pap) smear is 35%, CIN 20% and ICC is <1% approximately. However, in women without routine screening, the risk for cervical cancer is up to 4%.<sup>[12]</sup> The Pap test is used to find cellular abnormalities in cervical tissue, aiding early diagnosis. Majority of the women become infected with HPV at some point in their lives, soon after the onset of sexual activity.<sup>[13]</sup>

HPV is a necessary cause of cervical cancer, but it is not a sufficient cause. Other cofactors are necessary for progression from cervical HPV infection to cancer. Long-term use of hormonal contraceptives, high parity, early initiation of sexual activity, multiple sex partners, tobacco smoking and co-infection with HIV have been identified as established cofactors; co-infection with *Chlamydia trachomatis* and herpes simplex virus type-2, immunosuppression, low socioeconomic status, poor hygiene and diet low in antioxidants are other probable cofactors. Genetic and immunological host factors and viral factors such as variants of type, viral load and viral

integration are likely to be important, but have not been clearly identified.<sup>[14]</sup>

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## WHY VACCINATION IS THE BEST FORM OF PREVENTION

Currently, all genital HPV infections cannot be prevented except by abstinence and lifetime mutual monogamy. There is no clear evidence that barrier methods of contraception, most notably use of condoms, confer a protection against HPV infection. Secondly, except for genital warts, the infection is asymptomatic.<sup>[15,16]</sup> Adherence to routine screening by the susceptible female population through periodic Pap smears even in developed countries has been unsatisfactory, whereas in developing countries like India, large-scale routine screening is difficult to achieve.

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## DEVELOPMENT OF HPV VACCINE HISTORY

Recombinant DNA technology is used to express the L1 major capsid protein of HPV in yeasts (*Saccharomyces cerevisiae*), which self-assemble to form empty shells resembling a virus, called virus-like particles (VLPs). The VLPs have the same outer L1 protein coat as HPV but contain no genetic material. The vaccine uses these VLPs as antigens to induce a strong protective immune response; if an exposure occurs, the vaccinated person's antibodies against the L1 protein will coat the virus and prevent it from releasing its genetic material.<sup>[17]</sup>

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## TYPES OF HPV VACCINE

Two vaccines licensed globally are available in India; a quadrivalent vaccine (Gardasil™ marketed by Merck) and a bivalent vaccine (Cervarix™ marketed by Glaxo Smith Kline).<sup>[18]</sup> Both vaccines are manufactured by recombinant DNA technology that produces non-infectious VLPs comprising of the HPV L1 protein. Clinical trials with both vaccines have used efficacy against CIN-2/3 and adenocarcinoma *in situ* (AIS) caused by HPV strains contained in the concerned vaccine as primary end points. Both the vaccines have also looked at cross-protection against HPV strains not contained in the concerned vaccine. These vaccines do not protect against the serotype with which infection has already occurred before vaccination.

Gardasil™ is a mixture of L1 proteins of HPV serotypes 16, 18, 6 and 11 with aluminum-containing adjuvant. Clinical trials with three doses at 0, 2 and 6 months in more than 16,000 women aged 16–26 years from five continents, including Asia, have shown 100% efficacy at a median follow-up of 1.9 years against types 16/18-related CIN-2/3 and AIS in the per-protocol analysis (women who received all three doses of the vaccine and who remained

uninfected with vaccine HPV type at onset and for 1 month after completion of the vaccine schedule).<sup>[19]</sup> This vaccine confers protection against both cervical cancer and genital warts.<sup>[18]</sup>

Cervarix™ is a mixture of L1 proteins of HPV serotypes 16 and 18 with AS04 as an adjuvant. Clinical trials with three doses at 0, 1 and 6 months in more than 18,000 women globally has shown 90% efficacy against type 16/18-related CIN-2/3 and AIS at the 15-month follow-up in modified intention to treat analysis (included women who were at baseline negative for HPV DNA of vaccine type virus and who received at least one dose of the vaccine). Follow-up studies in a subset of participants over 4–5 years showed no evidence of waning immunity.<sup>[20]</sup> This vaccine confers protection only against cervical cancer.<sup>[18]</sup>

### EFFICACY

The bivalent and quadrivalent vaccines available are prophylactic, not therapeutic. No evidence exists for protection against disease caused by vaccine types for which participants had positive results on polymerase chain reaction at baseline. Participants who were already positive to any vaccine HPV types before vaccination acquired protection against disease caused by other vaccine types. Additionally, 99–100% efficacy was reported against vaccine-type related genital warts, vaginal intraepithelial neoplasia and vulvar intraepithelial neoplasia.

Follow-up studies over 5 years in a subset of participants showed persistent protection and good response to booster immunization. Immunogenicity studies in females aged 9–15 years showed antibody titers non-inferior to those aged 16–26 years.<sup>[21]</sup> Antibody titers of HPV-16 gradually decline after the third dose, but appear to plateau by 24 months. At 36 months, anti-HPV-16 titers in vaccinees remained higher than those in the placebo group who were seropositive at baseline (post-vaccination produced antibody titers were higher than in natural infection). No minimum protective titer has been determined. In a combined analysis of all participants over 3 years and a subset through 5 years, efficacy against vaccine-HPV type disease was 95.8% (95% CI, 83.8–99.5%) and efficacy against vaccine-type-related CIN or external genital lesions was 100% (95% CI, 12.4–100%). Longer follow-up studies are under way.

To evaluate how the vaccine would perform in younger female patients, immunogenicity studies in children aged 9–15 years were conducted. Anti-HPV responses after the third dose were similar to those of female patients of 16–26 years. At 18 months post vaccination, anti-HPV

titers in younger patients were two- to three-times higher than that in older patients.<sup>[22,23]</sup>

### DOSAGE AND SCHEDULE

The vaccine dose is 0.5 mL given intramuscularly, either in the deltoid muscle or in the antero-lateral thigh. It is available as a sterile suspension for injection in a single-dose vial or a prefilled syringe, which should be shaken well before use. Manufacturer's instructions for storage and administration of vaccines should be followed.<sup>[18]</sup>

The recommended age for initiation of vaccination is 9–12 years. Catch-up vaccination is permitted up to the age of 26 years. A total of three doses at 0, 2 and 6 months are recommended with Gardasil™ or 0, 1 and 6 months with Cervarix™ (minimum interval of 4 weeks between the first and the second dose, 12 weeks between the second and third dose and 24 weeks between the first and third dose). HPV vaccines can be given simultaneously with other vaccines such as Hepatitis B and Tdap. At present, there is no data to support the use of boosters.<sup>[24,25]</sup>

If the HPV vaccine schedule is interrupted, the vaccine series need not to be restarted. If the series is interrupted after the first dose, the second dose should be administered as soon as possible, with an interval of at least 12 weeks between the second and third doses. If only the third dose is delayed, it should be administered as soon as possible.<sup>[25]</sup>

### SIDE-EFFECTS AND CONTRADICTIONS

The most common adverse reactions are local reactions like pain (mild to moderate) in 83%, swelling with erythema in 25% and systemic adverse effects such as fever in 4% of the vaccinees. No serious vaccine-related adverse events have been reported.<sup>[25]</sup> The HPV vaccine is currently not licensed for use in female patients younger than 9 years or older than 26 years or for use in male patients. It is contraindicated in people with a history of immediate hypersensitivity to yeast or to any vaccine component. The vaccine should be deferred in patients with moderate or severe acute illnesses. The vaccine may be administered in a sitting or lying down position and the patient should be observed for 15 min post-vaccination for syncope.

The vaccine is not recommended for use in pregnant women. Although it has not been causally associated with adverse outcomes of pregnancy, data are limited. Any exposure to the vaccine during pregnancy must be immediately reported. Lactating women and immunosuppressed female patients can receive the vaccine. The efficacy and the degree of immune response could be poor in the latter group.<sup>[18,25]</sup>

## HPV VACCINATION IN MALES

HPV vaccine is not licensed for use among males. Efficacy studies among males are under way. Australia is the first country to approve the quadrivalent HPV vaccine in males (between 9 and 15 years old), and the vaccine was approved for administration to males between the ages of 9 and 26 years in other developed nations.<sup>[24]</sup>

## INDIAN ACADEMY OF PEDIATRICS RECOMMENDATION

The HPV vaccination is of public health importance. Compliance with cervical Pap smear screening is low in India. The currently available vaccines are safe and efficacious. The Indian Academy of Pediatrics Committee on Immunisation (IAPCOI) recommends offering HPV vaccine to all females who can afford the vaccine (Category 2 of IAP categorisation of vaccines). Because protection is seen only when the vaccine is given before infection with HPV, the vaccine should be given prior to sexual debut. The vaccine should preferably be introduced to parents as a cervical cancer-preventing vaccine and not as a vaccine against a sexually transmitted infection. Vaccines are not 100% protective against cervical cancer and not a replacement for periodic screening. Hence, screening programs should continue as per recommendations. Both vaccines available are equally efficacious and safe for protection against cervical cancer and precancerous lesions as of currently available data. The quadrivalent vaccine has, in addition, demonstrable efficacy against vaginal and vulvar cancers and protects against anogenital warts.<sup>[18]</sup>

The Advisory Committee on Immunization Practices currently recommends routine vaccination of females aged 11–12 years with three doses of the HPV vaccine. Vaccination can be given to females as young as 9 years as well as in those aged 13–26 years who have not previously completed vaccination. Pap testing and screening for HPV DNA or HPV antibody before vaccination is not needed. Routine cervical cancer screening should be continued.<sup>[26]</sup> The American College of Obstetricians and Gynaecologists recommends that HPV vaccination be offered to all female patients aged between 9 and 26 years who have not been previously vaccinated and also emphasizes continued regular cervical cytology screening.<sup>[27]</sup> In contrast, the American Cancer Society does not consider existing evidence to be sufficient to recommend or warn against routine vaccination for women older than 18 years. Because women aged 19–26 years are more likely to have been exposed already to HPV, the American Cancer Society suggests that the decision to vaccinate women in this age range should be made on an individual basis.<sup>[28]</sup>

## CONCERNS AND SAFETY

The primary obstacle to HPV vaccination is financial. Because of the high cost of the present vaccines, the affordability and accessibility of these vaccines is a major concern for a mass vaccination program in developing countries like India. Being very expensive (including 10% as taxes), some suspect that HPV vaccination is solely for profit of the vaccine makers/marketers. Had there been a cancer-cervix prevention program and the Government purchased vaccine in bulk, or if Indian manufactures are encouraged to manufacture vaccine, the cost will drop substantially. The documented attrition rate of antibody indicates that the protection will last decades. It is unscientific to wait until after longevity is documented before vaccine is used. We guess that the unlikely worst-case situation may require a booster.<sup>[29]</sup>

The two HPV vaccines are commercially available in India and approved by the Drug Controller General of India (DCGI), US Food and Drug Administration, European Medicines Agency and prequalified by the World Health Organization; and were approved for two vaccination projects. One studied operational feasibility of school-based and community-based vaccination, conducted by the State governments in collaboration with the Indian Council of Medical Research (ICMR) and PATH (a US-based not-for-profit non-governmental organization). The other was a multicentric clinical trial to investigate the immunogenic efficacy of two doses (6 months apart) compared with the conventional three doses (0–2–6 months) of Gardasil. There were allegations in the media of vaccine-caused death of four girls in north India, and the Union Government suspended both studies and initiated enquiry into the safety of both vaccines. The causes of death have been scrutinised by the State Government and reported to ICMR and DCGI; all were satisfied that no deaths were related to the vaccine.<sup>[29]</sup> The vaccines continue to remain as a licensed product approved by the DCGA. To date, no deaths have been causally associated with HPV vaccination in India or elsewhere.<sup>[30]</sup>

## LACUNAE AND FUTURE

Although results in the development of vaccines against HPV are promising, it will be a decade or more before they become available worldwide and are cost-effective. Routine screening should continue to detect and treat women who are infected prior to vaccination or with other HPV types not covered by the vaccine.<sup>[26]</sup>

More research is needed regarding duration of protection induced by these vaccines, need for boosters, effect on

prevalence and incidence of HPV types included in the vaccine. Further details on different HPV types of vaccines for different population, general safety and pregnancy outcomes, safety and immunogenicity of simultaneous administration with other vaccines has to be looked into. The efficacy in female patients older than 26 years and in male patients, the role of routine HPV vaccine in males for prevention of genital warts and emergence of other rarer HPV types after the current common types are controlled has to be studied in detail. The effect on cervical cancer screening practices, safe sex behavior and further economic analysis are a few questions to be answered in the future. As prophylactic, vaccines will be effective pre-exposure to virus and, hence, the target population for vaccination will be 9–10-year-old pre-pubertal girls, but this will raise cultural and social issues. There is an urgent need to conduct epidemiological studies in countries like India on the long-term efficacy, logistics and economics of universal HPV vaccination in eligible females.

## CONCLUSION

HPV vaccination is for primary prevention (serotype-specific with limited cross-protection) of carcinoma cervix. A cost-effective second-generation HPV vaccine is needed for developing countries to address various issues specific to the region. However, till such time, secondary prevention through periodic cervical cancer screening should be in place to use the existing infrastructure and cost-effective screening methods such as Pap smear and HPV DNA tests. There is no risk of getting an HPV infection from the vaccine as the vaccine does not contain live virus. HPV vaccination and regular cervical screening is the most effective way to prevent cervical cancer.

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**How to cite this article:** Karthigeyan K. Cervical cancer in India and HPV vaccination. *Indian J Med Paediatr Oncol* 2012;33:7-12.  
**Source of Support:** Nil, **Conflict of Interest:** None declared.

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