

## Human papilloma virus vaccination: Review article and an update

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### Abstract

Human papilloma virus (HPV) is sexually transmitted and associated with uterine cervix, vaginal, and vulvar cancers in females, oropharyngeal and anal cancer in both genders, and penile cancer in males. Moreover, genital warts are benign tumors which are HPV-related and can occur in both genders. This is a review of HPV

structure, HPV infection transmission, the global impact of HPV and its associated diseases, HPV vaccines and their efficacy and safety, public acceptance of HPV vaccines, the obstacles for its acceptance and strategies to address the barriers. Cervarix (a bivalent vaccine with protection against HPV types 16 and 18) and Gardasil (a quadrivalent vaccine with protection against HPV types 6, 11, 16 and 18) are 2 recommended vaccines. The longest follow up of 9.4 years has shown efficacy and protection of the vaccine against HPV types 16 and 18. The adverse effects have been minimal and the vaccine is considered safe. Numerous studies are conducted to follow the vaccinated individuals to better understand the effect of HPV vaccine on incidence of HPV-related cancers and precancerous lesions.

**Key words:** Human papilloma virus; Cervarix; Gardasil; Gardasil 9; Vaccine; Review

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**Core tip:** Human papilloma virus (HPV) is sexually transmitted in both genders and it is a global issue. High risk HPVs are associated with a variety of cancers and low risk HPVs are associated with genital warts. HPV types 16 and 18 account for 70% of cervical cancer in women. Bivalent (Cervarix), and quadrivalent (Gardasil) vaccines are recommended to prevent HPV 16 and 18 related cancers with additional protective effect of Gardasil against HPV 6 and 11. Herein, HPV-related cancers and their incidences, low risk HPV related neoplasms and HPV vaccines, their efficacy and safety are reviewed. Moreover, the obstacles for global vaccination are addressed.

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## INTRODUCTION

Human papilloma virus (HPV) is associated with cervical, vaginal, and vulvar cancer in females, oropharyngeal and anal cancer in both genders, and penile cancers in males<sup>[1-3]</sup>. HPV infection is underlying cause of cervical precancerous lesions including cervical intraepithelial neoplasia grade 2 (CIN II) and 3 (CIN III), and cervical adenocarcinoma *in situ*. HPV types 16 and 18 are the most common cause (64%) of HPV-associated cancers in both females (65%) and males (63%) in the United States<sup>[4]</sup> while HPV types 31, 33, 45, 52, and 58 account for 10% of HPV associated carcinomas in both females (14%) and males (4%)<sup>[5]</sup>. HPV 16 and 18 account for 66% and HPV types 31, 33, 45, 52, and 58 for 15% of cervical cancers<sup>[4]</sup>. Cervarix and Gardasil are two recommended vaccines for protection against HPV-related cancers. There have been barriers regarding HPV vaccination acceptance and its accessibility. This is a review of HPV, HPV vaccines, and the issues related to the vaccines.

## HPV

HPVs are small, circular, double-stranded, non-enveloped icosahedral DNA viruses. HPV genome contains 6800 to 8000 base pairs coding for early (E), and late (L) functions. E1 and E2 regulate viral DNA replication, and E2 regulates viral RNA transcription. E4 regulates cytoskeleton reorganization. Finally, E5, E6, and E7 regulate cell transformation. L1 and L2 are structural component of the viral capsid. E2 is the main regulator and regulates other viral genes. This is particularly true about E6 and E7<sup>[6]</sup>. HPV life cycle requires basal layer of epidermal or mucosal epithelial cells that is still able to proliferate. This usually occurs by micro-laceration of the skin or mucosa. During infection, HPV DNA genome integrates into the host DNA, resulting in the disruption of the *E2* gene and inability of late genes to express<sup>[7]</sup>. Loss of *E2* leads to up-regulation of *E6* and *E7* genes, which results in high expression of *E6* and *E7* proteins, genomic instability, and disruption of cell cycle. The infected cells divide and the infection spreads laterally. Following entry into the suprabasal layers, viral DNA is replicated, late viral genes are activated, and capsid proteins are formed. Viral particle formation are completed and the viral particles are released at the epithelial or mucosal surface, which may cause additional tissue infection then<sup>[6]</sup>. *E5*, *E6*, and *E7* pose proliferation-stimulating activity. *E5* is important at the early course of infection preventing apoptosis. *E6* and *E7* are oncogenes and play an important role in malignant transformation of the infected cells. *E6* inhibits the tumor suppressor activity of *P53* and *E7* inhibits activity of *RB*. Only *E6* and *E7* of high risk HPV types are immortalized human cells<sup>[6,8,9]</sup>.

## HPV INFECTION TRANSMISSION

HPV has an affinity to infect either anogenital and

oral mucosa ( $\alpha$ -papillomaviruses) or skin ( $\beta$ - and  $\gamma$ -papillomaviruses)<sup>[10]</sup>. Infection is commonly transmitted by sexual contact including vaginal, rectal sex and initially the pathologic changes in squamous epithelial cells are inconspicuous<sup>[11]</sup>. The age at first sexual intercourse, number of sexual partners, smoking, the age of the woman and her partner, and male circumcision are important risk factors for HPV transmission<sup>[12]</sup>. Open mouthed kissing and oral sex are associated with oral HPV infection<sup>[13-15]</sup>. Most of the infections are cleared by 6 to 12 mo after appearance, which is probably due to immunologic response to infection.

## HPV AND ITS GLOBAL IMPACT

HPV, by far, is one of the most common viral sexually transmitted diseases. At least 50% of adult population is infected with this virus during their lifetime<sup>[16-19]</sup>. The prevalence of HPV in cervical cancer has been estimated 85%-99% worldwide<sup>[20]</sup>. Cervical cancer is reported as the third most common cancer in females, and overall it is the seventh most common cancer<sup>[21]</sup>. Screening for cervical cancer has significantly decreased the incidence of cervical cancer in developed countries while the results in developing countries have been only marginal. According to International Agency for Research on Cancer, developing countries account for greater than 85% of the global burden, where 13% of all female cancers occur<sup>[16,21]</sup>. The highest rates of cervical cancer are seen in: (1) Western; (2) Eastern Africa (age standardized rates greater than 30 per 100000); (3) Southern Africa (26.8 per 100000); (4) South-Central Asia (24.6 per 100000); (5) South America; and (6) Middle Africa (23.9 and 23.0 per 100000 respectively). The lowest rates of cervical cancer are seen in North America, Western Asia, and Australia/New Zealand (less than 6 per 100000). In South-Central Asia, Melanesia, and Eastern Africa, cervical cancer is still the most common cancer in women<sup>[16,21]</sup>.

## INCIDENCE OF HPV IN HUMAN

### IMMUNODEFICIENCY VIRUS PATIENTS

HPV-related neoplasms tend to occur at a younger age in human immunodeficiency virus (HIV)-infected patients and exhibit a more aggressive and advanced stage compared to those in HIV-negative patients<sup>[22,23]</sup>. In fact, infection with HIV was listed as an important risk factor for cervical cancer<sup>[24,25]</sup>. Low CD4<sup>+</sup> counts ( $\leq 200$  cells/ $\mu$ L) are the most significant independent predictor for infection with both high risk and low risk HPV genotypes<sup>[26]</sup>. Moreover, HIV-infected patients with genital warts show more resistance to standard treatment for genital warts and even relapse is more likely in HIV-positive women treated for cervical neoplasia compared to the healthy HIV-negative population<sup>[26-28]</sup>. Large cohorts from the United States and Europe demonstrated standardized incidence

ratios ranging from 5-10 for cervical cancer for HIV-infected women compared with the healthy general population<sup>[29-32]</sup>. Several studies from sub-Saharan Africa with limited generalizability have reported similar proportion of HPV 16 and 18 related cervical cancers in HIV-infected women vs general female population<sup>[33,34]</sup>.

## HPV ASSOCIATED DISEASES

HPV is the underlying cause of a large number of benign, precancerous, and malignant conditions in both females and males. HPV shows a predilection to the skin and mucosa. Harald Zur Hausen made the most significant contribution in this field. He described the strong association between HPV infection and cervical cancer for first time. Using cloning and sequencing methods, he identified HPV types 16 and 18 from cervical cancer<sup>[35]</sup>.

### HPV-associated cancers

HPV infection is associated with greater than 50% of infection-related cancers in females and 5% in males worldwide<sup>[36]</sup>. The most well-known HPV-associated cancer is cervical cancer. In anogenital area, HPV contributes to more than 99% of cervical squamous cell carcinoma and adenocarcinoma<sup>[1,37]</sup>, 40% of vulvar cancers, 60% of vaginal carcinoma<sup>[38]</sup> and 97% of anal cancers<sup>[39]</sup>. Men having sex with men (MSM) and immunocompromised patients (HIV-infected patients and organ transplant recipients) are in greater risk for anal carcinoma<sup>[40]</sup>. HPV is associated with 45% of penile cancer<sup>[41]</sup>. In head and neck, HPV infection accounts for 47% of oropharyngeal cancers and 11% of oral and tongue cancers<sup>[42]</sup>.

### HPV-associated precancerous lesions

HPV infection is associated with high grade squamous intraepithelial lesions (SILs) of cervix (CIN II, CIN III)<sup>[43]</sup>, vagina (VAIN II, VAIN III), vulva (VIN II, VIN III), and anus (AIN II, AIN III).

Oral lichen planus (23%), leukoplakia (63%), epithelial dysplasia<sup>[37,44]</sup>, and erythroplakia (50%)<sup>[45]</sup> are considered precancerous disorders in oral cavity attributed to HPV infection. Common warts and flat warts of skin are also attributed to HPV infection<sup>[46]</sup>. Epidermodysplasia verruciformis is a complex disease which is associated with HPV infection<sup>[47]</sup>.

### HPV-associated benign lesions

Anogenital warts or condyloma acuminata, atypical squamous cell of uncertain significance, and low grade SIL of cervix are benign lesions associated with HPV in anogenital area. Oral squamous papilloma, verruca vulgaris (common wart)<sup>[46]</sup>, recurrent respiratory papillomatosis<sup>[48]</sup>, and focal epithelial hyperplasia (Heck disease) are benign HPV-associated lesions in head and neck area.

## HPV SUBTYPES AND THEIR ASSOCIATED DISEASES

The HPV are classified into low-risk and high-risk HPV types according to their oncogenic potential<sup>[49]</sup>. HPV types 16 and 18 are the most common high-risk HPV types causing anogenital and oropharyngeal cancers in both females and males. The most common low-risk HPV types are types 6 and 11, causing genital warts and laryngeal papilloma<sup>[50]</sup>. Worldwide, the overall HPV prevalence in cervical cancer is greater than 99%<sup>[1]</sup>. Cervical cancer is associated with several types of HPV. The most common type is HPV 16 (61%), followed by HPV 18 (10%), HPV 45 (6%), HPV 31 (4%), HPV 33 (4%), HPV 52 (3%), HPV 35 (2%), and HPV 58 (2%)<sup>[1,20]</sup>. HPV 16 and 18 are also the most common HPV types detected in cervical cancer biopsies in HIV-infected patients<sup>[51]</sup>.

HPV 16 and HPV 18 are the most common HPV types associated with vulvar (HPV 16, 32% and HPV 18, 4%)<sup>[38]</sup>, vaginal (HPV 16, 54%, HPV 18, 8%)<sup>[38]</sup> anal cancer (HPV 16, 75%, HPV 18, 3%)<sup>[39]</sup>. HPV types 16 (60%), and 18 (13%) are the most common HPV types associated with penile cancer in males followed by HPV-6/11 (8.13%), HPV-31 (1.16%), and HPV-45 (1.16%)<sup>[41]</sup>.

HPV 16 (45%), HPV 31 (9%), HPV 33 (7%), HPV 18 (7%), HPV 58 (7%), HPV 52 (5%), and HPV 35 (4%) are the most common HPV types detected in cervical high grade SILs<sup>[43]</sup>.

HPV 16 (9%), HPV 6/11 (5%), HPV 31 (4%), HPV 33 (2%), and HPV 18 (2%) are the most common HPV types detected in low-grade SILs of the cervix<sup>[37,52]</sup>.

Among benign anogenital lesions, HPV 6 (89%) and HPV 11 (11%) have been associated with condyloma acuminata<sup>[53,54]</sup>.

In head and neck, HPV 16 is strongly associated with oropharyngeal squamous cell carcinoma and oral cavity carcinoma accounting for 90% and 96% of cases, respectively<sup>[42]</sup>. HPV types 6 and 11 are associated with recurrent respiratory papillomatosis<sup>[48]</sup>, and oral squamous cell papilloma<sup>[55]</sup>.

### HPV vaccines

Targeting L1 and L2 proteins of HPV, major and minor capsid proteins, respectively, is the current strategy for the development of vaccines that are safe and effective. The expression of recombinant L1 in various hosts such as insect<sup>[56,57]</sup>, yeast<sup>[58]</sup>, bacteria<sup>[59]</sup> and even mammalian cells<sup>[60,61]</sup> generate virus-like particles (VLPs), which are similar to native virions both morphologically and immunologically. Studies have shown that L1 VLPs induces high titers of neutralizing serum antibodies, particularly immunoglobulin G (IgG). In fact, L1 VLPs are immunogenic and protective against HPV infecting skin or mucosa<sup>[57,62-64]</sup>. A conducted clinical trial by Koutsky *et al*<sup>[65]</sup> showed 100% protection from the natural acquisition of persistent HPV16

infection in individuals vaccinated with HPV 16 L1 VLPs, formulated in the adjuvant alum, over an average of 17.4 mo. The adjuvant is incorporated into a vaccine in order to enhance or direct the immune response of the vaccine<sup>[66]</sup>. Other clinical studies confirmed the high rate of protection and efficacy of L1 VLP vaccines against persistent infection of the same HPV type infection<sup>[67-73]</sup>. HPV vaccine is not recommended during pregnancy.

### **Cervarix**

Cervarix is a L1 VLP manufactured by GlaxoSmithKline Biologicals, based in the United Kingdom. It is a bivalent recombinant vaccine to prevent cervical cancer, high grade cervical intraepithelial neoplasia (CIN) grade 2 or worse, cervical adenocarcinoma *in situ*, and CIN grade 1 caused by HPV types 16 and 18. It was approved by the United States Food and Drug Administration (FDA) in 2009 for use in females 9 to 25 years of age. HPV types 16 and 18 account for 70% of all cervical cancers worldwide<sup>[74]</sup>. Immunization with Cervarix consists of 3 doses of intramuscular injection, 0.5-mL each, on 0, 1, and 6 mo<sup>[75]</sup>. Cervarix is produced and formulated in the proprietary Adjuvant System 04 (ASO4) using insect cells infected with recombinant baculovirus. ASO4 consists of aluminum hydroxide and TLR4 agonist monophosphoryl lipid A (3-O-desacyl-4'-monophosphoryl lipid A) (MPL). Cervarix is the first vaccine with MPL adjuvant, which is licensed by the FDA.

Syncope may occur immediately after receiving Cervarix. Therefore, it is recommended to observe the vaccinees for 15 min after administration of the vaccine. A tonic-clonic movements and other seizure-like activity might be associated with syncope which is usually transient. A supine or Trendelenburg position restores cerebral perfusion. Redness, swelling, and pain at the injection site are the most common local adverse reactions and are seen in greater than 20% of subjects. Fatigue, headache, myalgia, gastrointestinal symptoms, and arthralgia are reported as the most common general adverse effects. Severe allergic reactions, such as anaphylaxis, to any component of Cervarix is a contraindication<sup>[75]</sup>.

### **Gardasil**

Gardasil is a quadrivalent L1 VLPs recombinant vaccine manufactured by Merck and Co., Whitehouse Station, New Jersey, United States. It protects against cervical, vaginal, and vulvar cancers and precancerous lesions, and genital wart associated with HPV types 6, 11, 16, and 18<sup>[76]</sup>. HPV types 16 and 18 have demonstrated the strongest association between infection and cervical cancers and high grade SILs (CIN II and 3), and they are responsible for 70% of all cervical cancers and CIN II, and CIN III<sup>[77]</sup>. HPV types 6 and 11 are associated with 10% of low grade SILs<sup>[78]</sup>, and more than 90% of all genital warts<sup>[53,79]</sup>.

Gardasil consists of four types of L1 VLPs produced in

saccharomyces cerevisiae using recombinant DNA technology. The DNA-free VLPs are purified and adsorbed on a proprietary amorphous aluminum hydroxyphosphate sulfate adjuvant (225 mg per dose)<sup>[76]</sup>. Each dose is 0.5 mL containing 20, 40, 40, and 20 µg of VLPs for HPV types 6, 11, 16, and 18, respectively. The vaccine is administered by intramuscular injection as a three-dose regimen, at months 0, 2, and 6<sup>[76]</sup>.

### **Gardasil 9**

Gardasil 9 is a nonavalent recombinant human papillomavirus vaccine (by Merck and company, Kenilworth, New Jersey, United States) to prevent approximately 90% of cervical, vaginal, vulvar, and anal cancers caused by HPV types of 16, 18, 31, 33, 45, 52, and 58 and to prevent genital warts associated with HPV types 6 or 11. Compared to Gardasil, Gardasil 9 covers five additional HPV types including 31, 33, 45, 52 and 58, which account for approximately 20% of cervical cancers. The vaccine was approved by FDA for use in females ages 9-26 years and males ages 9-15 years in December 2014<sup>[80,81]</sup>. Gardasil 9 is administered as intramuscular injection in three doses. The combined follow up studies on females vaccinated by Cervarix, or Gardasil, and or Gardasil 9 confirm high efficacy of HPV vaccination in prevention of cervical precancerous lesions<sup>[81]</sup>.

## **HPV VACCINATION IN HIV-INFECTED PATIENTS**

The American Council of Immunization practices recommends HPV vaccination for HIV-infected patients ages 11-26 years. This recommendation is based on a few studies that evaluated the immunogenicity of the quadrivalent HPV vaccine in perinatally HIV-infected patients<sup>[82]</sup> and HIV-infected men<sup>[83]</sup>. A longitudinal, prospective, non-randomized, controlled, open-label clinical study on 46 HIV-infected adolescents and young adults ages of 13 to 26 years and 46 HIV-negative controls ages of 14 to 27 years was conducted to evaluate the long-term immunogenicity effect of Gardasil administered intramuscularly in three doses (0, 8 and 24 wk). Naïve (CCR7<sup>+</sup>/CD45RA<sup>+</sup>) and central memory (CM) (CCR7<sup>+</sup>/CD45RA<sup>-</sup>) CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes were diminished at 28 wk, whereas effector memory (EM) (CCR7<sup>-</sup>/CD45RA<sup>-</sup>) CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes were increased. No differences were noted between HIV-infected patients and HIV-negative healthy controls<sup>[84]</sup>.

### **Safety of HPV vaccination**

A Danish study reported post-vaccination symptoms in 35 females following vaccination with Gardasil. The patients were older than general target population (23.3 ± 7.1 years), with a high (71%) to moderate (29%) level of physical activity prior to vaccination, and BMI of 22.1 ± 4.7 kg/m<sup>2</sup>. The window period between vaccination



and onset of symptoms was 9.3 d. The symptoms included orthostatic intolerance (100%), postural orthostatic tachycardia syndrome (60%), nausea (94%), chronic headache (82%), fatigue (82%), palpitations (77%), reduced cognitive function (77%), skin changes for instance aggravation of acne (76%), intermittent tremor/myoclonic twitches (72%), neuropathic pain such as “burning”, “a deep stabbing”, or “jolts of electricity” starting distally, often in one limb, and then progressing proximally and often spreading to the contralateral side (68%), sleep disturbances described as new-onset insomnia and non-refreshing sleep (61%), and muscular weakness (61%). Symptoms were reported to appear after the first vaccination in 24%, after the second vaccination in 51%, and after the third vaccination in 25%<sup>[85]</sup>. Another study from the same center in Denmark reports more symptoms in addition to what they reported earlier in 53 females. Only symptoms that were experienced in more than 25% of the patients were presented. The mean age at symptom onset was  $21.0 \pm 7.4$  years. Mean time between vaccination and onset of symptoms was  $11.1 \pm 12.5$  d and symptoms were reported to appear after the first vaccination (40%), after the second vaccination (36%), and after the third vaccination (25%)<sup>[85]</sup>.

The additional symptoms included visual symptoms such as new-onset hypersensitivity to bright colors and light (70%), and intermittent blurring of vision (83%), gastrointestinal symptoms including feeling bloated (77%); abdominal pain of varying character, intensity and location (70%); and changes in bowel habits (55%), dyspnea (66%), voiding dysfunction with respect to frequency, urgency, nocturia and incomplete bladder emptying (59%), limb weakness, mostly experienced as muscle weakness and confined to lower extremities (57%), vascular abnormalities described as intermittent changes in skin color to blue, red, pale or blotchy in the lower parts of the legs and in fingers and toes - the color changes were often accompanied by painful swelling of the involved limbs (51%), irregular periods in females who did not take oral contraceptive pills reported as hypermenorrhea and worsening of menstrual discomfort and pain (48%), SICCA symptoms including new-onset dry mouth (40%), and dry eyes (28%), and hyperventilation in 18%<sup>[86]</sup>. An earlier study in 2006<sup>[76]</sup> reported injection-site reaction (pain, swelling, erythema, and pruritus) and fever as the most common Gardasil-related adverse effects.

The most commonly reported side effects of Gardasil 9 in 13000 females and males were swelling, redness, and pain at the injection site, and headaches<sup>[80]</sup>. HPV vaccines are considered safe even for immunocompromised individuals including HIV-infected women because they do not contain any live pathogens<sup>[34,83,87]</sup>.

### **Efficacy of HPV vaccines**

Phase III trials were conducted to evaluate efficacy of HPV vaccines for both bivalent and quadrivalent

HPV vaccines in young women<sup>[88]</sup>. All of the trials were relatively large, blinded, randomized, and controlled with at least 4 years of follow-up. The trials included 5500 to 18500 young women vaccinees with age range of 15-26 years (mean = 20 years). In the PATRICIA trial, the cohort-naïve analysis of the vaccinated young women showed 100% efficacy to protect against high grade CIN 3 related to HPV types 16 and 18<sup>[72,89]</sup>. Cervarix is reported a vaccine with a long term immunogenicity and efficacy in an 8.4-year follow-up after the first dose of vaccine<sup>[90]</sup>. Gardasil showed a high efficacy and protection against CIN 3 associated with HPV types 16 and 18 in the final intention-to-treat (ITT)-naïve analyses. Efficacy of quadrivalent HPV vaccine was greater than 95% against HPV 16 and 18 -related high grade vulvar intraepithelial neoplasia (VIN 2/3) or vaginal intraepithelial neoplasia (VAIN 2/3) and greater than 75% against genital warts in the ITT-naïve and ITT cohorts<sup>[91,92]</sup>.

### **Immunogenicity of HPV vaccines**

The immunogenicity of Cervarix and Gardasil are expected to vary due to their different adjuvants. ELISA (Enzyme-linked immunosorbent assay) is used to measure immune response for the bivalent HPV vaccine and competitive Luminex immunoassay (cLIA) for the quadrivalent HPV vaccine. The PBNA (pseudovirion-based neutralization assay) detects the neutralizing ability of the induced antibodies with highest accuracy<sup>[88]</sup>. The humoral response to Gardasil has been defined by total IgG and cLIA as a different method measuring immunogenicity of the vaccine<sup>[90,93]</sup>. The cLIA is a sensitive assay and it measures specific IgG level corresponding to a specific neutralizing epitope on each of the four HPV types of Gardasil, while the total IgG assay is less sensitive and measures a non-specific and broad response to HPV vaccine. Applying the cLIA assay, 98.5%, 64.8%, 90.2%, and 95.5%, of vaccinated women remained seropositive to HPV 16, HPV 18, HPV 6, and HPV 11, respectively, at month 48 while the total IgG cLIA assay showed 100%, 96.7%, 100%, and 100% of vaccinated women remained seropositive to HPV 16, and HPV 18, HPV 6, and HPV 11, respectively, at the same time. These results probably explain the possible differences among results of HPV-vaccine studies due to using different serologic assays<sup>[88,93]</sup>. Both the humoral and cellular immunity are responsible for viral clearance and long-term protection by HPV vaccine<sup>[94]</sup>. Moreover, a study showed similar efficacy and immunogenicity of quadrivalent HPV-vaccine in HIV-infected young adults and adolescent and in HIV-negative controls<sup>[95]</sup>.

### **Cost-effectiveness of HPV vaccines**

Multiple studies were conducted in the Europe and the North America indicating cost-effectiveness of HPV vaccination. However, the comparison among these studies might be challenging due to different adopted models<sup>[96-104]</sup>.

### Long-term protection

An HPV-16 vaccine (monovalent) trial was conducted by Merck and a long-term follow-up showed that up to 86% of young women aged 16-23 years remained seropositive for anti-HPV 16 antibodies, for an average of 8.5 years and there were no breakthrough cervical disease cases<sup>[105]</sup>.

Bivalent HPV vaccine protection was noted in women after 9.4 years follow-up. The efficacy of Cervarix was estimated 95.1% over the 9.4-year follow-up. All vaccinated women remained seropositive for both HPV types 16 and 18 and the serum antibody titers were several-times higher than naturally acquired levels. The safety of the vaccine was clinically acceptable<sup>[90,106]</sup>.

A study in boys 10-18 years received 3 doses of bivalent HPV vaccine showed a protection against HPV 16/18 after 24 mo of follow-up. Importantly, post-vaccination antibody titers against both HPV 16 and 18 were up to three times higher in boys than in young women and antibody levels against HPV 16 and 18 were four- and two- fold higher at month 2. A previous study reported a higher levels of antibodies detected against HPV 16 and 18 in 10-18 or 10-14 year old boys compared with 15-25 years old women or 10-14 years old girls<sup>[107]</sup>.

Women vaccinated with quadrivalent vaccine (Gardasil) showed protection against all four types of HPV 6, 11, 16, and 18 after a nine-year follow-up<sup>[71]</sup>. Using a total IgG Luminex immunoassay, seropositivity rates were 100%, 91%, 98%, and 96% respectively for HPV types 16, 18, 6, and 11 were at nine years<sup>[88,91]</sup>.

The efficacy of quadrivalent HPV vaccine to prevent HPV-related infection and genital disease in males has been assessed in 16-26 years old healthy boys and young men and followed up for three years. The quadrivalent vaccine was effectively prevented HPV types 6 and 11 related genital warts in 89.4% of cases compared with placebo<sup>[108]</sup>. The efficacy of Gardasil to prevent HPV types 6, 11, 16, and or 18 related anal intraepithelial neoplasia (AIN) was assessed in healthy HIV-negative males who have sex with males over 36 mo. The overall efficacy of Gardasil in preventing HPV types 6, 11, 16, and or 18 related AIN (anal intraepithelial neoplasia) was 77.5% (95%CI: 39.6%-93.3%) in the vaccinated study population<sup>[109]</sup>.

## ISSUES REGARDING HPV VACCINES

HPV vaccines provide type-specific immunity against HPV infection and do not prevent cancer caused by other types of HPVs. The bivalent HPV vaccine has developed to protect against infection and anogenital diseases related to HPV types 16 and 18 and the quadrivalent HPV vaccine protects against infection and anogenital disease associated with HPV types 6, 11, 16 and 18, respectively. Therefore, Cervarix and Gardasil together can prevent approximately 70% of all cervical cancer cases. Studies support that the overall protection against cervical cancer with these two vaccines is

probably close to 80% due to cross-reaction and close relation of HPV 16 and HPV 31 and HPV 18 and HPV 45<sup>[66,69,110]</sup>.

The 15 most common types of HPVs causing cervical cancer worldwide, in order of high to low frequency, are 16, 18, 45, 31, 33, 52, 58, 35, 59, 56, 39, 51, 73, 68 and 66. HPV type distribution in cervical cancer varies depends upon geographic region. The most common types of HPV detected in cervical cancer in Europe and North America are HPV types 16 and 18. North Africa shows higher frequency of HPV 16 than average, South Asia of HPV 18, sub-Saharan Africa of type 45, and Central and South America of HPV 31. Although Cervarix and Gardasil together could presumably prevent 70% of cervical cancers worldwide, their preventive impact would be potentially higher in Europe, North America, and Asia with regard to the variable geographic distribution of HPV. It was postulated that a vaccine with protection against the seven most common HPV types would prevent approximately 87% of cervical cancers worldwide, with minimal geographic variation<sup>[111]</sup>.

Overcoming these two issue, Gardasil 9, a non-avalent vaccine was developed to protect against infection with seven most common types of high-risk HPVs including 16, 18, 31, 33, 45, 52, and 58 and two types of low-risk HPVs including 6 and 11 to enhance protection against cervical cancer worldwide<sup>[78]</sup>.

An alternative approach is the application of cross-protective antigen, for instance minor capsid protein L2 to induce cross-neutralizing antibodies<sup>[112-114]</sup>. Clinical trials are designed to assess the efficacy and safety of HPV L2 vaccines.

Currently, HPV vaccine is recommended for girls in most countries. Only the United States, Canada, Austria, and Australia offer HPV vaccine to both males and females. The debate regarding cost-effectiveness and universal vaccination remains open. Studies in boys who received HPV vaccines have shown higher titers of antibodies against HPV 16/18 in comparison to those in females. It can be argued that vaccinating boys might be more effective in defeating cervical cancer since the virus is sexually transmitted. The HPV infection may persist through MSM, even if all the girls are vaccinated. In addition, the incidence of HPV-related head and neck squamous cell carcinoma is on the rise, which might be another consideration for universal HPV immunization<sup>[115]</sup>. HPV-related carcinoma is a global burden that affects both genders, female in particular.

## OBSTACLES OF ACCEPTANCE OF HPV VACCINE

Ethnicity, race, and income are considered important factors for acceptance and use of HPV vaccine in the United States<sup>[116]</sup>. Both incidence and mortality rate of cervical cancer are much higher among blacks, 25% and 95% respectively, and Latinos, 53% and 41% respectively, compared with whites<sup>[117]</sup>. Studies

show that there are significant differences among Blacks, Hispanic, and Whites in their age of first sexual experience, number of their sexual intercourses, and number of their lifetime partners. Having the first sexual experience before age 13 is reported to be more common in African-Americans (14%) and in Hispanics (7.1%), compared with Whites (3.9%)<sup>[118]</sup>. It is reported that Black teens (60%) have more often sexual intercourse compared with Latino (48.6%) and White (44.3%) teens. In addition, having four or more lifetime partners is more common in Black teens (24.8%), compared with Hispanics (14.8%) and Whites (13.1%)<sup>[118]</sup>. Therefore, the recommended age for HPV vaccination is 11-12 years in the United States since 6.2% of adolescent initiate their sexual activity prior to age 13 nationwide<sup>[118]</sup>. Despite the above facts, only 53% of the American female adolescents initiate the HPV vaccine and among them only 35% complete the HPV vaccine series<sup>[119]</sup>. Black mothers have expressed an interest in preventing cervical cancer and protecting their children after education about HPV vaccine and cervical cancer. They were concerned about: (1) lack of robust information; (2) long-term side effects; (3) vaccine being experimental; (4) challenges to completion of all three doses of HPV vaccine; (5) lack of health insurance, especially among the poor in Southern United States, and (6) language barriers and inaccurate information among foreign-born subgroups<sup>[120]</sup>. Concerns and issues for Hispanics were: (1) language barriers; (2) safety concerns; (3) not knowing where to get the vaccine; and (4) lack of health insurance, especially among the poor and undocumented immigrants. Asians' issues and concern were: (1) language barrier; (2) limited knowledge about HPV vaccine; (3) concerns about sexual activity, and finally (4) lack of health insurance, especially among the poor. The issues addressed above are mainly due to lack of mandatory school-based HPV vaccination programs in the United States. In general, vaccination in the United States is largely dependent on individual decision. Therefore, the overall HPV vaccination rate may be greatly influenced by factors such as personal awareness of HPV, health insurance status, race, and access to healthcare.

Vaccine cost is labeled as major obstacle for HPV vaccine acceptance in the Caribbean and Latin America, followed by public knowledge about cervical cancer as a health issue, political will, competition of HPV vaccine with other lifesaving vaccines, access to vaccine, and finally acceptance of the HPV vaccine among the high risk populations<sup>[121]</sup>.

It is estimated that cervical cancer affects the lives of 37500 women in Europe every year<sup>[21]</sup>. Moreover, genital warts are considered one of the most common sexually transmitted diseases in Europe; and its incidence is reported even more than 10% in women from the Nordic countries including Denmark, Finland, Iceland, Norway, and Sweden<sup>[122]</sup>. The HPV vaccine cost and a lack of knowledge about advantages of

vaccination were major barriers for vaccine acceptance. The main reason for vaccine acceptance was prevention of cervical cancer, followed by parental endorsement, providing financial support, personal experience of knowing someone with cancer and HPV vaccine recommendation by health-care professionals<sup>[123]</sup>.

In Africa, knowledge gaps regarding HPV and cervical cancer, lack of access to HPV vaccine, and its cost were among major obstacles for receiving HPV vaccine<sup>[124,125]</sup>. Over 50% of cervical cancer patients worldwide are from the Asia Oceania region<sup>[21]</sup>. The obstacles for receiving vaccines in these countries are its cost, followed by access to vaccines, and acceptance of HPV vaccination by the public<sup>[126]</sup>.

## STRATEGIES FOR THE FUTURE

Vaccine cost is considered as a major barrier worldwide. Finding ways to lower the cost of vaccine production can overcome this main obstacle. Public awareness of HPV and its association with cervical cancer and other related cancers and genital warts is the second most important step to enhance HPV vaccine acceptance. Willingness by local governments to support HPV vaccination and to facilitate public access to vaccine will increase the vaccine acceptance globally.

## CONCLUSION

HPV-related cancers, cervical cancer in particular, is a global health concern with a high burden on developing countries. Migration, changes in sexual behavior, discovery of HPV in a subset of head and neck cancers and of high percentage of anal cancers, increase in travel rate and having more global life are other reasons to act globally for HPV vaccination in both boys and girls. Meanwhile, more studies should be conducted toward producing low-cost vaccines with long time efficacy and minimal or no adverse effects. Public education will enhance vaccine acceptance.

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