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Review Article

HPV vaccination to prevent cervical cancer & HPV related diseases

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Abstract

Cervical cancer is a cause of significant disease worldwide. Human papillomavirus (HPV) infection is the cause of cervical cancer in almost 100% cases. HPV infection can also lead to genital warts, recurrent respiratory papillomatosis, vaginal, vulval, anal and penile cancers. HPV types 16 and 18 are responsible for more than 70% of HPV-related cancers whilst HPV types 6 and 11 cause approximately 90% of the cases of genital warts. Effective interventions to prevent HPV associated diseases can therefore prevent cervical cancers and genital warts.

Primary prevention of cervical cancer can be achieved by vaccination and secondary prevention by screening. Currently screening options of secondary prevention include visual inspection with acetic acid (VIA), cervical cytology and detection of high risk HPV-DNA viruses. Prophylactic HPV vaccines have been developed recently which will reduce the burden of HPV-related diseases in the community. For this primary preventive measure, two vaccines are available worldwide: quadrivalent HPV vaccine targeting HPV types -16, 18, 6 and 11 and a bivalent vaccine against HPV types 16 and 18. Clinical trials have shown that these vaccinations are safe, immunogenic and highly effective against type-specific HPV infections.

Key words – human papilloma virus; cervical cancer; warts; screening; vaccines

Introduction

This review aims to contribute to the understanding of the future clinical recommendations and practices regarding the use of HPV vaccination as a primary preventive measure against cervical cancer.

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Cervical cancer is a cause of significant disease burden. Human papillomavirus (HPV) infection is the cause of cervical cancer in almost 100% of the cases. HPV infection can also lead to genital warts, recurrent respiratory papillomatosis, vaginal, vulval, anal and penile cancers. HPV types 16 and 18 are responsible for more than 70% of HPV-related cervical cancers whilst HPV types 6 and 11 cause approximately 90% of the cases of genital warts. Effective interventions to prevent HPV associated diseases can therefore prevent cervical cancers, genital warts and other less common cancers. Primary prevention can be

achieved by vaccination and secondary prevention by screening.

A phenomenal breakthrough in preventive oncology has been made by the development and introduction of this prophylactic vaccine against cancer of the cervix- the first of its kind in the world of oncology. It promises to positively impact the personal lives of millions of women and their families' worldwide. Hopefully, it will prove to be a public health marvel, once successfully implemented.

Papanicolaou smears achieved a 60-70% reduction in cancer of the cervix within 3 years of implementation as a secondary preventive measure in those developed countries where the program was introduced effectively. Now with the addition of a primary preventive measure in the form of a prophylactic vaccine against cancer, the impact on the incidence rates of cervical cancer should be even more significant. In developing countries like India, wherein lies a quarter of the world's disease burden, screening alone as a national program is unlikely to work. Universal prophylactic vaccination of young adolescent girls will be a more workable and effective option. As a result, the state of many Indian women with advanced cervical cancer may well become history, provided the medical fraternity, in particular the gynecologists, pediatricians, general practitioners and the Ministry of Health support it as a universal immunization program.

Human papillomavirus (HPV)

Human papillomavirus is a non-enveloped double stranded DNA virus [1] that infects the skin and mucosae of the upper respiratory and anogenital tracts. More than 100 HPV types have been detected,[2] with >80 types sequenced and classified[3]. Approximately 30–40 types of HPV are anogenital, of which 15–20 types are oncogenic[2,3]. In an international meta-analysis, HPV types 16 and 18 were found to be oncogenic and accounted for more than 70% of all cervical cancers—the next 5 most prevalent types - 45, 31, 33, 52, 58 and 35 – in that order of frequency- account for an additional 17% of the cases [4]. Other oncogenic HPV types include 39, 51, and 56. HPV viruses have been classified as 'high-risk' and 'low-risk' types [5] based on their oncogenic potential.

In India HPV 16 and 18 account for more than 75% of the cervical cancer cases [6]. Low-risk HPV types are mainly responsible for genital warts. HPV type 6 and 11 account for approximately 90% of the genital warts [3,5]. Approximately 66% of the individuals who have had sexual contact with a partner with genital warts will develop genital warts [7].

HPV and infection - HPV infects its host by penetrating through mucosal tears in the basal membrane [8]. In benign HPV-associated skin lesions, the HPV virus maintains its genome as episomes at low copy numbers (10–200 copies/cell) in the basal cells of the epithelium, separate from the host cell DNA. To maintain its viral DNA as an episome, viral E1 and E2 proteins are expressed. Failure to express E1 leads to the integration of the HPV genome into the host cell chromosome [8]. Integration of HPV into the DNA of the infected host cell is commonly associated with high-risk oncogenic HPV types [9] and is considered an important step in tumor progression[10]. In malignant HPV-associated skin lesions, HPV DNA integration into the host cell's chromosome occurs regularly through a break in the viral genome around the E1/E2 region. Integration-mediated disruption of E2 may trigger uncontrolled expression of E6 and E7, resulting in cellular transformation [10]. The E6 protein associates with the tumor suppressor protein p53 and promotes proteolytic destruction of the protein. This leads to malignant transformation and loss of regulated cell growth. The E7 protein associates with the retinoblastoma protein (pRB), which inactivates the cell cycle restriction function of this protein [10].

Natural history of HPV infection of the cervix – Squamous intraepithelial lesions (SILs) are subdivided into low-grade squamous intraepithelial lesions (LSIL) and high-grade intraepithelial lesions (HSIL), based on cytology results. LSIL often is the marker of CIN 1, and HSIL of CIN 2 & 3 [11].

Incident HPV infection is the new detection of HPV infection in women who were previously HPV-negative. Although common in sexually active persons, more than 90% of the infections are spontaneously cleared by the immune system within approximately 1 year without treatment [12]. *Persistent HPV infection* is the detection of the same HPV type in follow-up visits 6–12 months apart in women who were naive for that particular HPV type at baseline [12].

The schematic diagram (Figure 1) shows the progression from oncogenic HPV infection to cervical cancer. The known steps from HPV infection to cervical cancer include oncogenic HPV infection of the cervix; development of undetected cellular changes, LSIL or HSIL; development of HSIL; and progression to cervical cancer. However, some LSIL may progress directly to cervical cancer, and some initial HPV infection may progress directly to HSIL. The literature suggests that one-third to two-thirds of the women with HSIL will progress to cervical cancer if left untreated [13].

Approximately 60% of CIN 1 lesions (or low-grade dysplasia), the most common clinical manifestation of cervical HPV infections, regress without treatment, 30% persist and about 10% can progress to CIN 2 and CIN 3 and 1% progress to invasive cancer [12, 14]. CIN 2 (moderate-grade dysplasia) also can regress in 40% and persist in 40% of the cases. In a meta-analysis of studies on the natural history of CIN, it was estimated that about 20-22% of CIN 2 lesions that were not treated will progress to CIN 3 [11, 14]. However, 5% women with CIN 2 run a risk for developing invasive cervical cancer. CIN 3 lesions (high-grade precancerous lesions and carcinoma in situ) are more likely to progress to cancer (in greater than 12% and even in up to two third cases), with regression being less common, occurring in only about 33% [12,14].

In Essence High-risk HPV infections are mainly transient and cause no clinical problems. Approximately 70% of the new infections clear within one year and approximately 90% infections get cleared off within two years. In more than 99% of cervical cancers, persistent infection due to high-risk HPV types can be detected. HPV types 16 and 18 have been found to be more common cause of persistence and disease than other high risk types of HPV. Time span between infection due to HPV and development of cervical intraepithelial neoplasia (CIN)-3 or cervical cancer usually varies from one to ten years[5] and may even go up to 20 years. The mean age of invasive cervical cancer is approximately 50 years. The mean age of women with HSIL is approximately 28 years of age [13]. This lag period of about 20 years provides enough window of opportunity to clinicians to screen for, detect and manage the HPV related CIN before it becomes an obvious invasive carcinoma.

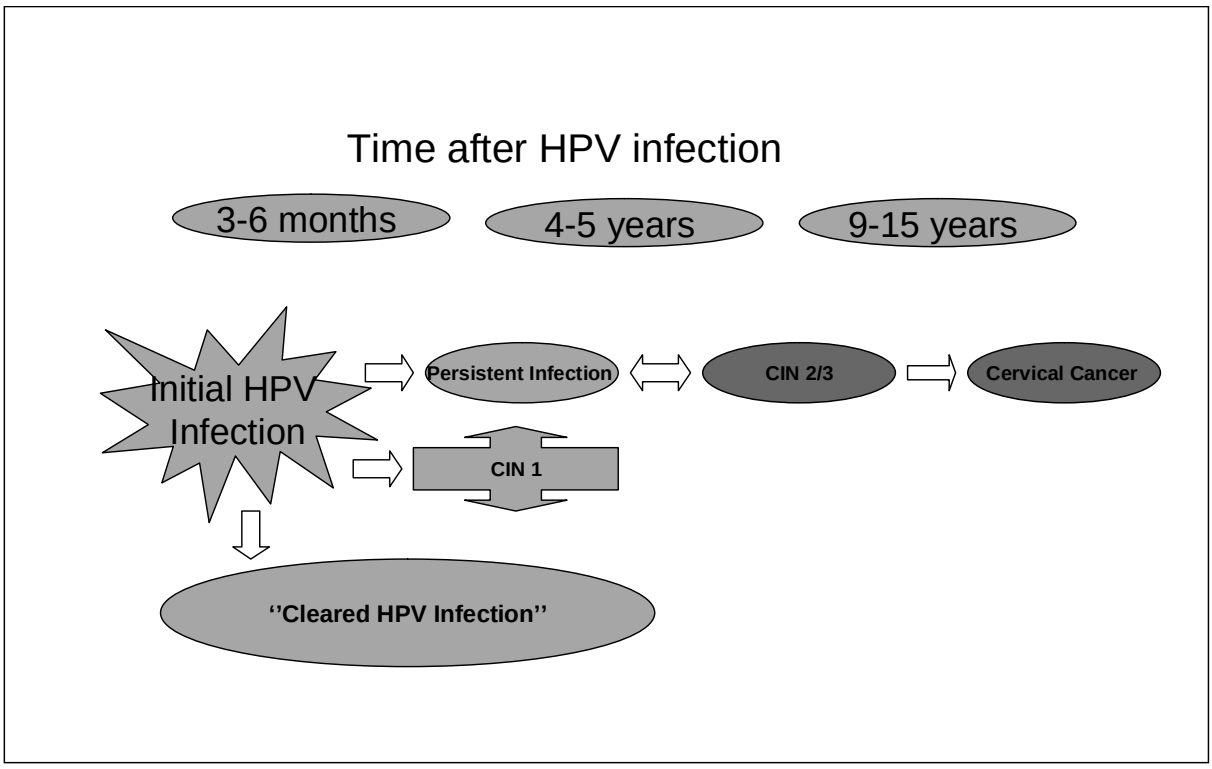

Figure 1. Schematic diagram of natural history of HPV infection

HPV and association with other cancers

HPV infection is also associated with other less common cancers that include vulval, vaginal[17], penile [16], and some cancers of the head and neck [19-21]. About 80-90% of anal cancers are related to HPV 16 & 18 [22,23]. More than 40% of vulvar cancers and 60-80% of vaginal cancers [18] are HPV related [24,25].

Overall about 42% of penile cancers are associated with HPV with an 80% association with basaloid type of penile cancer and 100% with the warty type of penile cancers [16]. Almost 100% of primary squamous cell carcinoma of the pendulous urethra has been found to be associated with HPV 16 virus. However, no association has been seen with bulbous and posterior urethral squamous cell carcinoma [18].

HPV 16 has also been found to be the predominant virus type with the occasional HPV 18 type in 18.3% cancers of the oropharynx, 24.7% of the tonsil [20,21] and to a lesser extent with laryngeal cancers [21,24]. HPV types 6 and 11 are frequently associated with recurrent laryngeal respiratory papillomatosis (in most circumstances acquired by vertical transmission) with increased risk of cancers of the larynx, esophagus and bronchi [26-28].

Other cancers with a reported link to HPV are non melanoma skin and cancer of the conjunctiva [24].

Immune response

The immune response can be divided into 2 types: innate immunity and acquired immunity.

Innate immunity: In humans, innate immunity is the first line of defense against pathogens. This non-specific resistance is provided by the skin and a variety of other responses, including interferon-á, cytokines, neutrophils and macrophages [15].

Acquired immunity: Acquired immunity is specific for each pathogen and can be further divided into humoral and cell-mediated immunity. Humoral immunity involves the production of antibodies by the B lymphocytes. These antibodies specifically bind to the recognized antigens making it easier for phagocytosis of pathogens or for lysis by complement. With cell-mediated immunity, specialized cells are produced that react with the foreign antigens. The reacting cells kill the virus-infected cells before the occurrence of viral replication[15]. Humoral responses are more important in the context of HPV vaccine.

Perspective of cervical cancer in India

As per GLOBOCAN data 2002, cervical cancer ranks as the most frequent cancer in Indian women [29]. In India, 365.71 million women above the age of 15 are at the risk of developing cervical cancer; 132,082 women are diagnosed with cervical cancer and 74,118 women die due to cervical cancer every year, accounting for 26.7% of the worldwide incidence and 27% of deaths worldwide. One woman in India dies due to cervical cancer every 7 minutes accounting for more than 200 deaths everyday [29]. The cumulative risk of incidence of cervical cancer in women in India (age 0-64yrs) is 2.4% compared to 1.3% for the world [29].

Cervical cancer is preventable. The effective interventions for prevention of cervical cancer include vaccination and screening. . HPV types 16 and 18 account for 76.7% of cervical cancers in India [29].

Primary prevention of cervical cancer: Vaccination

As cervical cancer is for the most part related to infection with HPV virus, it makes sense to prevent cervical cancer by preventing infection with HPV using a vaccine against possible future HPV infections. HPV vaccine candidates were studied in preclinical models of papilloma virus disease. Immunization with virus like particles (VLPs) of L1 protein of papilloma viruses has shown to induce serum anti-L1 neutralizing antibodies thereby resulting in protection against HPV infection. It has been seen that unvaccinated animals receiving serum transfusions from vaccinated animals also get protected from infection, suggesting induction of systemic anti-HPV responses. Thereby, HPV L1 VLP vaccines resulted in protection against HPV type specific infection [30].

Two vaccines have been licensed globally; a quadrivalent vaccine from Merck and the other a bivalent vaccine from GSK. Both vaccines are manufactured by recombinant DNA technology that produce non-infectious virus like particles (VLP) with HPV L1 protein [31].

Bivalent vaccine protects against HPV type 16 and

18 related cervical cancers. Quadrivalent vaccine protects not only against HPV 16 and 18 related cervical cancers but also protects against HPV types 6, 11, 16 and 18 related genital warts, vaginal intraepithelial neoplasia (VaIN) and vulval intraepithelial neoplasia (VIN) [31]. Both vaccines may also have a role in prevention against other rarer HPV 16 and 18 associated diseases.

Table 1 shows selected established qualitative findings on both quadrivalent and bivalent HPV vaccines. The findings shown of quadrivalent HPV vaccine are on the basis of per protocol efficacy results of a 2 year follow–up and findings for bivalent vaccine are from an interim report which included efficacy analyzed on the intention-to-treat population with a follow up time of 15 months [32].

Efficacy end points - US Food and Drug Administration (FDA) and the World Health Organization (WHO) have stated that the vaccine should demonstrate reduction in the incidence of CIN 2 and 3 or AIS by use of vaccine HPV types for licensure. Phase III trials using cervical cancer as an end point are practically not feasible, because the time from acquisition of HPV infection to the development of cancer is often more than 20 years, and standard of care is to screen and excise CIN 2 and 3 or AIS lesions prior to invasion. Hence, trials evaluating the impact of HPV vaccines on cervical cancer risk need to use surrogate markers [30].

Since no correlate has been established between antibody titers and protection, efficacy of the vaccine should be judged on the ability of the vaccine to reduce the incidence of CIN 2 and 3 or AIS and anogenital warts. Over a longer period of up to 20-30 years, its effectiveness can be assessed by the change in incidence of cervical, vulval and vaginal cancers in the vaccinated community.

Efficacy of vaccines in clinical trials– A combined analysis of four randomized trials by the FUTURE II study group reported that quadrivalent HPV is 99% efficacious against HPV 16/ 18 related cervical intraepithelial neoplasia grade 2/3 (CIN 2/3) or adenocarcinoma-in-situ (AIS) in per protocol analysis (women who received all three doses of the vaccine and who remained uninfected with vaccine HPV type at the onset and for 1 month after completion of the vaccine schedule) [32] as seen at the mean follow up at 3 years. Additionally Garland and his colleagues reported in the FUTURE I study that quadrivalent vaccine provides 100% efficacy against vaccine type (HPV Type 6, 11, 16 & 18) related genital warts, vaginal intraepithelial neoplasia (VaIN) and vulval intraepithelial neoplasia (VIN) in per protocol analysis [34] also at the mean follow up period of 3 years.

The results of bivalent vaccine have been reported from the PATRICIA trial. The PATRICIA trial demonstrated 90.4% efficacy against type 16/18 related CIN2/3 or AIS at 15 month follow up in modified intention to treat analysis. The vaccine also showed 89.2% efficacy against CIN 1[35]. The results of both vaccines cannot really be compared. Table 2 and 3 depict the summary of efficacy of both vaccines as reported by Garland et al in FUTURE I and in a combined analysis of four randomized trials by The FUTURE II study group for quadrivalent HPV vaccine and by the PATRICIA trial for the bivalent vaccine.

A certain level of cross protection against other HPV virus may also be conferred by both the vaccine types as suggested in their preliminary data. However, further results are awaited for details before making any clinical recommendations.

Adverse effects

Both vaccines were generally well tolerated [33-35]. People who received the HPV vaccination were seen to have adverse local events, most commonly pain, redness or swelling at the injection site followed by pruritus [33] for up to 2-4 days. With respect to systemic adverse events, a marginally higher percentage of recipients were seen to have fever (100^0F to 102^0F), fatigue, headache or myalgia within 7 days of receiving the vaccination. Syncope (vasovagal or vasopressor reaction) has been noticed to occur especially in adolescents and young adults. Hence they should be observed for 15 minutes after they receive HPV vaccination [39]. There were no statistically significant serious adverse effects or pregnancy related effects as a direct consequence of these vaccinations [35].

Any significant adverse effects or events after vaccination should be reported to VAERS at https:// vaers.hhs.gov even if causality is not certain. In addition, Merck has set up a vaccine in pregnancy registry to report any exposure to quadrivalent vaccine during pregnancy.

Duration of protection and need for booster – A critical test of utility of vaccines as public health interventions is duration of protection provided by vaccines. Anti-HPV geometric mean titers produced with quadrivalent HPV vaccine remained at or above those observed with natural infection even after 5 years. Furthermore, administration of immune challenge dose of quadrivalent vaccine at 5 yrs to previously immunized individuals produced potent anti-HPV 6, 11, 16 and 18 anamnestic response thus demonstrating immune memory, the hall mark of long term protection [38]. As with any other vaccine, a study over next few years will determine the need of booster with both the quadrivalent and the bivalent vaccines.

Role of HPV vaccine in males –The prevalence of HPV infection ranges from less than 10% to approximately 72% all over the world amongst predominantly heterosexual men forming a reservoir for HPV infection in the community. Genital warts are the most common complaint in both males and females. Most common site of infection is penile shaft followed by coronal glans penis, and scrotum. Most infections being asymptomatic in both men and women, transmission occurs readily between the sexual partners [36].

Several countries (e.g., Mexico and Australia) have licensed HPV vaccine for use in both males and females. Global policy recommendations for administration of HPV vaccines in males await HPV vaccine trial efficacy results in . Anti–human papilloma virus geometric mean titers levels in girls or boys (10–15 years of age) were non-inferior compared to the levels in women (16-23yrs of age) [37]. In Australia, the quadrivalent HPV vaccine is registered for use in females aged 9 to 26 years and males aged 9 to 15 years [36].

Role of HPV vaccine in anogenital warts – Garland et al show that quadrivalent HPV vaccination following a schedule of 0, 2, and 6 months with a follow up period of 3-years significantly reduced the incidence of HPV-associated anogenital warts as compared to placebo in women aged 16 to 24 years. Efficacy of vaccine was 100% in the per-protocol group [34].

Immunoassays used to measure anti-HPV antibodies - No international standards for harmonizing HPV serology and DNA assays have been developed yet. Therefore, valid inter-study comparison of antibody levels or intra-study comparisons of antibody response to various HPV VLPs is not possible. ELISA assays are used for bivalent vaccine, measuring both neutralizing and non neutralizing antibodies (Table 4) produced to the HPV virus like particles (VLPs) whereas, competitive radioimmunoassay (cRIA) and the competitive luminex immunoassays (cLIA), are used for quadrivalent vaccine, which are competitive assays that provide an indirect measure of serum antibodies that bind to neutralizing epitopes on the HPV VLPs. Assays have been developed on their own by the manufacturers to measure antibody titers [37]. Both assays thus measure different units and therefore responses cannot be compared.

Cost effectiveness **–** Analyses done using population-dynamic models considering HPV infection, transmission, and disease for United States have demonstrated that vaccination of all girls and women aged 12–24 years is cost-effective [30]. The overall cost for universal protection by primary vaccination may be for less than the total costs of treating cervical cancer in a community. Even for an individual paying for self vaccination, whether non-infected or infected with HPV or having low grade disease, the cost benefits of vaccination and screening will still be much less than bearing the total cost for treatment with the associated physical and mental morbidity of CIN or cervical cancer should it develop.

Clinical recommendations on immunization with HPV vaccine –

A. Licensing of HPV vaccination and clinical recommendations

Both the HPV vaccinations are licensed for use in over 70 countries worldwide. Though the quadrivalent vaccine is currently licensed in USA, the bivalent vaccine is awaiting licensing in USA. In most countries, both the HPV vaccinations are licensed for use in only females. In a few countries – Mexico, Australia and New Zealand, they are also licensed for use in males. Generally both vaccines are recommended for use in females between 9 and 26 years. Even those with previous HPV infection, with an equivocal or an abnormal Pap smear may be vaccinated because vaccination would provide

Table 1 - Key results from phase III trials of HPV vaccines[11]

Vaccine name	Quadrivalent vaccine	Bivalent vaccine
Time of follow-up	36 months (advanced)	15 months (Interim)
HPV types included	6, 11, 16, 18	16, 18
Antigen dose	20/40/40/20 µg	20/20 µg
Efficacy on HPV 16 or 18 CIN 2+	**Proven**	**Proven**
Efficacy on HPV 16 CIN 2+	Proven	Proven
Efficacy on HPV 18 CIN 2+	Proven	Proven in long term follow up of pahse II trials
Efficacy on 16 or 18 CIN 2	Proven	Proven
Efficacy on 16 or 18 CIN 3	Proven	Not yet reported
Efficacy on HPV 16 or 18 VIN 2/3	Proven	Not yet reported
Efficacy on HPV 16 or 18 VaIN 2/3	Proven	Not yet reported
Efficacy on HPV 6 or 11 genital warts	Proven	Not in target
Therapeutic efficacy	None	None
Safety at 6 years follow-up in clinical trials and post-licensing evaluation	Safe	Safe
Tolerability	Well tolerated	Well tolerated
Protection against 6-month persistent HPV infections of types other than 16 or 18	Against combined types 31/33/45/52/58	Against specific types 45, 31 and 52
Protection against CIN 2/3 related to HPV other than types 16 or 18	Reported	Not yet reported
Duration of protection corresponds to duration of trials in 2007	5–6+ years	5–6+ years
Immunogenic in preadolescents and older women	Proven	Proven
Immunogenic in boys	Proven	Not yet reported
Evidence of immune memory	Booster effect of a fourth dose at year 5	Enhanced production of memory B cells

CIN : Cervical intraepithelial neoplasia

HPV : Human papillomavirus

VaIN: Vaginal intraepithelial neoplasia

VIN: Vulval intraepithelial neoplasia

Table 2 - Summary of efficacy of quadrivalent and bivalent vaccine on the basis of clinical endpoint.

S. No	Endpoint HPV vaccine	Quadrivalent	95% CI	Bivalent HPV vaccine	95% CI
HPV Type 6/11/16/18					
1	Warts	100%[#]	92-100	Not Tested	
2	VIN 1/2/3	100%[#]	49-100	Not Tested	
3	VaIN 1/2/3	100%[#]	49-100	Not Tested	
HPV 16/18					
1	CIN 2	99%*	93-100	90.4%[$]	53.4-99.3
2	CIN 3				
3	AIS				

FUTURE I study

* Combined analysis of 4 trials

$ PATRICIA Trial - *Interim analysis at 15 months

Table 3. Summary of efficacy of quadrivalent and bivalent vaccine on the basis of HPV type.

HPV Type	Endpoint vaccine[*]	Quadrivalent HPV	95% CI vaccine[$]	Bivalent HPV	97.9% CI
16	CIN 2+	99%	92-100	93.3%	47-99.9
18	CIN 2+	100%	78-100	83.3%	-78.8-99.9
16/18	CIN 2+	99%	93-100	90.4%	53.4-99.3

***** Combined analysis of 4 trials

$ PATRICIA Trial - *Interim analysis at 15 months

Table 4 - Difference in assays used in clinical trials of quadrivalent and bivalent vaccine.

	Quadrivalent vaccine	Bivalent vaccine
Neutralizing antibodies	✓	✓
Non-neutralizing antibodies		✓

Table 5. Summary of recommendations for quadrivalent HPV vaccine by American organizations.

Recommendations	ACOG	AAFP	SAM	ACHA	AAP	ACIP
Routine vaccination in females 11-12 years old & catch-up vaccination in 13-26 year olds	✓	✓	✓	✓	✓	✓
Females 9-10 years old may also be vaccinated	✓	✓	✓	✓	✓	✓
Vaccinate regardless of previous HPV infection or abnormal Pap test results to protect against unexposed HPV types.	✓	✓	✓	✓	✓	✓
Continue Pap testing after vaccination	✓	✓	✓	✓	✓	✓

protection against infection with HPV vaccine types not already acquired by the patient.

As to genital warts, though the HPV vaccine will not have any therapeutic effect on existing HPV infections or warts, it will protect against fresh warts from the other HPV types included in the quadrivalent vaccine that have not yet infected the host.

Lactating women may receive HPV vaccination [39]

In immunocompromised patients the immune response and vaccine efficacy may be less than that in persons who are immunocompetent [39]. It may still be used in such patients, provided this fact is understood.

B. Vaccination administration and schedules [39]

Both the quadrivalent HPV and the bivalent vaccinations are administered in a three dose schedule with the second and third dose given two and six months after the first dose for the quadrivalent HPV vaccine and one and six months after the first dose for the bivalent HPV vaccine. If the quadrivalent HPV vaccine series are interrupted, the recommendation is that the second dose should be given as soon as possible and the interval between the second and third dose be at least 12 weeks. If only the third dose is delayed it should be given as soon as possible.

Since HPV vaccination is not a live vaccine it may be administered at the same visit as other age appropriate vaccinations using a separate syringe at a different anatomic site.

It is not necessary to do a Pap smear or test for high risk HPV infection prior to administering the vaccination. However, regular screening for cervical cancer must continue as usual for all the vaccinated individuals.

C. ***Contraindications to HPV vaccination*** [39]

1. Pregnancy is a contraindication to HPV vaccination. Should pregnancy occur after initiating the vaccination series, the remaining doses should be delayed to after pregnancy. If a vaccine dose has been administered during pregnancy, no intervention is required.
2. Vaccination should not be given in moderate or severe acute illnesses, though it may be administered to women with minor acute illnesses like diarrhea or mild upper respiratory tract infections.
3. In women with hypersensitivity or allergies to vaccine components like to those with an allergy to baker's yeast the quadrivalent HPV vaccine should not be used.

D. ***Recommendations regards HPV vaccination by professional bodies***

Advisory Committee on Immunization Practices (ACIP) [39] **–** ACIP (United States of America) recommendations are available only for quadrivalent vaccine as currently only the quadrivalent HPV vaccine is approved by USFDA (at the time of writing this article). The bivalent vaccine is awaiting FDA approval. ACIP has recommended quadrivalent HPV vaccination as:

- Routine vaccination of females aged 11–12 years.
- The vaccination series can be started at as young as 9 years of age.
- Vaccination also is recommended for females aged 13–26 years who have not been previously vaccinated or who have not completed the full series even if sexually active or previously exposed.

Recommendations by others - Recommendations by American College of Obstetricians and Gynecologists (ACOG) [40], Society for Adolescent Medicine (SAM)[41], American College Health Association (ACHA) [42], American Academy of Family Physicians (AAFP) [43], American Academy of Pediatrics (AAP) [44] have been summarized in Table 5. All these American organizations have based their recommendations on the use of the quadrivalent HPV vaccine since only that is currently FDA approved whereas the bivalent vaccine is awaiting FDA approval.

Indian Academy of Pediatrics (IAP) [31] recommends vaccine for Females 10 - 12 years.

- Catch up vaccination is permitted up to the age of 26 years.
- HPV vaccines can be given with other vaccines eg Hepatitis B
- Quadrivalent HPV vaccine protects against HPV type 6, 11, 16 & 18 related cervical cancers. In addition it also demonstrates efficacy against

vaginal and vulval cancers and protects against anogenital warts.

- Bivalent vaccine protects against HPV type 16 and 18 related cervical cancers.
- Screening programs should be continued as per recommendations.

Conclusions

HPV infection is the most common cause of cervical cancer, genital warts, anal, vulval, vaginal cancers, recurrent respiratory papillomatosis and some head and neck cancers. Annual number of deaths due to cervical cancer in India accounts for 27 % deaths worldwide. HPV type 16 and 18 are attributed to more than 70 % of the invasive cervical cancer cases whilst HPV 6 and 11 are attributed to approximately 90% of the genital warts. Cervical cancer can be prevented and effective interventions for prevention include both screening and vaccination.

Screening remains an integral part for prevention of cancer. The current development and availability of vaccines against cervical cancer hold tremendous promise for developing countries like India where cervical cancer is the most common malignancy amongst middle aged women and CIN threatening to develop as a problem in even younger women. Two vaccines available globally are the quadrivalent and bivalent vaccines. In PATRICIA trial, bivalent vaccine has shown 90.4% efficacy against HPV 16 & 18 related CIN2/3. AIS quadrivalent vaccine provided 99% protection against HPV 16 and 18 related CIN2/3 and 99-100% protection against HPV 6, 11, 16 & 18 related genital warts, vaginal intraepithelial neoplasia (VaIN) and cancer and vulval intraepithelial neoplasia (VIN) and cancer offering a broader protection against HPV related diseases in the HPV naïve individuals.

The confirmatory evidence of the vaccination's impact as a public health measure, however, will only be assessed over a period of 20 years in view of the natural history of the disease. It is advised that vaccinated individuals continue to be under strict screening surveillance and follow up as usual. In the meanwhile we must offer both vaccination and screening, as recommended, since denying these now may amount to negligence.

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