REVIEW

# HPV and Cervical Cancer Epidemiology - Current Status of HPV Vaccination in India

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## Abstract

**Cervical cancer (CaCx) is the second most fatal cancer contributing to 14% of cancers in Indian females, which account for 25.4% and 26.5% of the global burden of CaCx prevalence and mortality, respectively. Persistent infection with high-risk human papilloma virus (HPV- strains 16 and 18) is the most important risk factor for precursors of invasive CaCx. Comprehensive prevention strategies for CaCx should include screening and HPV vaccination. Three screening modalities for CaCx are cytology, visual inspection with acetic acid, and HPV testing. There is no Indian national policy on CaCx prevention, and screening of asymptomatic females against CaCx is practically non-existent. HPV vaccines can make a major breakthrough in the control of CaCx in India which has high disease load and no organized screening program. Despite the Indian Government's effort to introduce HPV vaccination in the National Immunization Program and bring down vaccine cost, challenges to implementing vaccination in India are strong such as: inadequate epidemiological evidence for disease prioritization, duration of vaccine use, parental attitudes, and vaccine acceptance. This paper reviews the current epidemiology of CaCx and HPV in India, and the current status of HPV vaccination in the country. This article stresses the need for more research in the Indian context, to evaluate interventions for CaCx and assess their applicability, success, scalability and sustainability within the constraints of the Indian health care system.**

**Keywords:** Cervical cancer-India-prevalence-Papilloma virus vaccines-risk factors

*Asian Pac J Cancer Prev,* **17 (8)**, 3663-3673

## Introduction

Cervical cancer (CaCx) is the seventh most common cancer among humans and fourth most among females (Globocan, 2012a). Around 85% of the global burden of CaCx exists in less developed regions where it accounts for almost 12% of all female cancers. According to the World Health Organization (WHO) estimates, 5,28,000 new cases of CaCx were detected worldwide in 2012 with an estimated 2,66,000 deaths, accounting for 7.5% of all female cancer deaths. Age adjusted incidence rates (AAIR) varied between 4.4 per 100, 000 populations in low risk regions to 30 per 100,000 populations in high risk regions, and mortality rates between 2 to 20 per 100,000 populations. The overall 5 year cumulative prevalence (2008-2012) of CaCx in the world was 1547,000 cases. Globocan projection suggests that by year 2020, globally, the total number of new CaCx cases will increase to 6, 09,270 (by 15.4%) and number of deaths to 3, 15,727 (by 18.7%) (Globocan 2012b). Less than 50% of females affected by CaCx in developing countries survive more than 5 years, compared to 66% in developed countries (Pisani et al., 1999). Moreover, CaCx generally affects multiparous females in their early post menopausal years, resulting in most expected years of life lost (Franco et al., 2003). CaCx thus remains a critical public health problem that is second only to breast cancer in overall disease burden for females throughout the world (Parkin et al., 2002). Worldwide incidence and mortality patterns of CaCx are depicted in Figures 1 and 2 (Globocan, 2012a).

CaCx is caused by prolonged infection with Human Papilloma virus (HPV). HPV can be classified as high-risk or low risk based on the oncogenic potential of the various HPV genotypes. HPV types 16 and 18 are considered to be two highest risk varieties responsible for about 70% of all CaCx cases worldwide (Bosch et al., 1995; Wallboomers et al., 1999; I.A.R.C., 2007; Chaturvedi et al., 2008; WHO/ICO, 2010). Recognition of the central role of HPV in the aetiology of CaCx has led to development of prophylactic vaccines as a new means of CaCx prevention. Prophylactic vaccines for CaCx target HPV 16 and 18 and are considered to provide primary prevention (Adams et al., 2009; Farhath et al., 2013).

Despite evidence showing protective effect of HPV

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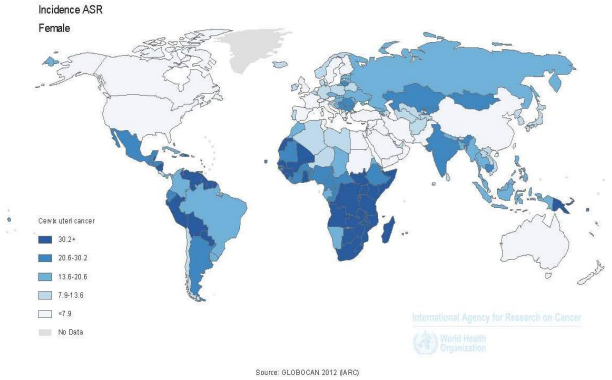


**Figure 1. Worldwide Age Adjusted Incidence Rates of Cervical Cancer (Globocan 2012)**

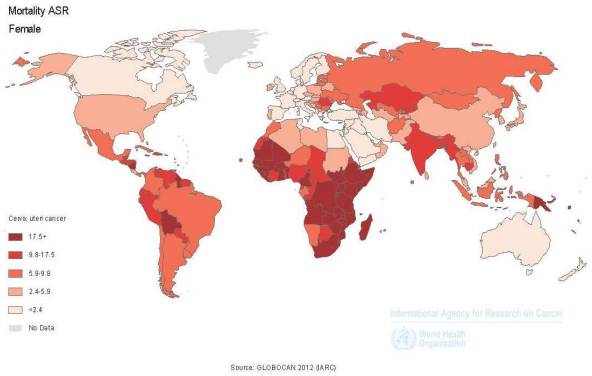


**Figure 2. Worldwide Age Adjusted Mortality Rates of Cervical Cancer (Globocan 2012)**

vaccine against CaCx, it is still a dilemma whether to introduce this vaccine as a routine in India and several other countries as in Sweden and Japan. In a recent HPV vaccine clinical trial from Sweden, one of the currently available HPV vaccines was reported to be associated with postural tachycardia syndrome (PoTS), supposed to be triggered by virus-like particles within the vaccine. While the European Union has still approved the vaccine for use among girls' above 9 years of age, Sweden and Denmark have raised concerns about vaccine safety and

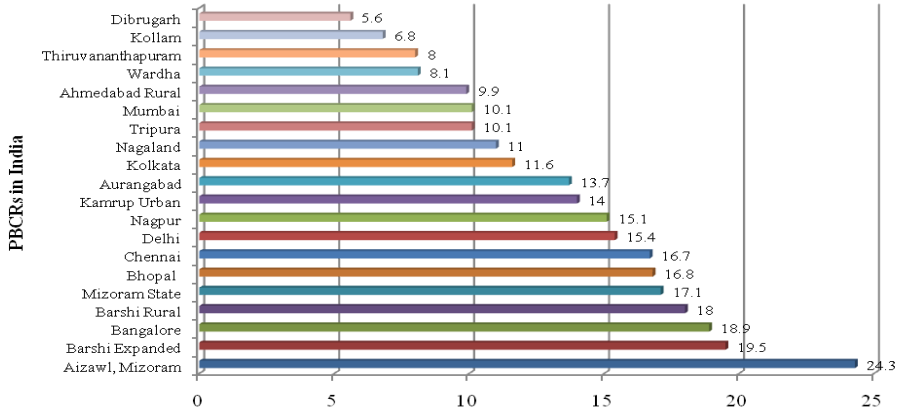


**Figure 3. Age Adjusted Incidence Rates Of Cervix Uteri-Females (Rate Per 100,000) in the Various Population Based Cancer Registries in India**

**Table 1. Key Differences and Characteristics of the Vaccines**

| Characteristics | GSK (Cervarix) | Merck (Gardasil) |
|---|---|---|
| Vaccine type | Bivalent-16/18 | Quadrivalent-16/18 |
| Adjuvant | ASO4 [500$\mu$g Al(OH)3 +50$\mu$g MPL] | Alum 225 $\mu$g [Al(PO4)] |
| Dosage | 0.5 ml | 0.5 ml |
| Administration route | Intramuscular | Intramuscular |
| Vaccination schedule | 0, 2, 6 months | 0, 1, 6 months |
| Antigen dose | VLP 16,18 (20, 20 $\mu$g) | VLP 16, 18, 6, 11 (40, 20, 20, 40 $\mu$g) |
| Previous trials | 560 vaccinees; 553 placebo | 768 vaccinees, 765 placebo |
| Trial countries | US, Canada, Brazil | US |
| Participant's age range | 15–25 years | 16–23 years |
| Eligibility criteria | No history of cervical lesions, few sexual partners | No history of cervical lesions, few sexual partners |
| Follow up period | Up to 54 months | Up to 36 months |
| Efficacy (% CI Intervals) | | |
| (a) Efficacy in preventing incident infections | 96.9 (81.3–99.9) | 91 (80–97) |
| (b) Efficacy in preventing persistent infections | 94 (63–99) | 89 (73–96) |
| (c) Efficacy in preventing cytological abnormalities | 97 (84–100) | Not published |
| (d) Efficacy in preventing pre-invasive lesions | 100 (42–100) | 100 (32–100) |
| Acceptable rate of adverse events | Yes | Yes |
| Serious adverse events | No | No |
| Immune response | | |
| (a) Seroconversion | 100% | 100% |
| (b) Antibody titers | 50-80 times natural infection | 10-20 times natural infection |

Japan has withdrawn its general recommendation for the HPV vaccine in 2013 due to concerns over the adverse reactions (Health Impact News, 2016).

WHO advises that epidemiology of the disease be known and be of sufficient importance to justify its prioritization, and that surveillance systems should be capable of assessing the impact of vaccine intervention following its introduction (WHO, 2015). CaCx surveillance in India is incomplete (Mattheij et al., 2012). The two main agencies in reporting incidence, prevalence and mortality of CaCx in India are the National Cancer Registry Program (NCRP) of India and the International Agency for Research on Cancer (IARC). The NCRP data cover only 7% of the Indian population and under-represent the rural, northern and eastern regions of the country. IARC's Cancer Incidence in Five Continents (C15) mainly represent west, south and central India and Globocan data are mainly derived from the west and south of the country. Although HPV prevalence is higher in CaCx patients (93.3%) than healthy patients (7.0%) and HPV types 16 and 18 are most prevalent in CaCx patients, population prevalence data are poor and studies highly variable in their findings (Mattheij et al., 2012). The aim of this paper is to review available information about epidemiology of HPV and CaCx and current status of HPV vaccination for CaCx prevention in India.

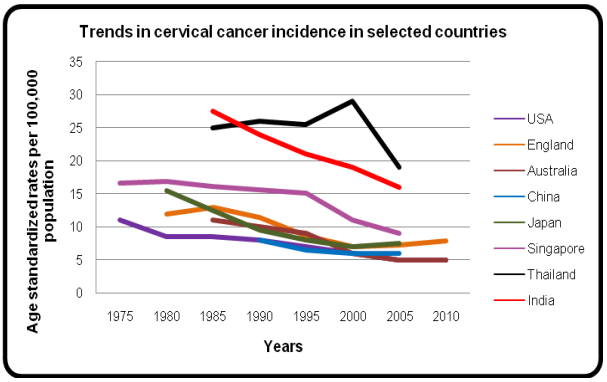


**Figure 4. Trends in Cervical Cancer Incidence In Selected Countries (1975-2010)**

## CaCx epidemiology in India

India contributes to 25.4% and 26.5% of the global burden of CaCx cases and mortality respectively (Kawana et al., 2009). According to the NCRP 2008-2009 data, CaCx is the second most prevalent cancer among females in India contributing to 14% of all cancers (NCRP, 2015). Among Indian females, the AAIR and age-adjusted mortality rate (AAMR) of CaCx are 27.0 and 15.2 per 100,000 populations respectively. CaCx is responsible for 25.9% of all new cancer cases and 23.3% of all cancer deaths among Indian females (Kawana et al., 2009).

The peak age of CaCx incidence in India is 55 to 59 years (Globocan, 2012c). AAIR of CaCx varies widely between and within states. Population based registries (PBCRs) in India report highest AAIRs (2009-2011, NCRP) from Mizoram (17.1), Aizawl district (24.3), Barshi Expanded (19.5), Bangalore (18.9), Bhopal (16.8), Chennai (16.7), Delhi (15.4) and Nagpur (15.1) (NCRP/PBCR, 2013). Hospital based cancer registries (HBCRs) in India report CaCx as the leading incident cancer site among females in Bangalore (27.3%), Chennai (25.4%), Guwahati (16.3%) and Chandigarh (18.4%) (NCRP/HBCR, 2013). Figure 3 shows the AAIRs of CaCx in various PBCRs in India.

The common histological type of CaCx found in ectocervix is squamous cell carcinoma (70-80%) and that in endocervix is adenocarcinoma (10-15%) (Satija, 2015). In absence of any organized CaCx screening program in India, opportunistic screening in various regions in India provide varying coverage for the population: 6.9% in the state of Kerala, 0.006% in Maharashtra and 0.002% in Tamil Nadu (Sankaranarayanan et al., 2007; Sankaranarayanan et al., 2009; Aswathy et al., 2012). Most cases (85%) present in advance stages and more than two-third (63%-89%) have regional spread at the

**Table 2. Epidemiological Studies from India Confirming High HPV Prevalence in Cervical Cancer Cases**

| Study Details | Study type | Study Area | HPV Types | Case-specific HPV prevalence | Other notes |
|---|---|---|---|---|---|
| Basu et al (2009) | Multi-center | | | | HPV-33* |
| | | South | HPV-16 & | 73.90% | 10.10% |
| | | North | HPV-18 | 78.30% | 2.20% |
| | | East | | 76.10% | 2.30% |
| | | Central | | 77.30% | 6.70% |
| Das et al (2013) | Hospital based | East | HPV-6/11 | 6% | |
| | | | HPV-16 | 88% | |
| | | | HPV-18 | 15% | |
| | | | HPV-31 | 4% | |
| | | | HPV-45 | 3% | |
| | | | HPV-58 | 1% | |
| | | | HPV-59 | 4% | |
| Franceschi et al (2005) | Community based | South | HPV | 16.90% | 74% samples among women with cervical abmormalities; 14% in those with no abnormalities. HR-HPV: 12.5% |
| Srivastava et al (2012) | Population based | North | HPV | 9.90% | Women symptomatic of cervical cancer |

* Alone or in combination

time of presentation (Dutta et al., 2013). Five year CaCx survival in Mumbai (PBCR, 1992-1994) was 47%. In the 1980s, Bangalore registry reported a 5 year survival of 38% (Nandakumar et al., 2009).

Though CaCx has been the one of the most important cancers females in India over the past two decades, time trend analyses have shown a steady decline in the disease incidence globally and in India (Figure 4). All urban PBCRs at Bangalore, Bhopal, Chennai, Delhi and Mumbai have shown a statistically significant decrease in AAIRs for CaCx (Nandakumar et al., 2009). A recent study from Mumbai assessing incidence over a 30 year period (1976 to 2005) reported a decreasing trend in CaCx similar to those reported in other South Asian countries (Dhillon et al., 2011) and other reports from India (Takiar and Srivastav, 2008; Chhabra et al., 2010). However, in Odisha, CaCx was the second most common cancer, with an increase in incidence of 3.1% from 2001 to 2011 (Hussain et al., 2012). It has been suggested that changing risk profiles-improved education, higher socioeconomic status, marriage at older age, delay in having the first child and lower parity may, in combination, partially explain changes in CaCx profile in India in the last decade.

Globocan projection estimates that the number of new CaCx cases in India will increase by 21% from 122844 in 2012 to 148624 in 2020. Similarly CaCx deaths will increase by 24% from 67477 in 2012 to 83370 in 2020 (Globocan, 2012b).

## Risk factors

Epidemiological studies suggest that sexual and reproductive factors, socio-economic factors (education and income), and other lifestyle factors such as smoking, diet and use of oral contraceptives all play an important role in occurrence of CaCx (Bahmanyar et al., 2012; Emeka et al., 2012; Liao et al., 2012; Schabath et al., 2012; Teixeira et al., 2012). A case control study carried out in North India on married females revealed age at marriage, socioeconomic status, education status and parity to be associated with CaCx with young age at marriage (Odds ratio (OR) 3.79) and low socioeconomic status (OR 3.81) to be independently associated with disease status (Capalash and Sobti, 1999). Another study from Chennai conducted on 205 CaCx cases and 213 matched controls demonstrated high parity (OR for >4 *vs.* ≤2 births=7.3, 95% CI 3.3, 16), a woman's report of her husband's extramarital sexual relationships (OR=10, 95% CI 5.1, 19.5) and early menopause (OR for <45 *vs.* ≥45 years=4.2, 95% CI 1.5, 11.9) to be significantly associated with invasive CaCx after controlling for HPV infection. However the study also detected HPV infection in all but one CaCx cases and in 27.7% of control females (OR=498, 95% CI 67.7, 999) (Franceschi et al., 2003).

## HPV and CaCx

Persistent infection with high-risk HPV (HR-HPV) is the most important risk factor for CaCx precursors and invasive CaCx (ICC) (Hariri et al., 2011). Several epidemiological studies have confirmed that one or more of the oncogenic HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 should be considered as a necessary cause for cervical neoplasia (Munoz et al., 2003). An international prevalence survey conducted in 22 countries by the IARC on HPV types confirmed that over 99% of the 1000 histologically confirmed ICCs were positive for HPV DNA. The most prevalent HPV types were HPV 16 (53%), HPV 18 (15%), HPV 45 (9%), HPV 31 (6%) and HPV 33 (3%). HPV 16 was the most common type in all geographical regions, followed by HPV 18 that was particularly, common in South-East Asia. The second set of studies evaluated by IARC were case-control studies carried out in 13 countries and included about 2000 cases and 2000 controls. Positivity, for any HPV DNA yielded OR of 70, (95% CI 57, 88) for CaCx. The association was very strong for both squamous cell (OR=74) and adenocarcinoma (OR=50) and for HPV 16 and 18 as well as for the less common HPV types (Munoz, 2000).

Most HPV infections are acquired through sexual contact and are asymptomatic. The lifetime risk of HPV infection for sexually active males and females is more than 50%. In sexually active females of less than 25 years of age, HPV prevalence is about 20%. At any given time, about 6.6% of females in the general population are estimated to harbour cervical HPV infection (Evander et al., 1995). Most females' immune system eliminate HPV infection spontaneously between 6 to 24 months including the high risk type viruses; however, for a very small proportion of females, infection may persist and can cause precancerous changes (Munoz et al., 2006). A study from Taipei, followed a large-scale community-based cohort for 16 years to investigate role of genotype-specific HPV persistence in predicting CaCx including invasive and in situ carcinoma. The study reported that HPV negativity was associated with a very low long-term risk of CaCx. Persistent detection of HPV among cytologically normal females greatly increased the risk. The report suggested that it is useful to perform repeated HPV testing following an initial positive test (Chen et al., 2006). HPV has thus often been described as an intermediate phenotype to CaCx (Sudenga and Shrestha, 2013) with studies suggesting that 6 month or 12 month HPV presence be considered as surrogate endpoints of progressive cervical disease (Syrjänen, 2011). HPV clearance rates may vary between oncogenic and non-oncogenic types of HPV. One study reported that non-oncogenic HPV infections cleared more rapidly than did oncogenic HPV infections (median, 180 days versus 224 days) (Goodman et al., 2008). A systematic review and meta-analysis of HPV persistence patterns worldwide also reported high-risk-HPV to be persisting longer (9.3 months) compared to low-risk HPV (8.4 months), with HPV-16, 31, 33 and 52 being most persistent (Rositch et al., 2013).

Viral oncogene deregulation, particularly integration of HR-HPV into the host genome plays a major role in HPV-related carcinogenesis as it is detected in 90% of all cervical carcinomas (Munoz et al., 2006). Several risk factors may contribute to this process. The mechanism of integration is not fully understood. However, points of chromosomal fragility are accessible to foreign DNA. It has been suggested that "an important intermediate

stage" in cervical carcinogenesis is characterized by transcriptionally silent HR-HPV integrants, which co-exist with viral episomes in infected cells (Pett and Coleman, 2007).

## HPV transmission

HPV is the most common sexually transmitted infection-through oral, vaginal, or anal sex with infected persons (CDC, 2015). Latent genital HPV infection can be detected in 5-40% of sexually active females of reproductive age (IARC, 1995). HPV can also be transmitted through mouth-to-mouth contact or by vertical transmission from infected mother to child during pregnancy (Rautava and Syrjanen, 2011). A study that examined transmission of HPV in 25 heterosexual, monogamous couples (25 men, 25 females), followed up over an average of 7.5 months, demonstrated that overall rate of HPV transmission from penis to cervix was 4.9/100 person-months, and was substantially lower than that from cervix to penis (17.4/100 person-months). Transmission between hands and genitals, as well as apparent self-inoculation events (primarily in men), were also observed (Hernandez et al., 2008).

## Prevention of HPV infection

Prevention of HPV infections has focused around minimizing cervical exposure to HPV and other cancer prevention methods. Behavioral risk factors considered in aetiology of HPV associated CaCx focus on the so-called 'male factor' such as having a large number of lifetime sexual partners, having concurrent partners and sex with prostitutes (Brinton et al., 1989). Several strategies have been suggested that are effective for prevention of any sexually transmitted disease and can help reduce risk of CaCx. These include counselling messages, male circumcision, selective choice in the number of sexual partners and delaying first intercourse and first full-term pregnancy. Micronutrients and supplements (available in dark green and deep yellow vegetables, Vitamins A and E) have been suggested to reduce risk of HPV infection, persistence, progression, and regression (Harper and Demars, 2014).

A few case-control studies CaCx have reported a protective effect from use of barrier methods of contraception (Celentano et al., 1987; Parazzini et al., 1989; Hildesheim, 1990). Two of these have attributed the protective effect to spermicides (Celentano et al., 1987; Hildesheim, 1990). There is very limited evidence for protective effect of condom use on HPV infection at population levels. (Franceschi et al., 2002). However, circumcision was associated with a decreased risk of HPV infection in men. Monogamous women whose male partners had six or more sexual partners and were circumcised had a lower risk of CaCx than women whose partners were uncircumcised (adjusted OR, 0.42; 95% CI 0.23 to 0.79 (Castellsagué et al., 2002).

Comprehensive HPV prevention strategies, mainly those geared at preventing CaCx should include screening and vaccination when affordable. Pap smear screening, which identifies cytological abnormalities of the cervical transformation zone, has helped reducing CaCx incidence and mortality rates by 80% in developed countries (Miller et al., 2000). Prophylactic vaccines against HPV, offer excellent hope of controlling HPV infection. A vaccine that protects against HPV types (16, 18, 31 and 45, responsible for causing 80% of CaCxs) has the potential to prevent a large fraction of CaCx cases worldwide.

## Prophylactic HPV Vaccine

HPV vaccines that prevent against HPV 16 and 18 infections are now available and have the potential to reduce incidence of cervical and other anogenital cancers (WHO/ICO 2010). Two vaccines licensed globally are also available in India; a quadrivalent vaccine, Gardasil (Sanofi Pasteur MSD/Merck) and a bivalent vaccine, Cervarix, (Glaxo Smith Kline). Both current commercially developed vaccines consist of recombinant proteins of the LI capsid of HPV 16 and 18 viruses which self assemble to form virus like particles (VLPs), combined with an adjuvant. VLPs are HPV type specific, similar in shape and size to the HPV virion, but do not contain viral DNA, and therefore non-infectious and non-oncogenic (Dochez et al., 2014). In addition, each vaccine has its own adjuvant used to promote durability of immune response (Harper and Demars, 2014). The key differences and characteristics of the vaccines are summarized in Table 1. Both HPV vaccines have been demonstrated to be safe, and very effective in preventing HPV-associated CaCx. Local reactions reported include pain, swelling and redness, but symptoms usually last for only a short duration. Systemic adverse reactions include fever, headache, myalgia, nausea and dizziness which too last for short periods. The vaccines can be safely administered along with other pediatric and adolescent vaccines. The HPV vaccines have been proven to be safe, providing long-term protection against primary infection with HPV vaccine types and moderate degree of cross-protection against some HPV non-vaccine types (Lehtinen and Paavonem, 2004).

## Epidemiology of HPV in India

Information on HPV epidemiology in India comes in mostly from research studies in selected locations in India. A meta analysis of nine epidemiological studies from India conducted on a total of 558, 52, 52 and 3061 females with ICC, high-grade squamous intraepithelial lesions (HSIL), low-grade squamous intraepithelial lesions (LSIL) and normal cytology/histology respectively showed an overall HPV prevalence of 94.6%, 86.5%, 65.4% and 12.0% in females with ICC, HSIL, LSIL and normal cytology/histology, respectively (Bhatla et al., 2008). The most common HPV types reported were (in descending order) HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. Estimated HPV-16/18 positive fraction was 78.9% in females with ICC (87.7% in North and 77.2% in South India). There was no statistically significant difference in overall HPV prevalence in CaCx between North and South India (P=0.063). However, HPV- 16 and 45 were more prevalent in North India compared to south (P=0.018 and

0.013, respectively), while HPV-35 appeared to be more prevalent in South India compared to north (P=0.033). Overall HPV prevalence in India was similar to high-risk areas in Latin America, but lower than that observed in some parts of sub-Saharan Africa (Clifford et al., 2005).

Table 2 shows the results from various Indian epidemiological studies that have confirmed high HPV prevalence in CaCx cases. Overall, HPVs associated with CaCx have been found in 6%-88% of females with CaCx in India (Arora et al., 2005; Franceschi et al., 2005; Sowjanya et al., 2005; Bhatla et al., 2008; Basu et al., 2009; Dutta et al., 2012; Srivastava et al., 2012; Vinodhini et al., 2012; Basu et al., 2013; Das et al., 2013; Sarma et al., 2015). Hospital based studies conducted on CaCx patients in south India confirmed HR-HPV types in majority of the samples (Sowjanya et al., 2005; Vinodhini et al., 2012). Population prevalence of HPV and cervical intraepithelial neoplasias (CIN) is an important indicator to judge disease burden in the community, to monitor performance of CaCx screening program and assess impact of HPV vaccination program. A case-control study in a hospital in Chennai found 23 different HPV types among 190 of 191 CaCx cases. HPV infection of any type was associated with a 498-fold increased risk for CaCx in this study (Bhatla et al., 2008). Pooled results from cross-sectional CaCx screening studies in eastern India showed an age-standardized HPV prevalence of 6% among unscreened women aged 30 -45 in eastern India (Basu et al., 2013). Similar results were reported from a New Delhi based cross-sectional study (Bhatla et al., 2008).

Infections with multiple HPV types are associated with a significantly increased risk of high grade neoplasia as compared with single infections (Cuschieri et al., 2005; Herrero et al., 2005). A study conducted among CaCx patients from northeast India reported multiple HPV infections to be 13% among subjects ≤ 18 years age and 22% among subjects ≥ 18 years age at first pregnancy; 23% subjects with irregular menstruation showed multiple HPV positivity (Das et al., 2013). Similar findings were reported from other studies in northern and southern parts of India (Franceschi et al., 2005; Bhatla et al., 2008; Vinodhini et al., 2012).

Unlike most populations in developed countries, HPV prevalence is generally constant across age groups in India, with no clear peak in young females (Datta et al., 2005; Sankaranarayanan et al., 2008). In the Osmanabad district study, the prevalence of HR-HPV types in the 30-39, 40-49 and 50-59 age groups were 9.8%, 10.4% and 12.2%, respectively (Sankaranarayanan et al., 2005). In a multicentre cross-sectional study in India, these were 7.0%, 6.8% and 7.5%, respectively (Sankaranarayanan et al., 2004). Also the population-based study in Dindigul, which included a broad age range of females 16-25 years, did not find any peak prevalence in younger age group (Franceschi et al., 2005). Low clearance of incident infections, and underrepresentation of teenagers in study samples have been stated as factors responsible for the constant, steady prevalence of HPV infection in different age groups in India.

Co-existing sexually transmitted infections (STI) including HIV have been considered as important co-factors for carcinogenesis induced by HPV. Several cross-sectional epidemiological studies in India documented high HR-HPV prevalence among HIV infected females which increased their persistence due to immune-suppression. Studies conducted from western and southern India report a HR-HPV prevalence between 35% to 41% among HIV affected females (Peedicayil et al., 2009; Mane et al., 2012; Joshi et al., 2014; ) compared to 20% and 25% among females from the northern and eastern parts of the country (Sarkar et al., 2008; Aggarwal et al., 2012). HPV prevalence was also high among female sex workers (72.2%), and injectable drug users (73.4%). Prevalence of cervico-vaginal infection with Trichomonas vaginalis and syphilis is also higher among HPV positive females compared to HPV negative females (Ghosh et al., 2012).

## HPV Vaccination and CaCx Screening in India

Three screening modalities for CaCx are cytology, visual inspection with acetic acid (VIA), and HPV test. In a cost-effectiveness study of different cervical screening approaches in India and other developing countries, screening females once in a lifetime, at the age of 35 years, with a one- or two-visit screening strategy involving VIA or HPV testing reduced lifetime risk of cancer by approximately 25-36% and cost less than 500 US dollars per year of life saved (Goldie et al., 2005). However, such screening practices for CaCx are inconsistent in India. Though effective screening tests such as the Pap smear are able to detect CaCx at its early stages, use of Pap smear as a sole indicator for the disease has limitations. The cytological interpretation becomes faulty if the smear is taken from an area that was inflamed; a situation frequently encountered among females from low socio-economic background. A meta-analyses indicated that average sensitivity of Pap cytology to detect CIN or ICC is 51% and its average specificity is 98%. High false negative rates are often attributed to slide interpretation errors, poor sample collection and slide preparation (Nanda et al., 2000). Also notification of results to females as well as visits required for cytologic screening pose programmatic and logistic challenges (Denny and Sankaranarayanan, 2006). Hence in a scenario of infrequent screening, screening with a test of high sensitivity may provide greater reassurance, that potential disease has not been missed in females who screened negative.

The newer test detecting HPV DNA was used for screening at various places in India, with reported sensitivity varying between 45.7% and 80.9% for detection of CIN grade 2 or worse (Sankaranarayanan et al., 2004). HPV testing is expensive and requires sophisticated laboratory infrastructure. It is an irony that middle and high socioeconomic females, who can afford HPV screening by molecular techniques, require it the least, owing to low prevalence of HPV in their social strata. An index study has identified illiterate females and those from rural and low-socioeconomic background to be at a greater risk for HPV (Aggarwal et al., 2009).

There is no organized cervical cancer screening

program and no national policy for CaCx prevention in India, and screening of asymptomatic females is practically non-existent. Beyond research studies and some demonstration projects and provincial efforts in selected districts, there are no serious efforts to introduce population-based screening by public health authorities in almost the entire country.Immunization against HPV is a promising means of protecting females against CaCx and a management option in primary prevention of the disease. Both Gardasil and Cervarix HPV vaccines have 100% efficacy against persistent HPV 16/18 infections (Adams et al., 2007). Analyses from current phase 2 clinical control trials show 100% sero-conversion among vaccinated subjects against persistent 16/18 HPV infections. Observed antibody titers were 10-80 times higher than observed in natural infection.

## Current Status of HPV Vaccination in India

HPV vaccines can make a major breakthrough in the control of CaCx for countries like India with high disease load. . Importance of vaccination against HPV is demonstrated by the recommendation of The US Advisory Committee on Immunization Practices that girls and females between the ages of 9 and 26 years should receive the quadrivalent HPV vaccine (CDC, HPV recommendations, ACIP, 2015). The WHO position paper on the HPV vaccine also recommends that the vaccine should be a part of national immunization programs worldwide. WHO recommends that HPV vaccine be given between ages of 9 and 13 years, prior to a girl's first coitus. However, they acknowledged nationwide administration of HPV vaccine would only be cost effective in countries that have high gross domestic products (WHO, HPV vaccines, 2015). The Indian Academy of Pediatrics Committee on Immunization (IAPCOI) also recommends offering HPV vaccine to all females who can afford the vaccine (Singhal, 2008).

In an effort to prepare health systems and communities in India to accept and embrace HPV vaccination, a population-based post-licensure study of HPV vaccine for prevention of CaCx titled "HPV Vaccine: evidence for Impact", was carried out by PATH (Program for Appropriate Technology in Health), an international NGO, in collaboration with the respective State Governments and the Indian Council of Medical Research (ICMR) in Districts of Khammam in Andhra Pradesh and Vadodara in Gujarat. PATH, a part of, a Global Project funded by Bill and Melinda Gates Foundation aimed at generating evidence that would enable policy makers to decide on possible public sector introduction and financing of the HPV vaccine. Besides India, the project was also carried out in Peru, Uganda and Vietnam. The study's first phase was a formative research designed to guide development of a vaccine delivery strategy, a communications strategy (for outreach to communities), and an advocacy strategy (for outreach to policymakers). The formative research in India reported that policymakers, health care providers, parents, and adolescents in both states would likely accept vaccination against cancer of CaCx, as long as it is safe, effective, affordable, and accessible. The findings from India were to provide insight into complexities of vaccine introduction in a country with a population of more than one billion people. As a next step, these strategies were implemented and evaluated through a demonstration project in each country. This involved vaccinating all eligible girls in 10-14 years age-groups. This part of the project was completed (all the 3 doses) in the Andhra Pradesh (13,791 girls), but in Gujarat only 9,637 out of 10,259 girls had received the third dose of the vaccine. The findings from the demonstration project were to serve as an evidence base for governments to decide when and how to incorporate HPV vaccination into a comprehensive CaCx prevention program (Final report of Committee, Govt. of India, 2011).

The PATH project, launched in 1996, was suspended in March, 2010 when a report on deaths of some girls who had received the HPV vaccine under the PATH project was published in the local newpapers. The matter was taken up by the Parliamentary Department-Related Standing Committee on Health & Family Welfare on Demand-for Grants of the Department of Health Research and an enquiry committee was constituted by the Govt. of India vide notification No.V.25011/160/2010-HR dated 15th April, 2010, to enquire into "Alleged irregularities in the conduct of studies use HPV vaccine" by PATH in India. The Committee reviewed all seven deaths (five deaths from AP in the Gardasil group and two deaths in Gujarat from Cervarix group), and observed that there was no common pattern to the deaths that would suggest they were caused by the vaccine. In fact, in cases where there was an autopsy, death certificate, or medical records, the cause of death could be explained by factors other than vaccine. The background death rates among girls 10-14 years of age in both Andhra Pradesh and Gujarat did not show any increase rate (Final report of Committee, Govt. of India, 2011). The report of the enquiry committee was submitted to the ICMR and Drug Controller General of India (DCGI). The vaccines continue to remain as licensed products approved by the DCGI.

According to a recently published report, the Government of India has decided to move forward and has asked its technical advisory group on immunization to look into safety and efficacy of HPV vaccine for its introduction in the National Immunization Program. While, the vaccine is not available in the government sector, it is currently widely used by private practitioners (The Asian Age, 2015). India has recently received $500 million aid from GAVI (The Global Alliance for Vaccines and Immunization), for rolling out a range of vaccines, which also includes the HPV vaccine. However, the HPV vaccine is not included in India's current 2013-2017 plan but may be considered in the next planning period, subject to the National Technical Advisory Group on Immunization (NTAGI) recommendation and political approval as the anti-vaccine movements against HPV vaccine are still active in country (Gavi, 2015).

## Issues with HPV Vaccination in India

*A) Health priorities and vaccine cost*

Though the advent of HPV vaccines has advanced hopes of CaCx eradication in the future, introduction of HPV vaccination into the immunization program in India has been debated strongly. India has several other health priorities and inclusion of HPV vaccine in the government program may not be among the top in the list. Public sector spending in health is very low (WHO, Weekly epidemiology report, 2009), which make it difficult for the government to independently take on the task of introducing such an expensive vaccine in the national immunization program without external support. Moreover, with an annual per capita income of INR 38,084 (2008-09), the average Indian cannot afford to pay for the HPV vaccine which costs INR 12,000 for 3 doses (2009 price) (Farhath et al., 2009). Health priorities also vary in different states in India. Legislative issues arise because health choices for states (not under central government) and health prioritization are not uniform for the country for political reasons (Ramanathan and Varghese, 2010).

*B) Epidemiological evidence on CaCx*

Epidemiological data on HPV and CaCx in India are inconsistent. The NCPR reports, Cancer Atlas, C15 and Globocan cancer data derive data from overlapping resources and under-represent some of the regions in India (Mattheij et al., 2012). A recent report on cancer epidemiology in India inferred that most common fatal cancer in females aged 30-69 years is CaCx with burden of 17.1% (Dikshit et al., 2012). Another study stated the highest age-adjusted mortality rate for CaCx to be 7.7 per 100,000 (Mattheij et al., 2012). Earlier evidence suggests this mortality rate to be around 65.5 in a rural area (Rastogi et al., 2008). Such large variance in range of estimates for disease burden varying from a low of 7.7 to a high of 65.5 pose significant problems for policy makers to estimate actual disease burden for implementation of CaCx vaccine program. Most cancer registries in India show that incidence rates of CaCx are significantly declining in India (years 1982 to 2005) (Dhillon et al., 2011). Other studies have projected a 46% decline in CaCx by 2015 (Swaminathan et al., 2011). Currently available surveillance data do indicate quite clearly that HPV infection and associated CaCx risk in India is a substantial burden and clear health priority which can be addressed now by a combination of screening and vaccination.

*C) Vaccine and duration of protection*

The aim of HPV vaccines is to prevent CaCx in the long run, but because of the long history of disease (average of about 20 years) it may take a couple of decades for the effect to be noted (WHO, HPV vaccines, 2015). Though most models assume that the HPV vaccines provide a 10 year or lifetime protection, there is no evidence on how many doses of vaccine are required for lifetime protection.. Studies, including those which have estimated cost effectiveness, having assumed three doses of the vaccine along with screening as sufficient to prevent lifetime occurrence of CaCx, showed an effective reduction of 63% of the lifetime risk (Diaz et al., 2008). The quadrivalent vaccine has been found to offer significant protection against HPV-16 or HPV-18 after follow-up for three years following the initial dose (FUTURE II Study Group, 2007). Hence a need for long-term follow-up is required to determine duration of actual protection.

*D) Vaccine acceptance*

Experts have pointed to the difficulty in creating acceptability for vaccine as it is going to generate several debates situated in moral and cultural contexts in India. This is primarily because HPV vaccine targets a sexually transmitted infection (STI) in female adolescents and young adults who have the potential to be stigmatized. A survey in Eastern India among educated urban men and females (n=121), with at least one girl child and belonging to middle or high socio-economic group, revealed that 72% had never heard of HPV. Only 46% of parents were in favor of vaccinating their daughters against an STI; however, after going through a brief information sheet about the HPV vaccine, 80% agreed to vaccination (Basu and Mittal, 2011). The social structure in India demands that parental consent be taken for vaccinating adolescent girls and young females who are the primary targets. Parents' attitude to vaccines in turn will depend on their awareness, knowledge and perceptions regarding vaccines and their outlook towards their children's sexuality and certain personal beliefs. This will also significantly influence willingness of health policy makers, health care providers, parents, and adolescent and young girls to receive vaccination.

*E) Vaccines and CaCx screening*

Vaccines cannot substitute screening for CaCx. There are several challenges for the vaccine to be successfully used to control this largely preventable disease, including endorsement by governments and policy makers, vaccine prices, education at all levels and overcoming barriers to vaccination. Hence, the best prevention strategy should consider both vaccination of adolescents before initiation of sexual activity and screening for surrogate markers of CaCx-such as precancerous lesions-and treating them.

## Conclusion

The WHO position paper states: "WHO recognizes the importance of CaCx and other HPV-related diseases as global public health problems and recommends that routine HPV vaccination should be included in national immunization programmes, provided that: prevention of CaCx or other HPV-related diseases, or both, constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost effectiveness of vaccination strategies in the country or region is considered". Tiered pricing with the help of WHO, international organizations, and other funding sources might make HPV vaccination in India possible. However, more research is needed in the Indian context, to evaluate interventions for CaCx and assess their applicability, success, scalability and sustainability within the constraints of the Indian health care system.

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