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REVIEW ARTICLE

Human Papilloma Virus Vaccination: Recent Trends in Prevalence and Recommendations in India

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ABSTRACT

Cervical cancer, mainly caused by human papilloma virus (HPV) infection, is the leading cause of cancer mortality and morbidity in Indian women. Vaccination being the most effective preventive option, and with the availability of two vaccines, quarries and controversies have stirred much debate and excitement regarding the mandatory vaccination, safety, boosters and cost effectiveness, especially in the Indian scenario.

Keywords: Human papilloma virus vaccine, Cervical cancer, Indian scenario.

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INTRODUCTION

Cervical cancer is the 5th most common cancer in humans and 2nd most common cancer in women world wide,[1] causing significant morbidity, mortality among women of all socioeconomic strata, that too in early and productive period of their lives. Compliance with cervical Papanicolou (PAP) Smear screening for cervical cancer is low in India, and health infrastructure for treatment is limited. Hence, prevention is the best cure. It is the only cancer where the etiological agent is very clearly identified.[2] On the basis of epidemiological and virological studies, human papilloma virus (HPV) is estimated to cause almost 100% of cases of cervical cancer.[3] Hence, there is a justifiable excitement about the use of vaccines against HPV types 16 and 18 and preventing these infections would theoretically avert approximately 70% of cervical cancer cases worldwide.

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BURDEN OF THE DISEASE

Global Prevalence

Globally, cancer of the cervix uteri is the second most common cancer among women with an estimated 529,409 new cases and 274,883 deaths in 2008.[4] About 86% of the cases occur in developing countries, representing 13% of female cancers.[4] Type 16 HPV causes nearly 50% and together with type 18 about 70% of invasive cervical cancers worldwide. The median age of incidence is 38 years and peak at around 55 years.[5]

Prevalence in India

India has 27% of global burden of cervical cancer. It ranks as the 1st most frequent cancer among the Indian women. The current estimates indicate about 13,2000 new cases diagnosed and 74000 deaths annually in India, being 1/3rd of the global cervical cancer deaths.[6]

Prevalence of HPV infection in general population of India is about 7.9%.[4] Cancer incidence is generally expressed as age adjusted or age standardized incidence rate (AAR) per 100,000 persons according to world standard population. Globally the AAR is 15.3 per 100,000. The AAR for Indian women is 27 per 100,000.[4] The cumulative lifetime risk for Indian woman of getting the disease is 2.8 as compared to the global figure of 1.6.[4] India has a population of 366.58 million women aged 15 years and older who are at risk of developing cervical cancer.[1] Types 16 and 18 account for 70% of the cases of invasive cervical cancer globally. A meta-analysis of human papilloma virus type distribution from India showed that in invasive cervical carcinoma (ICC), HPV16 was the predominant type (64.8%), followed by HPV 18, 45, 33, 35, 58, 59 and 31.[4] The estimated HPV 16/18 positive fraction was 78.9% in women with invasive cervical cancer (87.7% In North India and 77.2% in South India), 61.5% with high squamous intraepithelial lesion, 30.8% with low squamous intraepithelial lesion and 3.9% in women with normal cytology/histology. There was no difference in overall HPV prevalence in cervical cancer between North and South India. However, HPV 16 and 45 appeared to be more prevalent in North India, while HPV35 appeared to be more prevalent in South India.[4] It is estimated that HPV 16/18 vaccines will

provide over 75% protection against cervical cancer in South Asia. Oncogenic HPV serotype have also been implicated in causation of anal, vulvar, vaginal, penile and orophayngeal cancers. Additionally, nononcogenic HPV serotypes 6 and 11 are responsible for more than 90% of anogenital warts and most recurrent papillomatosis.

HPV Disease Spectrum

HPV is a small, nonenveloped DNA virus of Papillomaviridae family.[7] Out of over 100 serotypes, 15 to 20 are oncogenic. HPV-16 and 18 are the most common serotypes found in women worldwide, including Indian. Nononcogenic serotypes 6 and 11 contribute more than 90% of benign genital infections like genital warts.[8] Few oncogenic strains have been implicated in causation of anal, vulvar vaginal and penile cancers.[9]

Mortality

The cumulative risk of death due to cervical cancer in Indian women is 1.7 as compared to 0.9 in the women world over.[4] The crude mortality rate expressed as deaths per 100,000 women per year is 12.8. This is also higher as compared the world crude mortality of 8.2.

The relative 5 years survival reported some time earlier averaged 48.7%. Additionally, cervical cancer may occur early and strike at the productive period of a women's life.

There is no data on the burden of anogenital warts in the general community; warts have been reported in 2 to 25.2% of STI clinic attendees in India.[4]

Table 1: Incidence and death rates due to cervical cancer

	World	*India*
Annual no. of cases	529828	134420
Annual no. of deaths	275128	72825
Incidence rate/100000 women	15.3	27
Incidence of death/100000w	7.8	15.2
Cumulative risk of disease	1.6	2.8
Cumulative risk of death	0.9	1.7

Table 2: Efficacy of quadrivalent vaccine[21]

	Vaccine (n = 5305)		*Placebo (n = 5260)*		*Vaccine efficacy(%)*
	No. of cases	*Rate*	*No. of cases*	*Rate*	
CIN2/3 Adenocarcinoma *in situ*	1	<0.1	42	0.3	98
CIN grade 2	0	0	28	0.2	100
CIN grade 3	1	<0.1	29	0.2	97
Adenocarcinoma *in situ*	0	0	1	<0.1	100

The comparative data on incidence, cumulative risk of disease and death is summarized in the following Tables 1 and 2. GLOBOCON estimates of cervical cancer in Indian population.[4]

Transmission

HPVs are highly transmissible, and most sexually active men and women will acquire an HPV infection at some time in their lives. Whereas most HPV infections are transient and benign, persistent genital infection with certain viral genotypes can lead to the development of anogenital precancers and cancers. The lag period between infection with oncogenic HPV and invasive cervical cancer is 15 to 20 years. One-hundred serotypes of HPV have been discovered of which 15 to 20 are oncogenic. It is well recognized that HPV is a necessary cause of cervical cancer. Analysis of 932 specimens from women indicated that 99.7% of cervical cancers and over 90% of their precursor lesions (squamous intraepithelial lesions) contain HPV DNA. In India, high-risk HPV types were found in 97% of cervical cancers.[4] It infects the basal epithelium and results in cervical morphological changes ranging from normal to CIN-1/2/3 (Cervical intraepithelial neoplasia) and subsequently ICC (invasive cervical cancer).[10,11]

Risk Factors

Persistent infection with HPV types 16 or 18 is the single most crucial risk factor, with other cofactors contributing, like (a) young age at sexual initiation (<25 years), (b) number of sex partners, (c) inconsistent condom use, (d) number of pregnancies, (e) host genetic factors, (f) immune suppression.[12] Studies from US, show a cumulative incidence of HPV infection from 1st sexual exposure of 10% in the 1st month which rises to over 40% at 3 years.[13] We do not have any such robust study from India.

Vaccination *vs* other Modes of Prevention

All genital infections cannot be totally prevented except by abstinence and lifetime mutual monogamy with an uninfected partner.[13] Barrier methods like condoms have not shown promise in this issue. These infections being largely asymptomatic except genital warts,[14,15] adherence to routine screening by periodic PAPs smears in a large country with high illiteracy and lack of access to healthcare facilities, is very difficult to achieve. Hence, vaccination seems to be the best mode of prevention.

HPV Vaccines—the Development

As majority of the people are exposed to HPV once they becomes sexually active, an ideal way to prevent cervical

cancer is by preventing HPV infection. HPV infections are restricted to the intraepithelial layer of the mucosa and do not induce a vigorous immune response. Approximately half of all women infected with HPV develop detectable antibodies in the serum but these antibodies do not necessarily protect against subsequent infection by the same HPV type. The best and most type specific HPV antibodies are those detected against L1 protein of the virus. Hence, the current prophylactic HPV vaccines are subunit vaccines; that is, they consist of only a portion of the virus, the L1 protein of the virus coat or shell in the form of virus-like particles (VLPs). VLPs are empty protein shells immunologically identical to the virus but without the virus.[16] As HPV cannot be grown in tissue culture, creating the traditional live or attenuated viral vaccines is not possible. The vaccines are prepared from VLPs produced by recombinant technology. They do not contain any live biological product or DNA and so they are noninfectious.[17]

Available HPV Vaccines

At present, two HPV vaccines have been licensed globally for use, one contains VLPs of HPV 16 and 18 (Bivalent Vaccine, Cervarix™, developed by GSK) and second one having VLPs or HPV 16, 18, 6, 11 genotypes (Gardasil™, developed by Merck and Co.).[18] Both have been successfully evaluated in randomized placebo controlled clinical trials and are endorsed for use by IAP, FOGSI and IMA.[13]

Contents

- Each dose (0.5 ml) of Cervarix™ contains
- HPV 16 LA Protein 20 μ, HPV18 LA Protein 20 μ, 3-0 desacyl-4-monophosphonyl lipid 50 μg Aluminum Hydroxide-0.5 μg, whereas
- Gardacil™-each dose contains (0.5 ml) Purified LA VLPs HPV type 6\11\16\18 at 20\40\40\20 μg/dose respectively formulated on proprietary alum adjuvant.[18]

Schedule

0, 1, 6 months for Bivalent and 0, 2, 6 months for Qudrivalent. But it is recommended that subject who receive the 1st dose of Cervarix™ should complete the 3 dose course with Cervarix™ only.[18]

Route of Administration

IM injection in the deltoid/anterolateral aspect of thigh.

Side Effects

Local pain, swelling, redness and headache, myalgia, fatigue, fever are common for both vaccines. No serious side effects have been reported.[19]

With quadrivalent vaccines, the most common side effect reported is syncopal attacks. It should be prevented by giving it in lying down position and allowing her to continue in this position for 15 minutes before going home.[13]

Contraindications

Known hypersensitivity to any component of the vaccine. Relative contraindications are coagulation/bleeding disorder and pregnancy. However, in women who become pregnant before completion of the course, postpone the remaining doses till after pregnancy, but termination is not indicated.[13] Lactating women can receive HPV vaccine and continue breastfeeding as the vaccine is without live viral DNA.[18,19]

Storage

Both the vaccines should be stored at 2-8'c, should never be frozen.[18]

Efficacy

Bivalent: A recent Indian study group studied 330 subjects, showed 95% efficacy and high HPV 16 and 18 antibody titers (April 2010).[2,20]

Quadrivalent Vaccine

Latest studies by Amy Eva et al in April 2013 during a Swedish National cohort study from 2006 to 2010 involving 12,4000 girls shows 93% efficacy if vaccinated before 14 years of age.[22]

Controversies Surrounding the Vaccine

Whom to Vaccinate?

Age: Ideally, according to statement by SAGE in 2009, WHO supports that the most effective time to vaccinate is prepubertal and pubertal girls between 9 and 13 years (before 1st exposure to HPV), as they mount a stronger immune response than adults.[13] The same has been recommended by IAP, FOGSI and IMA.[13]

Mid-adult women: Sexually active mid adult women (24-45 years) also benefit from HPV vaccination, as very few have been exposed to all vaccine HPV types. The Future III study found the quadrivalent HPV vaccine to be 91% effective in reducing the combined incidence of HPV6/11/16/18 associated persistent infection, CIN among these women.[23]

Males: As of March 2012, HPVvaccine has also been studied in males by ACIP(Advisory committee on immunization), for prevention of genital warts.[13] Australia is the 1st country to approve the quadrivalent vaccine in males between 9 and 15 years. It is not yet licensed for use in males in India.[24]

Are Boosters Needed? (Duration of Immunity)

Available data show that long-term immune memory was induced, with anti HPV genometric mean titers after 7.3 years (for bivalent) and 5 years (for quadrivalent) remaining above those observed with natural infection.[2,25,26] As of now, no booster is recommended, but in times to come, the need of a booster will become clearer.

Is Prevaccination Screening for HPV Necessary?

No, PAP testing/antibody is not routinely recommended prior to vaccine at any age. However, mid adult women must be told of the benefits limited to protection against HPV genotype with which they have not been infected.[2]

Our views on Concerns for Universal Immunization with HPV Vaccine in India

The primary obstacle in India is financial, being a relatively costly vaccine. However, the same scenario we faced with hepatitis B vaccine, *H influenza* B vaccine, etc. a few years ago. Also, the economic burden of investigations and treatment of this dangerous morbid disease often goes underestimated. If we have a cervical cancer prevention program and the government purchases in bulk or Indian manufacturers are encouraged to manufacture the vaccine, the cost might become manageable.

Booster: It is unscientific to wait for longevity of the vaccine to be proved, at the most, we may need a booster in worst case scenario.

Safety: There were allegations in the media regarding the vaccine causing deaths of 4 girls in India during a multicentric trial to investigate the efficacy of 2 *vs* 3 doses of Gardasil™. But the causes of death have been scrutinized by ICMR and DGCI, all were satisfied that no deaths were related to the vaccine. To date, no deaths have been causally associated with HPV vaccination in India and globally.[27]

The Future Challenges—A Bumpy Road Ahead?

Cost and availability remain the main challenges for its routine use in India.

Also, more research regarding the need of boosters, safety and efficacy in mid adult women and males, the social and cultural taboos regarding a preventive vaccine in a preadolescent girl against an STD, etc. are needed, especially in our circumstances.

Mathematical models of cost effectiveness in Indian scenario are needed where outcomes are measured with ICER (increased cost effectiveness ratios) in units of quality adjusted life years (QALYs) gained.

CONCLUSION

HPV vaccination is the best available mode of cancer cervix prevention, even more in developing countries like India with limited access to healthcare. But till a more cost effective vaccine is available for use in India, we should continue regular cancer cervix screening program. The change has begun, and in the right direction and hopefully, it will not take too long before universal HPV vaccination is adopted for eligible females in India.

REFERENCES

1. Kaarthigeyan K. Cervical cancer in India and HPV vaccination. Indian J Med Paediatr Oncol 2012 Jan-Mar;33(1):7-12.
2. Shah RC. Prevention of cervical cancer-HPV vaccines. Pediatr Infect Dis 2009 July-Sept;1:134-145.
3. Bosch FX, de Sanjose S. Chapter 1: HPV and cervical cancer burden and assessment of causality. J Natl Cancer Inst Monogr 2003;313.
4. Yewale V, Choudhury P, Thacker N, editors. IAP guide book on immunization 2009-2011. Mumbai, Maharasthra: Indian Academy of Pediatrics; 2011. p. 88-93.
5. Singh N. HPV and cervical cancer—prospect for prevention through vaccination. Indian J Med Pediatr Oncol 2005;26(1): 20-23.
6. WHO/ICO Information centre on HPV and cervical cancer. Summary Report on HPV and Cervical cancer statistics in India 2007 [cited 2008 May 1].
7. Howley PM, Lowy DR. Papillomaviruses and their replication. In: Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, Roizman B, Straus SE, editors. Fields virology. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.
8. World Health Organization. HPV IARC monograph summary. Lancet Oncol 2005;6:204.
9. Dunne EF, Markowitz LE. Genital human papillomavirus infection. Clin Infect Dis 2006;43:624-629.
10. Carter JJ, Koutsky LA, Hughes JP, Lee SK, Kuypers J, Kiviat N, Galloway DA. Comparison of human papillomavirus types 16, 18 and 6 capsid antibody responses following incident infection. J Infect Dis 2000 Jun;181(6):1911-1919.
11. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet 2007 Sep 8;370(9590):890-907.
12. Castellsague X, Munoz N. Cofactors in human papillomavirus carcinogenesis. Role of parity, oral contraceptives, and tobacco smoking. J Natl Cancer Inst Monogr 2003;(31):20-28.
13. Cherry J, Demmler-Harrison GJ, Kaplan SL, Steinbach WJ, Hotez P. Feigin and Cherry's Textbook of Pediatric Infectious Diseases. Philadelphia, PA: WB Saunders; 2013. Chapter 5. p. 310-312.
14. Winer RL, Hughes JP, Feng Q, O'Reilly S, Kiviat NB, Holmes KK, Koutsky LA. Condom use and the risk of genital human papillomavirus infection in young women. N Engl J Med 2006 Jun 22;354(25):2645-2654.
15. Ferenczy A, Franco E. Cervical-cancer screening beyond 2000. Lancet Oncol 2001 Jan;2(1):27-32.
16. Huang CM. Human papillomavirus and vaccination. Mayo Clin Proc 2008 Jun;83(6):701-706.

17. Human papillomavirus laboratory manual. 1st ed. Immunization, Vaccine and Biological World Health Organization; 2009.
18. Indian Academy of Pediatrics Committee on Immunization (IAPCOI). Consensus recommendations on immunization. Indian Pediatr 2008 Aug;45(8):635-648.
19. Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER. Centers for disease control and prevention (CDC); Advisory committee onImmunization Practices (ACIP). Quadrivalent Human Pappilomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2007 Mar 23;56(RR-2):1-24.
20. Bhatla N, Suri V, Basu P, Shastri S, Datta SK, Bi D, Descamps DJ, Bock HL. Indian HPV Vaccine Study Group. Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine in healthy Indian women. J Obstet Gynaecol Res 2010 Feb;36(1):123-132..
21. Stanely M. Prevention strategies against the human papillomavirus: the effectiveness of vaccination. Gynecol Oncol 2007 Nov;107(2 Suppl 1):S19-S23.
22. Amy Eva, et al. 2003 (April). Swedish National Control study. (2006-2010).
23. Luna J, et al. Safety, efficacy and immunogenicity of quadrivalent HPV vaccine (Gardasil) in women aged 24-45. Presented at 24th International Papillomavirus Congress, November 3-9, 2007, Beijing [abstract PA1-04].
24. Schiller JT, Frazer IH, et al. HPV vaccines. In: Plotkin SA, Orenstein WA, editors. Vaccines. 5th ed. Philadelphia: Saunders; 2008. p. 243-277.
25. Frazer I. Correlating immunity with protection for HPV infection. Int J Infect Dis 2007 Nov;11 (Suppl 2):S10-S16.
26. Einstein MH, Baron M, Levin MJ, Chatterjee A, Edwards RP, Zepp F, Carletti I, Dessy FJ, Trofa AF, Schuind A, et al. Comparison of the immunogenicity and safety of Cervarix and Gardasil human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18-45 years. Hum Vaccin 2009 Oct;5(10):705-719.
27. Singhal SC. Human papilloma virus vaccines and current controversy. Indian Pediatr 2011 Mar;48(3):248-249.