Review Article

Human papilloma virus vaccines: Current scenario

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Abstract

Genital human papillomavirus (HPV) infection is the most common sexually transmitted infection with an estimated worldwide prevalence of 9–13% and approximately 6 million people being infected each year. Mostly acquired during adolescence or young adulthood, HPV presents clinically as anogenital warts and may progress to precancerous lesions and cancers of the cervix, vagina, vulva, penis and anus, and oropharynx. HPV infection is considered to contribute to almost 100% cervical cancers and at least 80% of anal and 40–60% of vulvar, vaginal, and penile cancers. At present, two prophylactic HPV vaccines are commercially available and both are prepared from purified L1 structural proteins. These proteins self-assemble to form virus-like particles that induce a protective immunity. Gardasil® is a quadrivalent vaccine against HPV types 6, 11, 16, and 18 and is recommended for use in females 9–26 years of age, for the prevention of cervical, vulvar, and vaginal cancers and intraepithelial neoplasia and condyloma acuminata and recently for vaccination in boys and men 9–26 years of age for the prevention of genital warts. Cervarix™ is a bivalent vaccine approved for the prevention of cervical cancer and precancerous lesions caused by HPV 16 and 18, in females 10–25 years. HPV vaccines are safe and efficacious against type-specific HPV-induced anogenital warts, precancerous lesions, and cervical cancer. The vaccines are most effective when given before the onset of sexual activity and provide long-term protection. Effective vaccination coverage in young adolescent females will substantially reduce the incidence of these anogenital malignancy-related morbidity and mortality. There is need to generate India-specific data on HPV epidemiology and HPV vaccination efficacy as well as continue worldwide surveillance and development of newer vaccines.

Key words: Cervical cancer, human papilloma virus vaccine, India, trials

INTRODUCTION

Genital human papillomavirus (HPV) infection is a common infection and is primarily transmitted by sexual contact. It is the most common sexually transmitted infection (STI) with around 630 million people already infected and approximately 6 million people being infected each year.[1] The prevalence of HPV increases with age from 14 to 24 years and then declines.[2] Up to 80% of women will acquire an HPV infection in their lifetime.[3] The cumulative risk of acquiring cervical HPV infection in women with only one sexual partner is 46% at 3 years after the first sexual encounter.[4] Majority of HPV infections are transient and subclinical and undergo subsequent clearance by the immune system. Persistence of infection results in development of anogenital warts as well as precancerous lesions and cancers of the anogenital tract and oropharynx. Anogenital warts are very common in sexually active adolescents and young adults with an annual incidence rate ranging from 182 to 229/100,000 population in developed countries such as USA, UK, and France.[5] Precancerous lesions associated

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with HPV infection may involve the cervix [cervical intraepithelial neoplasia or cervical intraepithelial neoplasia (CIN) and adenocarcinoma in situ or adenocarcinoma in situ (AIS)], vagina ([vaginal intraepithelial neoplasia or vaginal intraepithelial neoplasia (VaIN)], vulva [vulvar intraepithelial neoplasia or vulvar intraepithelial neoplasia (VIN)], or anus (anal intraepithelial neoplasia or AIN). Among the HPV-induced cancers, cervical cancer tops the list followed by cancer of the vagina, vulva, penis, and anus and a subset of head and neck cancers.[6]

In 2005, there were about 500,000 cases of cervical cancer and 260,000 related deaths worldwide.[6] As per an estimate, the global burden of cervical cancer by the year 2050 will be more than 1 million new cases every year.[7] Cervical cancer incidence rates vary from 1 to 50 per 100,000 females; rates are highest in Latin America and the Caribbean, sub-Saharan Africa, and south-central and South-East Asia.[6] In India, cervical cancer ranks number one among cancer in females with an annual incidence of more than 132,000 and around 740,00 deaths every year.[8]

The HPV virus and types

HPV, a member of the Papillomaviridae family of viruses, is a non-enveloped, double-stranded deoxyribonucleic acid virus. The HPV genome is enclosed in a capsid shell composed of major (L1) and minor (L2) structural proteins. More than 100 HPV genotypes are known, of which approximately 40 infect the anogenital region and around 13 are considered high risk, associated with anogenital and oropharyngeal cancers.[2] Low-risk HPV types 6 and 11 cause 90% of external anogenital warts and low-grade changes in cervical cells.[9] Other low-risk HPV types include HPV 40, 42, 43, 44, 54, 61, 70, 72, and 81.[10] The high-risk types 16 and 18 are known to cause about 70% of all cases of invasive cervical cancer.[11] HPV 16 has the greatest oncogenic potential and continues to be the dominant oncogenic type worldwide. Other oncogenic HPV types including 31, 33, 35, 45, 52, and 58 are phylogenetically related to HPV 16/18 and account for an additional 18% of all cases.[12] In India, HPV 16, 18, 31, 33, and 45 account for more than 90% of cervical cancer cases.[13]

Immunology of natural HPV infection and oncogenesis

HPV exhibits a specific tropism for the squamous epithelium of the skin and mucosae and evades local immune responses by many mechanisms—lack of viral-induced necrosis or inflammation, lack of viremia, exclusive intraepithelial localization of the infection, lack of activation of Langerhan cells by the uptake of HPV capsids, and inhibition of interferon synthesis and receptor signalling, among others.[14] The host's humoral immune response to natural HPV infection is usually slow, weak, and variable. Neutralizing antibodies to HPV specifically recognize or react with L1 capsid proteins and are important for inhibition of early infection before viral entry into cells.[15] Among women infected with oncogenic virus types, only 50% develop antibodies to HPV infection, and seroconversion may take as long as 18 months.[16] Further, these antibodies are not necessarily protective against reinfection by the same HPV type over time.[6]

Persistent HPV infection may lead to CIN of moderate grade 2 or severe grade 3 or to AIS. Untreated CIN 2/3 and AIS have a high probability of progressing to invasive squamous cell cancer or adenocarcinoma of cervix, respectively. It is estimated that progression to CIN3 takes 7–15 years and progression to invasive cancer 20 years or more.[17] Risk factors for progression to high-grade dysplasia and cancer include persistence of HPV infection, infection with oncogenic HPV types, age more than 30 years, infection with multiple HPV types, and immunosuppression.[2]

HPV vaccines

In view of the morbidity and mortality associated with genital HPV-induced lesions and the poor immunity conferred by natural infection, the need for effective prophylactic vaccines has always been felt. At present, two prophylactic HPV vaccines are available internationally and both have been prepared from purified L1 structural proteins by recombinant technology. These proteins self-assemble to form virus-like particles (VLPs) that induce a protective host immune response. Compared with immunity-acquired following natural infection, the vaccine-induced immunity is much stronger, long lasting, and includes partial cross-protection to non-vaccine-related serotypes. The difference in the immune response generated by vaccination and natural infection is attributable to high immunogenicity of VLPs inducing much higher concentrations of neutralizing antibodies to L1, higher antigen dose in VLPs, and direct exposure of capsids to systemic immune responses.[14] The mechanisms by which these vaccines induce protection have not been fully defined but apparently involve both cellular immunity and neutralizing immunoglobulin G antibodies.[15,18] HPV vaccines are designed for prophylactic use only; they

do not clear existing HPV infection or treat HPV-related disease.[19]

The two commercially available vaccines, Gardasil®[20] and Cervarix™,[21] substantially differ in their composition [Table 1].

Indications and licensing

The list of currently FDA-approved indications for both the vaccines is given in Table 2. In India, both vaccines have been licensed for use in females (primary vaccination at 10–12 years, catch-up upto 26 years) since October 2008 (Gardasil®) and February 2009 (Cervarix™).

Storage and administration

Both the vaccines are available as a sterile suspension in single-use glass vials or single-use prefilled syringes that should be maintained at 2–8°C (not to be frozen). Recommended route of administration is intramuscular with doses of 0.5 ml each time. The quadrivalent vaccine is given at baseline and repeated at 2 and 6 months. A minimum interval between successive doses of 4 weeks between the first and second dose, and 12 weeks between the second and third dose is recommended.[22] The bivalent vaccine is given at baseline and repeated at 1 and 6 months; the second dose may be administered between 1 and 2.5 months after the first dose if flexibility in the schedule is required.[23] If the vaccination schedule is interrupted, restarting the three-dose series is not necessary; remaining vaccine doses should be administered as close to the recommended schedule as possible.[6] Currently, a booster dose has not been recommended for any of the HPV vaccines following completion of the primary series.

Age of vaccination

The ideal time of vaccination for HPV vaccines would be before the onset of sexual activity, i.e., before the first exposure to HPV infection. It is currently recommended that HPV vaccine be administered to girls at 11–12 years, with catch-up vaccination for those who have not completed or initiated the series between 13 and 26 years.[24-26] The recommended age range for Gardasil® in males is 9–26 years.

Immunogenicity studies

After three doses of the vaccine, almost all adolescent and young females initially naive to the vaccine-related HPV types develop an antibody response.[27,28] Data available up to 5–6.4 years after vaccination have shown that antibody titres in vaccines peak after the third dose decline gradually and then level off by 24 months after the first dose, though they remain higher than in natural infection.[6] Coadministration of HPV vaccines with most other vaccines has not shown any significant impairment of the immune response to any of the involved antigens.

Vaccine efficacy in young women

Results of multiple phase II and III studies are available for both vaccines. The USFDA recommended surrogate clinical end point for cervical cancer (development of CIN grade 2 or worse) has been used as the primary outcome measure in most HPV vaccine studies.[29] Published analyses have included variable study populations [Table 3].[29,30] Since obtaining cervical specimens from girls or young adolescents is considered unethical, clinical efficacy in younger girls (9–14 years) is extrapolated from immunobridging studies comparing vaccine immunogenicity in them with older females (15–26 years). Both vaccines have shown high efficacy rates for various clinical end points including condyloma, low- and high-grade CIN and AIS, as well as VaIN and VIN,

Table 1: Salient differences between the two commercially marketed HPV vaccines

Vaccine characteristic	Quadrivalent vaccine (Gardasil®)	Bivalent vaccine (Cervarix™)
Manufacturer	Merck	GlaxoSmithKline (GSK)
Antigens	HPV types 6, 11, 16, and 18 (20 µg, 40 µg, 40 µg and 20 µg/dose)	HPV types 16 and 18 (20 µg and 20 µg/dose)
Antigen expression system	Yeast	Baculovirus
Adjuvant	Alum (225 µg aluminum hydroxyphosphate sulphate)	ASO4 (500 µg aluminum hydroxide and 50 µg 3-deacylated monophosphoryl lipid A)
Route of administration	Intramuscular injection	Intramuscular injection
Dosing and schedule	0.5 ml at 0, 2, and 6 months	0.5 mlL at 0, 1, and 6 months
Diseases prevented	Anogenital cancers and their precursor lesions, subset of head and neck cancers Anogenital warts and laryngeal papillomas	Anogenital cancers and their precursor lesions, subset of head and neck cancers.
Price per dose	Approximately US $ 120 (US) Rs. 2800 (India)	Approximately US $ 100 (US) Rs. 3300 (India)

Table 2: FDA-approved indications for Gardasil® and Cervarix™

FDA-approved indications for Gardasil®[20]
Prevention of vulvar and vaginal cancer
Vaccination in females 9-26 years of age for prevention of the following diseases caused by HPV types 6, 11, 16, and 18:
Cervical cancer
Genital warts (condyloma acuminata) and the following precancerous or dysplastic lesions:
AIS
CIN grade 2 and grade 3
VIN grade 2 and grade 3
VaIN grade 2 and grade 3
CIN grade 1
Vaccination in boys and men 9-26 years of age for the prevention of genital warts caused by HPV types 6 and 11
Vaccination in people 9-26 years of age for the prevention of anal cancer and associated precancerous lesions due to human papillomavirus (HPV) types 6, 11, 16, and 18
FDA-approved indications for Cervarix™[21]
Prevention of cervical cancer, CIN grade 2 or worse and AIS, and CIN grade 1, caused by oncogenic HPV types 16 and 18, in females 10-25 years of age

Table 3: Typical characteristics of different types of study populations analyzed in HPV vaccine trials (may differ in some aspects in different studies)

According-to-protocol (ATP) or per-protocol susceptible population:
Negative for relevant HPV types (by serology and PCR) at baseline and through 1 month after the third dose
Received all three doses
No protocol violations
Case counting after month 7
Represents an ideal population under ideal study conditions (approximates to a sexually naive population)
Unrestricted susceptible population (USP) or total vaccinated cohort (TVC) population
Negative for relevant HPV types (by serology and PCR) at baseline
Received ≥1 vaccination dose
Had any follow-up visit
Case counting after day 1
Represents a broader population than per-protocol susceptible population, including subjects completing the full three vaccination doses and others who received only one or two doses Intention to treat (ITT) population
Baseline HPV status not considered
Received ≥1 vaccination dose
Had any follow-up visit
Case counting after day 1
Represents population of women with past and current exposures to HPV as well as well presumable naive women.
It is an approximation of the effectiveness of the intervention in the general public. Modified intention to treat (MITT) analysis
Negative for relevant HPV types (by serology and PCR) at baseline
Received ≥1 vaccination dose
Case counting after day 1 or month 1
Falls somewhere between ATP and ITT

associated with vaccine-related HPV types. The characteristics of three large phase III trials of Gardasil® (FUTURE I and II study) and Cervarix™ (PATRICIA study) conducted in young women and the prophylactic efficacies from these trials are summarized in Table 4. While the efficacy for prevention of HPV-16/18 related CIN-2/3 ranged from 90.4% to 98%, the overall HPV vaccine type-related CIN efficacy has ranged from 89.2% to 100%.[31-33] The quadrivalent vaccine also demonstrated 91% to 100% efficacy against HPV-6/11/16/18-related VIN-2/VIN-3 or VaIN-2/VaIN-3 and 96% to 100% efficacy against HPV6/11/16/18-associated condyloma.[32,33] High efficacy rates have been reported in the ATP analyses of most studies. However, efficacy has been lower in the MITT and ITT analyses [Table 4]. This may reflect, at least in part, lesser protection with single dose compared with three doses. More importantly, the lower efficacy in ITT (which includes women already exposed to vaccine-related HPV) clearly suggests that women naive to vaccine-related HPV types are likely to benefit the most with prophylactic vaccination.[29] Further analyses of the findings of FUTURE I/II and PATRICIA trials over longer follow-up periods have reinforced the efficacy of both HPV vaccines.[30,34]

Table 4: Outline and efficacy outcomes of three large phase III studies of HPV vaccines conducted in young women

Characteristic	PATRICIA[31]	FUTURE I[32]	FUTURE II[33]
Vaccine	Cervarix™	Gardasil®	Gardasil®
Number of participants	18,644	5,455	12,167
Mean age (years) (range)	20 (15-25)	20 (16-24)	20 (15-26)
Screening frequency (months)	12	6	12
Mean follow-up duration (months)	15	36	36
Primary clinical end-point	HPV-16/18 related CIN2+	HPV-6/11/16/18 related CIN1+, AIS and external genital lesions	HPV-16/18 related CIN2+ and AIS
Secondary end-points	Persistent infection or CIN1+ by any type, and adverse events	Adverse events	Adverse events
Efficacy*			
Efficacy for CIN (1+ or 2+), AIS			
ATP	NR	100 (94-100)	98 (86-100)
MITT	89 (59-99) for CIN1+ 90 (53-99) for CIN2+	98 (92-100)	95 (85-99)
ITT	NR	55 (40-66)	44 (26-58)
Efficacy for external genital lesions			
ATP	NR	100 (94-100)	NR
MITT	NR	95 (87-99)	NR
ITT	NR	73 (58-83)	NR
Efficacy for HPV persistence (6 months)			
ATP	NR	NR	NR
MITT	80 (70-87)	NR	NR
ITT	NR	NR	NR
Efficacy for HPV persistence (12 months)			
ATP	NR	NR	NR
MITT	76 (48-90)	NR	NR
ITT	NR	NR	NR

*95% confidence intervals, except 97.9% confidence intervals used in PATRICIA.; AIS: Adenocarcinoma *in situ*; ATP: According to protocol; CIN: Cervical intraepithelial neoplasia; CIN1+: CIN grade 1 or worse; CIN2+: CIN grade 2 or worse; FUTURE: Females united to unilaterally reduce endo/ectocervical disease; ITT: Intention to treat; MITT: Modified intention to treat; NR: Not reported; PATRICIA: Papilloma trial against cancer in young adults.

The protective efficacy of both vaccines has been maintained throughout their respective observation periods (currently 5 years for Gardasil® and 8.4 years for Cervarix™).[35,36] A model estimated that antibody levels will remain detectable near lifelong in 99% of vaccinated females.[18,37] This suggests that a booster dose may not be required, although longer follow-up studies are warranted.

Gardasil® vs Cervarix™

Differences among the efficacy trials of the two vaccines in terms of choice of placebo recipients, immunological assays, and populations analyzed preclude direct comparison of results. A recent observer-blind head-to-head randomized controlled trial sponsored by GSK has compared the immonogenecity and safety of the two vaccines in 1106 women stratified by age (18–26, 27–35, and 36–45 years). At month 7 after first vaccination, analysis of women in the ATP cohort showed that the geometric mean titres of serum neutralizing antibodies ranged from 2.3- to 4.8-fold higher for HPV-16 and 6.8- to 9.1-fold higher for HPV-18 after vaccination with Cervarix™ compared with Gardasil®, across all age strata.[38] The incidence of adverse events was comparable between groups. The better immune response with Cervarix™ may reflect a longer duration of protection with HPV-16/18, although long-term studies are needed to confirm this. The obvious advantage of Gardasil® over Cervarix™ is the additional protection available for HPV-6/11-associated condyloma.

Cross protection to non-vaccine-type oncogenic HPV

The quadrivalent vaccine has shown statistically significant but limited protection against CIN2+ associated with non-vaccine-type oncogenic HPV (especially HPV-31, 45, and 33) that are phylogenetically related to HPV 16 and 18.[39-41] No statistically significant protection was detected against persistent infection with HPV-52 and 58. Cross-protection against incident infection,

persistent infection and CIN2+ related to HPV-31 and HPV-45 has also been reported with the bivalent vaccine (with a 66 months of follow-up).[34,42] The added benefit of cross-protection may result in further reductions in incidence of cervical cancer and precancerous lesions following vaccination.

Vaccination of older females

Older women remain at risk of acquiring and developing persistent infection by high-risk HPV, leading to an increased risk of carcinoma when compared with younger women.[43] While sexually naive girls and young women will be the highest beneficiaries of prophylactic HPV vaccination, recent studies have shown vaccination benefits for older women as well, many of whom may have acquired transient infections in the past or had active infection at the time of vaccination. Muñoz *et al.* in their quadrivalent vaccine trial involving 3,819 older women (24–45 years old) observed 90% efficacy against combined incidence of vaccine HPV-related 6-month persistent infection, CIN 1-3 or external genital warts.[44] Further, Olsson *et al.* have demonstrated that even among women who had detectable serological evidence of vaccine-type-related HPV infection in the past but no DNA evidence of active infection at enrolment, prophylactic vaccination provided nearly 100% protection against CIN2+ associated with the vaccine HPV type with which the women had been previously infected.[45]

Vaccination of boys and men

Extension of routine HPV vaccination to males is a matter of debate. Vaccinated males will benefit from prevention of HPV-related disease (anogenital warts, AIN, and anal cancer). Giuliano *et al.* have reported an efficacy of 90.4% against external genital lesion and 85.6% against persistent infection by HPV-6/11/16/18 following administration of the quadrivalent vaccine to 4,065 healthy, predominantly heterosexual males 16–26 years of age.[46] Although less than 25% of HPV-related cancers occur in men, some subgroups, including men who have sex with men (MSM) and those with immunodeficiency, are at a markedly increased risk and are likely to benefit from vaccination.[47] In one study, involving MSM, Gardasil® provided 77.5% protection against development of AIN.[48] Men are also at a higher risk than women of developing oropharyngeal cancers, 50% of which may be HPV-related.[49] The argument that vaccinating boys could indirectly contribute to reduction of cervical cancer by "herd immunity" sounds logical. However, current analyses suggest that cost-effectiveness of vaccinating a girl far exceeds that of vaccinating a boy.[50]

Vaccinaton of immunocompromised individuals

Although HPV vaccine can be safely given to HIV-positive and other immunocompromised individuals, the efficacy has been found to be lesser compared with immunocompetent people.[6] Following administration of Gardasil® to 109 HIV-1-infected men in an open-label, multicenter clinical trial, seroconversion rates of upto 98%, 99%, 100% and 95% were observed for HPV types 6, 11, 16, and 18, respectively. No adverse effects (AEs) on CD4 counts and plasma HIV-1 RNA levels were observed.[51] In another trial, 126 HIV-infected children (7–12 years old) were blindly assigned to receive a dose of Gardasil® or placebo at 0, 8, and 24 weeks. Seroconversion to all four antigens occurred in more than 96% of vaccine recipients (irrespective of the baseline CD4 counts), compared with none in placebo recipients. Adverse events were infrequent, and there was no alteration of HIV viral load.[52] Thus, current evidence suggests that vaccination should be offered to all irrespective of their immunocompetence status.

Adverse effects

A recent systematic review and meta-analysis of seven clinical trials has shown that both vaccines are safe and well tolerated with no statistically significant difference in the risk for vaccine-related serious AEs between vaccine and control groups.[12] Pain at injection site was the most frequently reported AE, ranging from 83% to 93.4% in vaccine groups versus 75.4–87.2% in control groups. Injection-site erythema and swelling were also common. Headache and fatigue were the most common vaccine-related systemic AEs observed in approximately 50–60% of vaccines. Observation of vaccines for 15 min after the injection is recommended, since an increased occurrence of syncope accompanied by tonic–clonic movements has been reported.[2] In June 2007, WHO's Global Advisory Committee on Vaccine Safety (GACVS) concluded that both vaccines had good safety profiles and this was confirmed, in a postmarketing surveillance of the quadrivalent vaccine in 2008.[6]

Contraindications and precautions

HPV vaccines are contraindicated in people with history of severe allergic reactions after a previous vaccine dose or to a vaccine component (yeast allergy for Gardasil®, latex allergy for Cervarix™ prefilled syringes). In individuals with severe acute

illness, delaying HPV vaccination is recommended. A history of abnormal Pap smear or anogenital warts is not a contraindication and Pap smears or HPV testing are not required prior to vaccination.[2] Since vaccines do not contain live biological products or viral DNA, they are non-infectious.

Pregnancy and lactation

No adverse pregnancy outcomes or fetal risk in animals and data on women who became pregnant during the vaccine trials indicate no increased risk of adverse events (including congenital anomalies) compared with controls.[53,54] However, since adequate and well-controlled studies in pregnant women are lacking (pregnancy category B), vaccine should not be given to women known to be pregnant. Women who accidentally receive the vaccine while pregnant should delay further shots till pregnancy is over. A pregnancy test is not required prior to vaccine administration. Breastfeeding is not a contraindication although caution is recommended.[2]

Cervical cancer screening in vaccinated females

Although HPV-16/18 have been implicated in the causation of up to 70% cervical cancers, the remaining 30% cases are associated with other HPV types. A vaccinated female may subsequently become infected with a carcinogenic HPV type for which the current vaccines do not provide protection, and thus it has been recommended that cervical cancer screening in national programs for vaccinated females should remain the same as for non-vaccinated females.[55]

Impact of HPV vaccines on population health

Models predict that vaccination programmes for young adolescent females will substantially reduce the incidence of cervical cancers associated with vaccine-related HPV types if coverage is high (>70%) and vaccine-induced protection lasts for ≥10 years.[6] Considerable reductions in incidence may also be expected for cancers of the vagina, vulva, anus, and head and neck associated with HPV-16/18. Vaccination with the quadrivalent vaccine will substantially reduce the incidence of anogenital warts, low-grade cervical abnormalities caused by HPV-6/11 and, possibly, recurrent respiratory papillomatosis,[6] Since the vaccines protect females who are naive for the vaccine-related HPV types at the time of immunisation, a high coverage of young adolescent girls before first intercourse is expected to have a much larger impact than vaccinating older females.[56]

WHO recommendations

WHO recommends that routine HPV vaccination should be included in national immunization programmes, provided that prevention of cervical cancer or other HPV-related diseases, or both, constitutes a public health priority; vaccine introduction is programmatically feasible; financially sustainable; and is cost effectiveness in the country.[6] Programs should initially prioritize high coverage in the primary target population which should be selected based on data on the age of initiation of sexual activity and feasibility of reaching young adolescent girls through schools, or healthcare and community-based settings. Vaccination of secondary target populations of older adolescent females or young women is recommended only if this is feasible, affordable, cost-effective, does not divert resources from vaccinating the primary target population or effective cervical cancer screening programmes, and if a significant proportion of this target population is likely to be naive to vaccine-related HPV types.[6] The benefits of vaccination should be available to all irrespective of their HIV status. HPV vaccination of males is not recommended. The choice between the two vaccines should be based on the scale of the prevailing HPV problem, the target population, delivery strategies, safety concerns and the price, supply, and cold-chain requirements of the products.[6]

Cost-effectiveness and economic feasibility of HPV vaccination

In general, models show that a substantial reduction in costs associated with cervical cancer screening and follow-up of abnormal screening tests, diagnosis, and treatment of precancerous states and cancer is expected with nationwide programs that achieve high coverage in young adolescent girls, at least in countries where gross domestic product is high.[57] HPV vaccination may be cost-effective in low-income and middle-income countries (where quality screening is not widespread) if the cost per vaccinated girl (including three doses of vaccine and programmatic costs) is <US$ 10–25, which is substantially lower than current costs in high-income countries.[58] Quadrivalent HPV vaccination is expected to further reduce the costs associated with the diagnosis and treatment of genital warts in high-income settings.[6] The respective cost of a single 0.5-ml dose of Gardasil® and Cervarix™ is approximately $120 and $100 in the USA versus Rs 2,800 and Rs 3,300 in India. The cost in India for the entire three dose schedule turns out to be Rs 8,400 and Rs 9,900, respectively. The vaccine cost may drop

substantially if the Government purchases vaccine in bulk by policy, or if Indian manufacturers are encouraged or enabled to manufacture vaccine.[59] The long-term cost-effectiveness of mass HPV vaccination needs to be specifically evaluated for India, comparing the expected economic burden incurred by cost of vaccines and infrastructure for the programme against the financial benefit of reduced health costs for diagnosis and treatment of CINs, cervical cancers and anogenital warts.

Indian scenario

Cervical cancer is the leading cause of cancer-related mortality in Indian females. Both HPV vaccines have been licensed for use in Indian females and have been recommended by the Indian Academy of Pediatrics (IAP) and the Federation of Obstetric and Gynaecological Societies of India (FOGSI). However, high-cost, low public awareness and a relatively conservative nature of the society are key barriers for successful implementation of the vaccination program in India.[60]

Social factors

The median age of initiation of sexual debut in Indian adolescents has been reported to range from 15 to 16 years to 17.37 ± 1.72 years with earliest debut seen as early as 13 years of age.[61] Thus, even in Indian females, the vaccine will be most effective if given at a younger age (prior to expected sexual debut). However, the concept of premarital sexual exposure is taboo in the Indian society and socio-cultural barriers exist to effective communication between physicians and parents regarding the sexual activities of their adolescent girls and boys. Explaining to the parents about importance of prophylactic vaccination of their children and their consent for the same is expected to be a difficult task and would require formulation of guidelines for effective counseling. It needs to be stressed upon that the risk of HPV infection and consequent cancer risk is not necessarily predicted by one's own sexual promiscuity alone as a woman is also at risk because of her partner's past or present sexual activities.[59]

Clinical trials in India

Only two HPV vaccination projects were initiated in India. One was a post-licensure observational study for operational feasibility of school-based and community-based vaccination in Khammam district (Andhra Pradesh, Gardasil®) and Vadodara (Gujarat, Cervarix™), conducted by the State Governments in collaboration with Indian Council of Medical Research and PATH (a US based non-profit non-governmental organization). The other was a multicentric clinical trial to investigate immunogenic efficacy of two doses (6 months apart) compared with conventional three doses (at 0-2-6 months) of Gardasil®, which if found successful would have resulted in 33% cost reduction.[59] Following media allegations of "vaccine-induced" deaths of four girls in Khammam, both studies have been suspended by the Union Government.[62-64] The deaths have since been investigated and confirmed as unrelated to the vaccine.[64] However, the studies have not been resumed (till the time of writing this article). The scepticism for the need and safety of HPV vaccines in the Indian context continues. To achieve effective prevention of HPV infection related morbidity and mortality by vaccination in India, the health authorities and Government should resort to more effective and sympathetic dialog with people to address their reasonable concerns and dispel their fears based on misinformation.[62]

Future trends

The quadrivalent and bivalent vaccines provide only limited cross-protection to development of persistent infection and CIN 2-3/AIS caused by non-vaccine HPV types. Thus, a multivalent vaccine against a multitude of HPVs will be a major breakthrough in providing near-complete prevention of HPV-related diseases, and indeed, efforts to develop a nine-type L1 VLP combination vaccine are ongoing.[14] Preclinical and human volunteer studies have also suggested that immunization against the minor capsid protein 2 with the candidate prophylactic/therapeutic vaccine HPV-16 L2E6E7 might work as a pan-HPV vaccine against different genotypes of HPVs.[65] Development of low-cost vaccines using plant species such as tobacco, potatoes, and tomatoes for the production of VLPs is also underway.[66-68] Therapeutic vaccines incorporating the E6E7 proteins such as the HPV-16 E6E7 ISCOMATRIX vaccine are being investigated for treatment of HPV-related anal intraepithelial neoplasia in HIV-infected men.

CONCLUSIONS

HPV vaccines are safe and efficacious against type-specific HPV-induced anogenital warts, precancerous lesions, and cervical cancer. The vaccines are most effective when given before the onset of sexual activity and provide long-term protection. While new clinical trials and follow-up of older trials will yield more information on issues such as efficacy, safety, duration of protection, need for booster dose, current evidence supports the introduction of HPV vaccination as part of a coordinated strategy

to prevent cervical cancer, and other HPV-related diseases. India-specific guidelines need to be based on cost-effectiveness and feasibility of implementing HPV vaccination as a part of national immunisation schedule. Vaccination alone will not be successful unless it is coupled with education about healthy sexual behavior and information about the diagnosis and treatment of precancerous lesions and cancer.

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Multiple Choice Questions

Q.1. What percentage of invasive cervical cancers are attributable to infection with HPV-16 and 18?
a. 25%
b. 55%
c. 70%
d. 100%

Q.2. Which of the following statements regarding the development of immune response to natural HPV infection with oncogenic types in women is incorrect?
a. More than 90% develop significant antibody titres
b. Antibodies to HPV specifically recognize L1 capsid proteins
c. Seroconversion may take upto 18 months
d. Antibodies may not be protective against subsequent infection by the same HPV type

Q.3. The currently recommended route of administration and dosing schedule for the quadrivalent HPV vaccine is
a. Subcutaneous; three doses at 0, 1, and 6 months
b. Subcutaneous; three doses at 0, 2, and 6 months
c. Intramuscular; three doses at 0, 2, and 6 months
d. Intramuscular; two doses at 0 and 6 months

Q.4. The bivalent HPV vaccine is not indicated for the prophylaxis of
a. Condyloma acuminata
b. CIN 1
c. CIN 2/3
d. Cervical cancer

Q.5. An important recommended precaution for physicians administering HPV vaccines is that
a. Patient with past history of anogenital warts should not be vaccinated
b. Vaccinated individuals should be observed for 15 minutes after the injection
c. Vaccination should be deferred in individuals with mild fever
d. HIV positive individuals should not be vaccinated

Answers:
1. c. 70%
2. a. More than 90% develop significant antibody titres
3. c. Intramuscular; three doses at 0, 2, and 6 months
4. a. Condyloma acuminata
5. b. Vaccinated individuals should be observed for 15 minutes after the injection