Community Dental Health (2015) **32,** 117–128
Received 28 May 2014; Accepted 23 January 2015

doi:10.1922/CDH_3460Chattopadhyay12

Human papillomavirus and oral cancer: a primer for dental public health professionals

A. Chattopadhyay[1], D. Weatherspoon[2] and A. Pinto[3]

Public Health, Dubai Healthcare City, Dubai, UAE; Department of Pediatric Dentistry, University of Illinois at Chicago, College of Dentistry, USA; Department of Oral and Maxillofacial Medicine and Diagnostic Sciences, School of Dental Medicine, Case Western Reserve University, Cleveland, OH, USA

There is strong evidence for causal association between human papillomavirus (HPV) and cervical cancer, evidence of association of HPV and oropharyngeal cancer is beginning to mount. ***Objectives:*** To review the HPV-oral cancer literature for a comprehensive assessment of the issues involved. ***Methods****:* Literature search conducted using PubMed, Google Scholar and Google search engine. ***Results****:* Both available HPV vaccines are efficacious and safe although expensive. Policy for mandatory HPV vaccination for cervical prevention is mired in political issues stemming from negative cost-effectiveness balance. Dental professionals are not ready to discuss the role of HPV vaccine in cancer prevention. This review discusses the impact of HPV on cervical cancer, transmission of HPV among humans, impact of HPV in oral health, and its plausible role in oral and oropharyngeal cancer, prevention of HPV transmission, available vaccines against HPV, testing, cost, policy and use of HPV vaccines internationally and dentists readiness related to HPV associated health communication. ***Conclusions:*** Given the mounting literature on the association between HPV and oropharyngeal cancer, the dental community must be prepared to answer patients' HPV-related questions and to educate patients about the role of HPV as a risk factor for oral and oropharyngeal cancers.

Key words: *oropharyngeal neoplasms, vaccines, papillomavirus vaccines, human papillomavirus, public health, dentists, cost-benefit analysis, decision making*

Introduction

Dental health care personnel including dental public health professionals should have a basic understanding of Human Papillomavirus (HPV), and be knowledgeable about the role of HPV in carcinogenesis and the association of HPV with oropharyngeal cancers. This knowledge will enable prompt referral of patients with suggestive symptoms for appropriate assessment. "*Dental professionals can play an important role in increasing patients' knowledge about HPV and oropharyngeal cancers*" (Cleveland *et al.*, 2011).

HPV infection has attracted a great deal of attention as prolonged infection with certain types of HPV can cause cervical cancer. It has been suggested that HPV may also play a role in some other types of cancers, such as anal, vaginal, vulvar, penile, oral, oropharyngeal, and squamous cell skin cancers (NCI, 2014). HPVs can be classified as high-risk or low risk viruses based on their oncogenic potential. HPV types 16 and 18 are considered to be the two high risk varieties of the virus and are responsible for about 70% of all cervical cancer cases worldwide (Chaturvedi *et al.*, 2008; IARC, 2007; Sturgis and Cinciripini, 2007; Walboomers *et al.*,1999; WHO/ICO, 2010).

HPV-16 and HPV-18 have been detected in 20–30% of oral squamous cell carcinomas (Chang *et al.*, 1991). Studies in the US have found that about 7% of people have HPV in their oral cavity, but only 1% of have the type of oral HPV that is found in oropharyngeal cancers (type 16). Oral HPV is about three times more common in men than in women (CDC, 2014a).

This review will discuss the impact of HPV on cervical cancer, transmission of HPV among humans, impact of HPV in oral health, and its plausible role in oral cancers (ICD-10 codes: C00-C06) and oropharyngeal cancers (ICD-10 codes: C09-C10) (Warnakulasuriya, 2009), prevention of HPV transmission, available vaccines against HPV, testing, cost, policy and use of HPV vaccines internationally and dentists readiness related to HPV associated health communication. We have used the term "*oral cancer*" to indicate cancer of the oral cavity including the tongue, whereas "*oropharyngeal cancer*" indicates cancer of the oropharynx.

HPV Structure

The National Cancer Institute, Bethesda, MD, USA (2014), has defined HPV as a type of virus that can cause abnormal tissue growth (for example, warts) and other changes to cells. They are classified by the molecular similarity of their genetic material and are assigned a genotype number. HPV has over 200 varieties (genotypes). HPVs are circular, non-enveloped double stranded DNA viruses and are small, about 55 nm, with about 8,000 base pairs in their genome. They belong to the family Papillomaviridae that has two late transcription regions and seven early transcription regions as well as regulatory regions. The first late region, L1, produces a protein that represents the outermost coat of the virus (Bonnez *et al.*, 2009). Though these viruses have never been cultured in vitro, they have been characterized by molecular methods. HPV has 16 identified genera with

Correspondence to: Amit Chattopadhyay, Mohammad Bin Rashid Academic Medical Center, District 1, IBN Sina Building (No.27) Block C Ground Floor, Dubai Healthcare City, Dubai, UAE. Email: amit.chattopadhyay@dhcc.ae

most having several species (α, β, γ, δ, ε, ζ, η, θ, ι, κ, λ, μ, ν, ξ, ο, π). α-HPV infect mostly mucosa membranes (sometimes skin); whereas β-HPV and γ-HPV infect skin (IARC, 2007). Recent epidemiological data demonstrate more frequent association of specific species of α-HPV with higher risk of cancer. Low cancer risk HPV types include: 6, 11, 40, 42, 43, 44, 53, 54, 61, 72, 73 and 81; whereas high risk types include: 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and 70 (Burd, 2003).

HPV and Cervical Cancer

Persistent infection with high-risk HPV is the most important risk factor for cervical cancer precursors and invasive cervical cancer (Hariri *et al.*, 2011). Most HPV infections are acquired through sexual contact and are asymptomatic and most viruses are cleared within 6 to 24 months including the high-risk type viruses. For example, a study from Taipei, followed a large-scale community-based cohort for 16 years to investigate the role of genotype-specific HPV persistence in predicting cervical cancer including invasive and *in situ* carcinoma. The study reported that HPV negativity was associated with a very low long-term risk of cervical cancer. Persistent detection of HPV among cytologically normal women greatly increased risk. The reports suggested that it is useful to perform repeated HPV testing following an initial positive test (Chen *et al*., 2011). HPV clearance rates may vary between oncogenic and non-oncogenic types of HPV. For example a study from Canada reported that the monthly clearance rate was higher for nononcogenic types than for oncogenic HPV infections (12.2%, 95%CI 9.6,15.4 vs. 9.5%, 95%CI 7.5,11.9) (Franco *et al.*, 1999).

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 (Pett and Coleman, 2007). Several risk factors may contribute to this process. The mechanism of integration is not fully understood. However, there 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* (Reviewed in Pett and Coleman, 2007)… *Using crude incidence rates, cervical cancer ranks as the 3rd most frequent cancer in women in the World, and the 2nd most frequent cancer among women between 15 and 44 years of age. After age-standardization, cervical cancer ranks as the 2nd most frequent cancer in women in the world*" (WHO/ICO 2010). Knowledge regarding cause and pathogenesis of cervical cancer, especially its association with HPV is expanding rapidly - persistent infection with one of about 16 high risk genotypes of carcinogenic HPV causes almost all cases of cervical cancer (Burd, 2003; Schiffman *et al.*, 2001).

According to World Health Organization (WHO) estimates, the world has a population of 2.3 billion women aged 15 years and above who are at risk of developing cervical cancer: about 1.8 billion (78%) in developing regions and 0.5 billion in developed regions. WHO estimates indicate that "*every year 529,409 women are diagnosed with cervical cancer and 274,883 die from the disease*." Furthermore, "*about 11.4% of women in the general population are estimated to harbor cervical HPV infection at a given time, and 70.9% of invasive cervical cancers in the world are attributed to HPV types 16 and/or 18*" (WHO/ICO, 2010).

Factors that may increase the risk of developing cancer following a high-risk HPV infection include smoking; having a weakened immune system; having many children (for increased risk of cervical cancer); long-term oral contraceptive use (for increased risk of cervical cancer); poor oral hygiene (for increased risk of oropharyngeal cancer); and chronic inflammation (Schiffman *et al.*, 2001).

HPV Transmission

HPV is the most common sexually transmitted infection - through oral, vaginal, or anal sex with infected persons despite condom use because HPV can infect areas that are not covered by a condom (CDC, 2010a; 2014a;b).

HPV can also be transmitted through mouth-to-mouth contact or vertical transmission from infected mother to child during pregnancy (Rautava and Syrjänen, 2011). A recent sudy demonstrated that the overall rate of HPV transmission from the penis to the cervix was 4.9/100 person-months, which was substantially lower than that from the cervix to the penis (17.4/100 person-months). Transmission between the hands and genitals, as well as apparent self-inoculation events (primarily in men), were also observed (Hernandez *et al.*, 2008). There is growing evidence that HPV-related cases, particularly oropharyngeal cancers, are associated with sexual behavior including the practice of oral sex (WHO/ICO 2010). A recent study examined HPV type concordance between couples to provide evidence for oral - genital transmission of HPV. The study found that oral - oral concordance of HPV type between couples was low, but concordances of oral - genital and genital - genital HPV types were higher. HPV type concordance of male oral HPV infection with their partners' vaginal HPV infection was also reported to be high (Vogt *et al.*, 2013).

Oral HPV

HPV carriage in oral mucosa is very low at only about 1.9% of children, 3-5% of adolescents and 5-10% of adults (D'Souza *et al.*, 2009; Smith *et al*., 2007; Summersgill *et al.*, 2001). About 5.1% adult women who were genital HPV-negative showed a positive HPV-polymerase chain reaction (PCR) in the oropharynx whereas among those who tested positive for a genital HPV infection, 54.3% had a positive HPV-detection in the oral cavity and oropharynx (Meyer *et al.,* 2014). However, a recent systematic review assessing studies of HPV prevalence in oral cavity among women with cervical HPV infection found the prevalence of oral HPV infection to vary between 2.6% to 50% in different studies and the prevalence of oral/genital HPV type-specific concordance was 27.0% (Termine *et al.,* 2011).

Topography of the oral mucosa may impact the distribution of HPV within sub-sites in the oral cavity being more predominant in the vermilion border, labial commissures and hard palate. A recent study reported that "*distribution of positive HPV findings on the oral mucosa seems to be more associated with a particular anatomical site than the diagnosis itself*" (Mravak-Stipetić *et al.*, 2013). Another recent study demonstrated that prevalence of oral HPV infection varied with self-rated poor oral health, possibility of gum disease, reported use of mouthwash to treat dental problems in the past week, and higher number of teeth lost (Bui *et al.*, 2013).

A recent report examining prevalence of HPV in various sites found prevalence estimates to be 45·8% (95%CI 38·9,52·9) for oropharynx, 22·1% (16·4-28·3) for larynx (including hypopharynx), and 24·2% (18·7-30·2) for oral cavity (highest prevalence in sub-sites: tonsils (53·9%, 95%CI 46·4,61·3)). Furthermore, HPV16 accounted for 82·2% (95%CI 77·7,86·4) of all HPV DNA positive cases (Ndiaye Ndiyae *et al*., 2014). The authors further reported that percentage positivity of p16(INK4a) positive cases in HPV-positive oropharyngeal cancer cases was 86·7% (95%CI 79·2,92·9) and of E6/E7 mRNA positive cases was 86·9% (73·2,96·8). Their estimate of HPV attributable fraction in oropharyngeal cancer defined by expression of positive cases of E6/E7 mRNA was 39·8% and of p16(INK4a) was 39·7% (Ndiaye *et al*., 2014).

Of the known HPV types, at least the following 25 types have been detected in oral lesions: 1, 2, 3, 4, 6, 7, 10, 11, 13, 16, 18, 31, 32, 33, 35, 40, 45, 52, 55, 57, 58, 59, 69, 72, 73 (Syrjänen, 2003). Table 1 outlines types of HPV that are commonly associated with oral diseases such as oral warts (verruca vulgaris, squamous cell papillomas, condyloma acuminate), focal epithelial hyperplasia and also with oral leukoplakia with dysplastic change (Syrjänen, 1987; Syrjänen, 2003), lichen planus, leukoplakia, erythroplakia, oral cancer and oropharyngeal cancer (Grce and Mravak-Stepetic, 2014).

Table 1. HPV Types associated with oral diseases (Chang *et al.*, 1991; Grce and Mravak-Stepetic, 2014; Shetty *et al.*, 2005)

HPV Type	*Oral Diseases*
1	Verruca vulgaris
2	Verruca vulgaris
4	Verruca vulgaris
6	Squamous cell papilloma, Condyloma acuminatium, Lichen planus, Leukoplakia, Erythroplakia,
7	Verruca vugaris
11	Squamous cell papilloma, Condyloma acuminatum, Lichen planus, Leukoplakia, Erythroplakia
13	Focal Epithelial Hyperplasia
16	Oropharyngeal squamous cell carcinoma, Oral squamous cell carcinoma, Lichen planus, Leukoplakia, Erythroplakia
18	Oropharyngeal squamous cell carcinoma, Oral squamous cell carcinoma
32	Focal Epithelial Hyperplasia , Oral warts in HIV-infected persons

HPV and Cancer of Oral Cavity and Oropharyngeal Region

In 2008, about 400,000 new cases of the oral cavity and the pharynx (excluding nasopharynx) and 223,000 deaths occurred worldwide. Two-thirds of cases occurred in developing countries (Lambert *et al.*, 2011). The majority of head and neck cancers are associated with high tobacco and alcohol consumption. However, there are about 15-20% of these cancer cases that are associated with HPV with growing evidence that these HPV-related cases, particularly oraoharyngeal cancers, are associated with sexual behavior including the practice of oral sex (WHO/ICO 2010).

Though current research has expiscated much useful information related to the association of HPV with cancers of the oral and oropharyngeal region, there are several aspects that need careful assessment and thorough measurement. For example, the risk estimates of multiple risk factor exposures for oral and oropharyngeal cancers have not yet been thoroughly examined. Mortality data is critical in calculating important statistics on which much policy decisions may be based. A recent report assessed inaccuracies in the cancer site coded as the underlying cause of death on death certificates vs. cancer site in a population-based cancer registry (SEER-9) and found that mortality was severely underestimated (by about 70–80%) using underlying cause for cancer of tonsils (that are strongly associated with human HPV infection). Furthermore, for those aged under 65 years, deaths from oral and pharyngeal cancers were underestimated by about 22–35% (Polednak, 2014).

Previous research has demonstrated a strong association between HPV infection and oropharyngeal cancers, irrespective of tobacco or alcohol use (D'Souza *et al.*, 2009; Gillison *et al.*, 2000; Lambert *et al.*, 2011). Over the last 30 years, the incidence of oral cavity cancer related to tobacco and alcohol has decreased in conjunction with public health efforts that have led to decreased cigarette smoking and alcohol consumption. During the same time period, however, an increasing trend in HPV-related oropharyngeal cancer has been observed (Chaturvedi *et al.*, 2008; Sturgis and Cinciripini, 2007). It is interesting to note that racial/ethnic differences have also been observed in oropharyngeal cancers. Two studies using the Surveillance Epidemiology End Results program (SEER) data to examine recent trends in oral cavity and pharyngeal cancer noted a strong increasing trend in oropharyngeal cancer incidence in white men over time, as compared to declining or stable incidence rates observed in all other racial/ethnic/gender groups (Brown *et al.*, 2011; 2012).

In 2013, oral cavity and pharyngeal cancer accounted for an estimated 41,380 new cases and 7,890 deaths in the US (SEER, 2014). These cancers represented approximately 2.5% of all new cancer cases during the past year. Oral cavity and pharyngeal cancer had a 5-year relative survival rate of 62% during the period of 2003-2009, which is rather low compared to other common cancers (SEER, 2014). The anatomy of the head and neck region is complex, and the specific anatomic location of oral cavity and pharyngeal cancer is an important factor in the epidemiologic characteristics of these cancers (Ryerson *et al.*, 2008). The oral cavity is a region in the head and neck that is generally defined as the lips, buccal mucosa, anterior two-thirds of the tongue, floor of the mouth, and the hard palate (Lambert *et al.*, 2011). The pharynx is also a part of the head and neck region, and is composed of the oropharynx, hypopharynx, and nasopharynx, with the oropharynx consisting of the posterior one-third of the tongue, soft palate and uvula, tonsils, and the pharyngeal wall (Lambert *et al.*, 2011). HPV is mostly associated with cancer of oropharynx, and possible posterior one-third of tongue and tonsils and not much with the oral cavity. It has been suggested that epidemiology of cancer of oral cavity and that or oropharyngeal region may be different and sub-site analysis should be conducted routinely (Chattopadhyay, 2014). Such distinction will allow correct assessment of the impact of HPV on cancers or the oral and oropharyngeal region.

Traditional, well-established risk factors for oral cavity cancers include tobacco and heavy alcohol use (Radoi *et al.*, 2013). These two risk factors account for three-fourths of all cancers in the head and neck region (Sivasithamparam *et al.*, 2013). The risk of developing oral cavity cancer increases with the frequency, duration, and lifetime cumulative consumption of tobacco and alcohol, with these risk factors showing a multiplicative joint effect in combination (Radoi *et al.*, 2013). However, these traditional risk factors do not appear to play the same role for cancer risk in the oropharyngeal region (Lambert *et al.*, 2011).

HPV Type 16 is the most common type found in HPV-positive oropharyngeal cancers, being identified in approximately 90% of these cancers (Radoi *et al.*, 2013). A global systematic review of HPV detection by PCR methods (Kreimer *et al.*, 2005) found a substantially higher percentage of HPV-16 detected in North American oropharyngeal cancers (42.1%) as compared to oral cavity cancers (10.1%), whereas more recent North American studies detected HPV-16 in a range of up to 82% of oropharyngeal cancers, and as low as 4% of oral cavity cancer cases (Cleveland *et al.*, 2011; Machado *et al.*, 2010; Singhi and Westra, 2010).

The distinction between HPV-positive and HPV-negative cancers is critical from the view point of research as well as policy implications because HPV-positive oropharyngeal cancers have a better prognosis, demonstrating superior survival rates compared to HPV-negative ones (Ang *et al.*, 2010; Fakhry *et al.*, 2008; Ragin and Taioli, 2007). HPV-positive oropharyngeal cancers demonstrate a better response to radiation and chemotherapy although the exact mechanisms for the better responses are not known (Fakhry *et al.*, 2008). One hypothesized explanation for the better response is the possibility that radiation and chemotherapy reactivate p53 (a tumor suppressing protein whose gene is silenced but not mutated by HPV as it is in tobacco/carcinogen caused cancers) in HPV-positive oropharyngeal cancers, thereby making the tumor suppression protein active again to aid in the treatment of the cancer (Scudellari, 2013; Xie *et al.*, 2013). Other possibilities for better responses include a generally healthier patient population seen with HPV-positive cancers, and a wider range of mutations observed in HPV-negative cancers which may make them more likely to resist therapy (Mroz and Rocco 2013; Scudellari, 2013). Although continued research is needed to determine the exact mechanism for the improved treatment prognosis and survival associated with HPV-positive oropharyngeal cancer, current evidence suggests that future research on the risks and benefits of treatment modalities should consider the different effects of treament and survival between HPV-positive and HPV-negative patients (Fakhry *et al.*, 2008).

Prevention of HPV Infection

Prevention of HPV infections has focused around reducing cervical exposure to HPV and other cancer prevention methods. Several strategies have been suggested that are effective for prevention of any sexually transmitted disease and can help reduce the risk of cervical cancer. These include counseling messages for tobacco cessation, condom use, circumcision, selective choice in the number of sexual partners, delaying age at first intercourse and at first full-term pregnancy, as well as increasing duration of combined hormonal oral contraceptive use. Micronutrients and supplements have been suggested to reduce the risk of HPV infection, persistence, progression, and regression while it has also been suggested that cervical cancer is best prevented by screening (Harper and Demars, 2014). Unlike cervical cancer, however, there are no secondary screening tests universally acknowledged to detect HPV-associated pre-cancers of the head and neck, penis, anus, vulva, or vagina (Harper and Demars, 2014, Wu *et al*., 2012).

Prophylactic HPV Vaccine

HPV vaccines that prevent against HPV 16 and 18 infections are now available and have the potential to reduce the incidence of cervical and other anogenital cancers (WHO/ICO, 2010). HPV vaccines contain replicates of the L1 protein called virus-like particles (VLPs) that are HPV type specific. Current HPV vaccines are produced using recombinant technology, by inserting the L1 gene into a host (e.g. yeast or baculovirus), which then produces L1 proteins in abundance. These L1 proteins self-assemble into empty shells or virus like particles (VLPs). VLPs are similar in shape and size to the HPV virion, but do not contain viral DNA, and are therefore non-infectious and non-oncogenic (Dochez *et al.*, 2014). In addition, each vaccine has its own adjuvant used to promote the durability of the immune response (Harper and Demars, 2014).

Two HPV vaccines licensed in 2006 by the US Food and Drug Administration and international regulatory bodies are currently available for use: a bivalent and a quadrivalent vaccine (CDC 2010a;b). The bivalent vaccine (Cervarix®, GlaxoSmithKline, Brentford, England, 2009) protects against HPV-16 and HPV-18 for the prevention of cervical cancer and precancerous lesions in women (Dochez *et al.*, 2014; Harper and Demars, 2014). The quadrivalent vaccine (Gardasil®/Silgard®recombinant HPV vaccine (types 6, 11, 16, 18), Merck, Whitehouse Station, NJ, 2006) protects against HPV (types 6, 11, 16, 18) and has been indicated for the prevention of cervical cancer, precancerous lesions, and genital warts associated with HPV in females; prevention of vaginal and vulvar cancer in females; prevention of genital warts in males; and prevention of anal cancer and precancerous lesions in both males and females (Dochez *et al.*, 2014; Harper and Demars, 2014).

Recent phase III trials have demonstrated very encouraging results for a 9-valent vaccine upgrade of Gardasil® (Gardasil®5+) (Joura et al., 2013; Luxemborg, 2013). Cervarix® has substantial direct evidence of cross-protective efficacy against five oncogenic infections not included in its HPV VLP formulation (HPV 31, 33, 45, 52, 58). By adding five oncogenic VLPs, Gardasil®5+ (9-valent) shows efficacy against these persistent infections. The maximal efficacy against cervical intraepithelial neoplasia (CIN) grades 2 and 3 by Gardasil®5+ is estimated to be 75-85% on the basis of the original Gardasil® studies ((Joura et al., 2013; Luxemborg, 2013; Harper and Demars, 2014).

Both Cervarix®and Gardasil®are given intramuscularly over a 6-month period in a three-dose schedule at 0, 1 and 6 months for the bivalent vaccine and 0, 2 and 6 months for the quadrivalent vaccine. Both HPV vaccines have been demonstrated to be safe, and very effective in preventing HPV-associated cervical cancer (Dochez *et al.*, 2014; Harper and Demars, 2014). Local reactions reported include pain, swelling and redness can occur, but symptoms are usually of only short duration. Systemic adverse reactions could include fever, nausea, dizziness, fatigue, headache and myalgia which too last for short periods. The vaccines can be safely administered along with other pediatric and adolescent vaccines (WHO/ICO, 2010).

Gardasil® vs. Cervarix®

A recent study comparing the immunogenicity and reactogenicity of Cervarix® and Gardasil® in adults infected with the HIV found that both vaccines were immunogenic and well tolerated. Compared with Gardasil®, Cervarix® induced superior vaccine responses among HIV-infected women, whereas in HIV-infected men the difference in immunogenicity was less pronounced (Toft *et al.*, 2014). However, an earlier study comparing the two vaccines noted that both vaccines were generally well tolerated and the incidence of unsolicited adverse events was also similar between the two. "*The incidence of solicited symptoms was generally higher after Cervarix®, injection site reactions being most common. However, compliance rates with the three-dose schedules were similarly high (>84%) for both vaccines*" (Einstein *et al.*, 2009). The authors stated that "*although the importance of differences in magnitude of immune response between these vaccines is unknown, they may represent determinants of duration of protection against HPV-16/18*" suggesting that long-term studies are needed to assess the duration of efficacy after vaccination for both vaccines.

Table 2 compares the efficacy of Cervarix® and Gardasil® across various characteristics. To date, all efficacy studies show that prevention of type-specific HPV infections is most easily accomplished by type-specific vaccination before the infection. Both Cervarix® and Gardasil® are effective in populations that have already been sexually active or exposed to HPV, but efficacy is lower compared to populations that are naive to the HPV types before vaccination. Gardasil® efficacy in males is restricted to short follow-up times and more rapid loss of antibody titers than seen in females. Currently, there are no efficacy studies of Cervarix® in males (Harper and Demars, 2014).

Testing for HPV

Overall, the several HPV detection methods can be divided into two broad categories - 1, Target amplification techniques: Consensus primer PCR; Detection and/or genotyping of consensus PCR products; Type-specific PCR; and mRNA amplification; 2, Signal-amplification techniques: Liquid-phase signal amplification techniques; and Morphological signal-amplification techniques.

Table 2. Comparison of efficacy of Cervarix® and Gardasil® (Adapted from Harper and Demars, 2014).*

Characteristic	*Characteristic sub-type*	*Efficacy % (95%CI)*	
		Cervarix®	*Gardasil®*
Abnormal cytology/excisional therapy	Atypical squamous cells of undetermined significance	23 (17, 39)	22 (9, 36)
	Low grade squamous intraepithelial lesion	24 (14, 33)	17 (9, 24)
	High grade intraepithelial lesion	54 (5, 79)	45 (28, 54)
	All abnormal cytology	27 (21, 33)	17 (10, 24)
	Reduction in colposcopies	29 (22, 36)	20 (12, 27)
	Reduction in excisional therapies	70 (58, 79)	42 (28, 54)
Cross-protection	HPV 31	77 (67, 84)	46 (15, 66)
	HPV 33	43 (19, 60)	29 (-45,66)
	HPV 45	79 (61, 89)	8 (-67,49)
	HPV 51	26 (12, 37)	---
	HPV 52	19 (3, 32)	6 (-54,42)
	HPV 31/33/45/52/58		96 (94, 97) [9-valent vaccine]*
Histologic cervical intraepithelial neoplasia (CIN).	CIN 2+ caused by HPV 16/18 only	95 (88, 98)	100 (91,100)
CIN 2+: Cervical intraepithelial neoplasia grade 2, grade 3, invasive squamous cervical cancer, adenocarcinoma *in situ*, and adenocarcinoma.	CIN 3+caused by HPV 16/18 only	92 (67, 99)	100 (91,100)
	Adenocarcinoma *in situ* caused by HPV 16/18 only	100 (16,100)	60 (NA)
CIN 3+: Cervical intraepithelial neoplasia grade 3, invasive squamous cervical cancer, adenocarcinoma *in situ*, and adenocarcinoma.	CIN 2+ caused by any HPV	65 (53, 74)	43 (24, 57)
	CIN 3+ caused by any HPV	93 (79, 99)	43 (13, 63)
Efficacies in populations with HPV exposure	CIN 3+ caused by any HPV	46 (29, 59)	16 (0, 30)
	Adenocarcinoma *in situ* caused by any HPV	77 (16, 96)	63 (54, 69)

* The maximal efficacy against CIN 2/3 by Gardasil+ 5 is estimated to range between 75% to 85% based on the original Gardasil studies (Harper and Demar, 2014; Joura et al., 2013; Luxemborg, 2013).

In general, consensus PCR followed by reverse hybridization is a very sensitive method for detecting HPV. This results in the most extensive HPV typing information for many kinds of clinical specimens, including those containing multiple infections (Brink *et al.*, 2007). In practice, different types of HPV detection techniques used in the laboratories include: p16 immunostaining, HPV DNA *in situ* hybridization, Consensus HPV PCR (End point PCR (qualitative)), HPV-Type-specific real-time quantitative PCR, HPV E6/E7 mRNA PCR (reverse-transcriptase PCR or RT-PCR), and HR-HPV E6/E7 mRNA *in situ* hybridization (RNAscope). None of the above methods provide optimal sensitivity and specificity levels. Therefore, stepwise algorithms that combine different HPV tests have been proposed as a strategy to compensate for the limitations of individual tests. Two diagnostic algorithms have emerged and are used in several institutions and US trials. Both algorithms use p16 immunostaining as the first-line assay. Sensitivity of this technique is close to 100%. Thereafter, only p16-positive patients undergo further investigation with a more specific high-risk HPV detection method. The p16-negative patients are considered HPV-negative (Mirghani *et al.*, 2014).

A recent study assessing HPV prevalence rates and clinicopathological correlations obtained with three distinct commonly used HPV detection methods found that the concordance analysis revealed a good agreement between two HPV DNA detection methods: p16-immunohistochemistry (IHC), HPV DNA viral load by real-time PCR (qPCR), and HPV genotyping by a reverse hybridization-based line probe assay (INNO-LiPA (k=0.65). They found that when both tests were positive; the depicted HPV subtypes were always concordant (Melkane *et al*., 2014). Other studies reported that there was 86% agreement (55/64) between the p16 and ProEx C stains on tissue specimens and 84% of cytology negative specimens demonstrated false-positive staining (Oberg *et al*., 2010).

For HPV detection among the commercially available kits, the AdvanSure HPV Screening real-time PCR assay and the Abbott Real Time PCR assay are less sensitive but more specific than the digene HC2 HPV DNA assay, but they can simultaneously differentiate type 16/18 HPV from other types (Hwang and Lee, 2012). Table 3 summarizes the results of the three tests for cervical cancer screening from a recent study (Chung *et al.*, 2014). All three tests show relatively good clinical sensitivities, but the AdvanSure PCR had lower clinical specificity than the Abbott PCR and the digene HC2 assay. The AdvanSure PCR and the Abbott PCR assays are automated and can distinguish between HPV types 16/18 and other types of HPV. It has been suggested that the two real-time PCR assays could be useful tools in HPV testing for cervical cancer screening (Chung *et al.*, 2014).

Cost Issues of HPV Vaccine

In the US, HPV-related diseases are estimated to cost at least $4 billion in direct medical expenses annually (excluding lost productivity). A pharmacoeconomic study reported the cost estimate to be US $360 for a course (3-doses) of vaccine whether bi- or quadrivalent (Insinga *et al.*, 2005) making the HPV vaccine among the most costly vaccines. Sinanovic *et al.* (2009) developed a static Markov state transition model to describe the screening and management of cervical cancer within the South African context. The incremental cost-effectiveness ratio of adding HPV vaccination to the screening program ranged from $1,078-1,460 per quality-adjusted life year gained and $3,320-4,495 per life year saved, mainly depending on whether the study was viewed from a health service or from a societal perspective. Using discounted costs and benefits, the threshold analysis indicated that a vaccine price reduction of 60% or more would make the vaccine plus screening strategy more cost-effective than the screening only approach (Sinanovic *et al.,* 2009).

In Greater Manchester, UK, modeled analysis predicted that primary HPV screening would be both more effective and cost saving than current practice with cervical cytology for a number of potential strategies in both unvaccinated and vaccinated cohorts (Kitchener *et al.*, 2014). However, in Colombia in 2010, it was seen that commercially, the two vaccines were not cost-effective alternatives compared to the existing screening strategy. The results were influenced by the cost and efficacy values of the vaccines which made it difficult for the authors to determine with confidence which of the two vaccines had the best cost-effectiveness profile. They suggested that "*to be 'cost-effective' vaccines should cost US$141 and US$147 per vaccinated girl at the most. But at lower prices such as those recommended by WHO or the price of other vaccines in Colombia, HPV vaccination could be considered very cost-effective*" (Aponte-González *et al.*, 2013).

Tracy *et al.* (2014) sought to predict the impact and cost-effectiveness of an HPV vaccination program in an example low-resource country with a high burden of cervical cancer. Using novel compartmental mathematical models they suggested that HPV vaccination in Mali (West Africa) will reduce cervical cancer burden by a factor roughly equal to vaccine coverage. Their models, simulated in a cohort of 333,146 urban and 588,982 rural Malian women, age 10-14 years, predicted that a 50% vaccination scenario averted 1,145 cervical cancer deaths in the urban areas and 2,742 in the rural areas.

Table 3. Comparison of HPV testing methods (Adapted from Chung *et al.*, 2014)*

Test	*Test type*	*Clinical sensitivity % (95%CI)*	*Clinical specificity % (95%CI)*	*Positive predictive value % (95%CI)*	*Negative predictive value % (95%CI)*
HC2	Hybrid Capture 2 High-Risk HPV DNA Test	100 (84.4,100)	83.3 (80.0,86.2)	18.0 (11.7,26.0)	100 (99.3,100)
Abbott PCR	Multiplex Real Time PCR	95.5 (77.1,99.2)	86.4 (83.4,89.1)	20.6 (13.2,29.7)	99.8 (98.9,100)
AdvanSure PCR	Multiplex Real-Time PCR	95.5 (77.1,99.2)	61.6 (57.6,65.6)	8.4 (5.3,12.6)	99.7 (98.5,100)

* Concordance between the Abbott PCR and the HC2 for high-risk HPV detection was 92.1% (kappa 0.74, 95%CI 0.67–0.81). Overall, the two real-time PCR assays could separately detect oncogenic, high-risk HPV types 16/18. Among 619 patients, HPV types 16/18 were detected in 28 and 26 patients by the AdvanSure PCR and the Abbott PCR, respectively. They showed excellent agreement (99.4% agreement, kappa 0.92). The clinical specificities of the detection of HPV types 16/18 for the detection of cervical intraepithelial neoplasia of grade 2 or worse by the AdvanSure PCR and the Abbott PCR were 98.5% and 97.8%, respectively (Chung *et al.*, 2014).

The cost per discounted life-year saved in this scenario was $1,030 in urban areas and $725 dollars in rural areas. From this, we, this paper's authors, calculated a convenient average figure to be $880 per vaccinated person. Further, the cost per life-year saved was higher at 90% coverage, but was still in the range of a "*cost-effective*" public health intervention.

A recent study in the US used a simplified model of HPV transmission to estimate the reduction in the health and economic burden of HPV-associated diseases in males and females as a result of HPV vaccination. This study reported that the incremental cost per quality-adjusted life year gained by adding male vaccination to a female-only vaccination program was $23,600 in the lower female coverage scenario (20% coverage at age 12 years) and $184,300 in the higher female coverage scenario (75% coverage at age 12 years). The cost-effectiveness of male vaccination appeared less favorable when compared to a strategy of increased female vaccination coverage. Therefore, even if in some situations, male vaccination is found to have value and is cost-effective, increasing female coverage could be a more efficient strategy than male vaccination for reducing the overall health burden of HPV in the population (Chesson *et al.*, 2011).

Clear global cost estimates of HPV testing are not available. However, Mirghani *et al.* (2014) estimated the technical cost for various HPV detection methods from European research laboratories in Euros. The costs converted to US$ at current exchange rates are: p16 Immunostaining ($34); HPV DNA *In situ* hybridization ($67); Consensus HPV PCR (End point PCR, qualitative) ($52); HPV Type-specific "*real-time*" quantitative PCR (qPCR) ($100); E6/E7 mRNA PCR (reverse-transcriptase PCR or RT-PCR) ($144); and E6/E7 mRNA *in situ* hybridization ($162) for every slide/sample.

The discussion above is about the cost of the vaccine itself. However, the actual cost for vaccination will be more because at point of delivery/care, overhead costs add to the vaccine cost such as: professional services, clinic overheads, staff time, equipment charges and other overheads. In some countries, service tax and other taxes may also be involved. The Centers for Disease Control and Prevention (CDC) states that HPV vaccine protection is "*long-lasting*" and "*current studies have followed vaccinated individuals for six years, and show that there is no evidence of weakened protection over time*" (CDC, 2014b). However, in absence of long term studies, it may be assumed that there might be a case for re-vaccination at some point for which the vaccine may incur still more cost to obtain the benefits of prolonged protection.

HPV Vaccine Use Internationally

Until 2008, countries that had recommended HPV vaccination in a primary targeted population (mostly, pre-/early-teenage girls and in some cases, boys) included Australia, Austria, Belgium, Canada, France, Germany, Greece, Italy, Lichtenstein, Luxemburg, Portugal, Spain, Switzerland, UK and the US (Koulova *et al.*, 2008). Adoption of HPV vaccine use varies substantially across the world and is mired in politics (see next section). Cost is a major barrier, especially in the developing world (see earlier section). Furthermore, estimating the need, cost and potential benefit of adopting HPV vaccine is dependent on available data, existence of surveillance and disease tracking system and a structure that could monitor a vaccine program.

PATH is a US-based international nonprofit organization that works as an international non-governmental organization in the global health field. In a recent development, a PATH study to assess the possibility of launching a cervical cancer vaccination program in India resulted in the death of seven children and the trial was consequently stopped by the Government. An Indian parliamentary committee has recommended legal action against PATH alleging failure to follow proper procedures, adequately monitor events or obtain informed consent from all participants. PATH has denied any misconduct (Kumar and Butler, 2013). This case exemplifies many issues stemming from political, cultural, economic and scientific aspects in assessing of evidence to create grounds for firm and valid scientific conclusions towards adoption of HPV vaccination.

For example, a recent study of cervical cancer from India claimed that neither the epidemiological evidence nor the current cancer surveillance systems justify the general rollout of a HPV vaccination program either in India or in the two states where PATH was conducting its research. HPV vaccination programs should only proceed where there is both strong epidemiological evidence and where there are adequate surveillance and monitoring systems (Mattheij *et al.*, 2012). This stand was however questioned by Forman *et al*. (2012) stating "*The surveillance data that we have, indicate quite clearly that HPV infection and associated cervical cancer risk in India is a substantive burden and clear health priority which can be addressed now by a combination of screening and vaccination*."

A study investigating key challenges and barriers towards HPV vaccine introduction in the Western Cape Province, South Africa reported that vaccination via schools along with the involvement of other stakeholders such as sexual and reproductive health and the advanced program on immunization could enable vaccine acceptance in the population (Harries *et al.*, 2009). Policy influencers stated that the ways in which a vaccine against genital HPV is promoted will be critical to its acceptance and compliance amongst young girls and parents. The study further stated that it did not anticipate opposition to the HPV vaccine if the vaccine was marketed as preventing cervical cancer rather than a sexually transmitted infection. Furthermore, poor community knowledge of cervical cancer and the causal relationship between HPV and cervical cancer suggests the need for continued education around the importance of regular cervical screening. There was a concern about cost of the vaccine among policy personnel. Many community participants in a study in South Africa, due to their socio-economic circumstances wanted the vaccine to be free (like other childhood immunizations) or available at low cost (Harries *et al.*, 2009).

A recent study reviewing HPV vaccine policy articles published between 2000 and 2011 in the developing world concluded that the subtypes of HPV involved in cervical pathology, their associations, and natural history (clearance and persistence rates) differ between the developing countries and the industrialized world. Furthermore, a mandatory HPV vaccination policy "*is currently unachievable in the developing world because of the cost of the vaccine, the lack of adequate cytology and follow-up infrastructures*" (van Bogaert, 2013).

Despite easy and low cost screening tests being available for cervical cancer, for many reasons, such as insufficient education, availability of trained personnel, follow-up and referral systems, and cost, the burden of cervical cancer has not decreased in the developing world. "*Health-care budget allocation in the developing world has to make difficult choices between competing priorities, mainly infectious diseases like malaria, tuberculosis, HIV/AIDS, air-borne, and water-borne infections*" (van Bogaert, 2013).

Governments of most developing countries will weigh the cost-benefits of an expenditure outlay of $360 per targeted vaccinated person compared to an estimated average cost of $880 per life year saved based on its current socio-political-economic perspective. Realpolitik decisions will perhaps rate current savings over future savings. Van Bogaert's assertion that at the current cost of $360 for a course of vaccine (bi- or quadri-valent), mass vaccination was not affordable for most public health systems in the developing world seems a more likely outcome.

HPV Vaccination Policy

Currently in the US, no federal laws for controlling HPV vaccination exist. Some states, however, have enacted laws related to this issue. States with HPV vaccination laws and policies are enumerated and briefly reviewed by Osazuwa-Peters (2013). Politics have become a key part of the HPV vaccine debate. With massive money involved, public debate on the issue of mandatory testing has involved science raising several ethical questions. The central question is whether HPV vaccine should become mandatory. In the US, 41 states have introduced legislation related to HPV vaccine; only Texas (revoked), Virginia, and the District of Columbia have enacted HPV vaccine mandates. Both Virginia and the District of Columbia offer generous "*opt-outs*" at parents' discretion (Gostin, 2011).

Gostin took a hawkish stand on mandatory HPV vaccine policy stating that "*Government should implement a well-funded campaign to increase HPV vaccination rates as part of a comprehensive sexually transmitted infection prevention package: pay for the vaccine or require public or private coverage; launch health education and social marketing campaigns; and reduce associated harms through early screening and treatment. If voluntary vaccination proves unsuccessful, states should seriously consider compulsory vaccination laws without generous exemptions*" (Gostin, 2011). Such a stand is based on the estimate that the total public health impact of HPV vaccination is very large and overall cost savings very high.

Factors influencing the extent to which HPV was perceived as a problem meriting policy action included political forces that facilitated and impeded policy adoption such as interest-group opposition and structural and ideological features of the states' political environments; and factors affecting which policy alternatives received consideration (Abiola *et al.*, 2013). A study interviewed 73 key informants in six states experienced in legislative and policy deliberations with respect to the HPV vaccine (Colgrove *et al.*, 2010) and finding that proponents of mandatory "*HPV immunization cited the severity of cervical cancer and the efficacy of the vaccine as primary motivations for wanting to ensure that all girls were vaccinated*". Factors that countervailed HPV vaccine mandates included newness of the vaccine, sexually transmitted nature of HPV, non-transmissibility of HPV in the classroom setting, discomfort with the vaccine manufacturer's involvement, price of the vaccine, antipathy toward governmental coercion, anti-vaccination activism, and aspects of the policymaking process itself. Among the interviewees, "*there was wide agreement that it was inappropriate to mandate a vaccine within a few months after its licensure*" (Colgrove *et al.*, 2010). Active and aggressive lobbying by the pharmaceutical companies became a part of the push for mandating HPV vaccination which was generally acceptable to most stakeholders (Mello *et al.*, 2011). However, it may be questioned if companies should participate aggressively in cases involving obvious conflicts of interests. "*Some of their advertising campaign slogans, such as 'cervical cancer kills x women per year' and 'your daughter could become one less life affected by cervical cancer,' seemed more designed to promote fear rather than evidence-based decision making about the potential benefits of the vaccine*" (Tomljenovic and Shaw, 2012).

Whereas "*policymakers acknowledge the utility of manufacturers' involvement in vaccination policymaking, industry lobbying that is overly aggressive, not fully transparent, or not divorced from financial contributions to lawmakers risks undermining the prospects for legislation to foster uptake of new vaccines*" (Mello *et al.*, 2012) as demonstrated by the case of HPV vaccination. It has been suggested that the politics and debate around the HPV vaccination debate demonstrates "*an erosion of the persuasiveness of public good arguments around collective immunization programs in the policy discourse*" (Mah *et al.*, 2011).

Prophylactic HPV Vaccine and Oral Cancer

Due to the rising incidence of oropharyngeal cancer related to HPV infection, there is interest in determining the effectiveness of these HPV vaccines for the prevention of HPV-positive oropharyngeal cancers. To date, the effectiveness of these vaccines in the prevention of HPV-positive oropharyngeal cancer is unknown (Cleveland *et al.*, 2011). Because HPV-16 has been identified in approximately 90% of HPV-positive oropharyngeal cancers; the current HPV vaccines hold a promising potential for preventing these cancers, however, clinical trials on their effectiveness are needed (Gillison *et al.*, 2008).

HPV-positive head and neck squamous cell carcinomas also represent a distinct set of tumors that exhibit better prognosis than their HPV-negative counterparts. However, there may exist a subset, which behaves more aggressively (Kaka *et al.*, 2013). Salazar *et al.* (2014) demonstrated that p16 protein expression immunohistochemistry alone has potential as a prognostic test for oropharyngeal cancer survival, but combined p16/HPV testing is necessary to identify HPV-associated non oropharyngeal head and neck cancers with better prognosis.

A recent double-blind controlled trial in Costa Rica assessing vaccine efficacy of the bivalent HPV 16/18 vaccine against prevalent oral HPV infections reported that "*HPV prevalence four years after vaccination with the ASO4-adjuvanted HPV16/18 vaccine was much lower among women in the vaccine arm compared to the control arm*". The authors insinuated that HPV vaccines could be helpful in prevention or HPV-associated oral cavity/oropharyngeal cancers (Herrero *et al.*, 2013). The study, however had a very low oral prevalence of identifiable mucosal HPV (1·7% i.e. 1·3% for oncogenic HPV types and 0·8% for non-oncogenic types) i.e. 99 women across two randomized groups. The results are, however, encouraging in that vaccine was efficacious in reducing prevalence of HPV in the oral cavity.

Whereas targeting females with HPV vaccines for cervical cancer prevention may be judicious, in order to develop policies for advocating HPV vaccination for prevention of oropharyngeal cancer, an additional benefit over prevention of cervical cancer has to be demonstrated. CDC estimates that 11,967 new cases of HPV-associated cervical cancer and more than 2,370 new cases of oropharyngeal cancers in women and nearly 9,356 in men are diagnosed each year in the US (CDC, 2014c). If HPV vaccine is efficacious in preventing oropharyngeal cancer, the above statistics suggest there may be a case for examining the benefits of using HPV vaccine for prevention of oropharyngeal cancer (incidence greater in men than women) and there is a potential for a synergistic effect on prevention of cervical and oropharyngeal cancer at the population level.

HPV Vaccine and Dental Professionals

A recent study assessing oral health providers' intention and capacity for engaging in primary and secondary prevention of HPV-related oral cancers found startling results (Daley *et al.*, 2014). Only a small proportion of the study sample responded to the survey questions. Among these, the stage of readiness of the oral health provider to discuss HPV vaccine with female patients was: providers in pre-contemplation: 52% (men 50.7%; women 55.2%); contemplation: 39.5% (men 43.4%; women 31%); action 8.6% (men 6.6%; women 13.8%). Although the reference category for assessing "*most cited HPV vaccine information sources*" was not clearly described, a crude model showed that dentists were 1.34 times as likely to obtain HPV vaccine information from an oral health colleague compared to professional journal/publication; and 1.37 times as likely from an oral health colleague over continuing education. The authors diplomatically concluded that there exists a serious "*liability and perceived role as processes of change necessary to guide dentists to primary prevention of HPV-related oral cancer despite high levels of knowledge*" and that dentists seek approval and guidance from their professional organizations, such as the American Dental Association, ADA (Daley *et al.*, 2014).

Dentists should be prepared to discuss the role of HPV in oropharyngeal cancers emphasizing that conclusive causal relationships have not been established, but that substantial evidence exists to this purported causality. However, there is little evidence of causal associations between HPV and oral cavity cancers. Dentists may also refer their patients to the ADA Council on Scientific Affairs' statement that "*Further research is required to improve understanding of the natural history of oral HPV infection, transmission risks, screening/testing, and the predictive value of a positive HPV test for the subsequent development of oropharyngeal cancer*" (ADA, 2014).

Conclusion

HPV is a complex virus that is highly prevalent worldwide. As the association between HPV and oral and oropharyngeal cancers becomes clearer, the potential for a population-based preventive measure such as HPV vaccination is being examined the world over. The evidence-base for use, efficacy and effectiveness of the vaccines is being developed. There will likely be several cost-related, scientific and political challenges that prophylactic HPV vaccination will face before its true impact on preventing cervical, oral and oropharyngeal cancer can be fully assessed. Given the mounting literature on the association between HPV and oropharyngeal cancer, the dental public health community must be prepared to answer patients' HPV-related questions and to educate patients about the role of HPV as a risk factor for oral and oropharyngeal cancers.

References

Abiola , S.E., Colgrove, J. and Mello, M.M. (2013): The politics of HPV vaccination policy formation in the United States. *Journal of Health Politics, Policy and Law* **38**, 645-681.

ADA Council on Scientific Affairs (2014): *Statement on human papillomavirus and squamous cell cancers of the oropharynx*. www.ada.org/en/about-the-ada/ada-positions-policies-and-statements/statement-on-human-papillomavirus-and-squamous-cel

Ang, K.K. Harris, J., Wheeler, R., Weber, R., Rosenthal, D.I., Nguyen-Tân, P.F., Westra, W.H., Chung, C.H., Jordan, R.C., Lu, C., Kim, H., Axelrod, R., Silverman, C.C., Redmond, K.P. and Gillison, M.L. (2010): Human papillomavirus and survival of patients with oropharyngeal cancer. *New England Journal of Medicine* **363**, 24-35.

Aponte-González, J., Fajardo-Bernal, L., Diaz, J., Eslava-Schmalbach, J., Gamboa, O. and Hay, J.W. (2013): Cost-effectiveness analysis of the bivalent and quadrivalent human papillomavirus vaccines from a societal perspective in Colombia. *PLoS One* **18**, e80639.

Bonnez, W. and Reichman, R.C. (2009): Papilloma viruses. In: *Principles and practice of infectious diseases, 7th edn*. Eds. Mandell, G.L., Bennett, J.E., Dolin, R. pp 2035-2050. Philadelphia: Churchill Livingstone.

Brink, A.A.T.P., Snijders, P.J.F. and Meijer, C.J.L.(2007): HPV detection methods. *Disease Markers* **23**, 273-281.

Brown, L.M., Check, D.P. and Devesa, S.S. (2012): Oral cavity and pharynx cancer incidence trends by subsite in the United States: changing gender patterns. *Journal of Oncology* **2012**, 649498.

Brown, L.M., Check, D.P., Devesa, S.S. (2011): Oropharyngeal cancer incidence trends: diminishing racial disparities. *Cancer Causes and Control* **22**, 753-763.

Bui, T.C., Markham, C.M., Ross, M.W. and Mullen, P.D. (2013): Examining the association between oral health and oral HPV infection. *Cancer Prevention Research* **6**, 917-924.

Burd, E.M. (2003): Human Papillomavirus and Cervical Cancer. *Clinical Microbiology Reviews* **16**, 1-17.

CDC, Centers for Disease Control and Prevention (2010a): FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report* **59**, 626-629.

CDC (2010b): FDA licensure of quadrivalent human papillomavirus vaccine (HPV4, Gardasil) for use in males and guidance from the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report* **59**, 630-632.

CDC (2014a): *Human papillomavirus (HPV) and Oropharyngeal Cancer - Fact Sheet.* www.cdc.gov/std/hpv/stdFact-HPVandoralcancer.htm

CDC (2014b): *Human papillomavirus (HPV)*. www.cdc.gov/std/hpv/stdfact-hpv-vaccine-young-women.htm

CDC (2014c): *Human Papillomavirus (HPV)-Associated Cancers*. www.cdc.gov/cancer/hpv/basic_info/index.htm

Chang, F., Syrjänen, S., Kelloskoski, J. and Syrjänen. K. (1991): Human papilloma virus (HPV) infection and their associations with oral disease. *Journal of Oral Pathology and Medicine* **20**, 305-317.

Chattopadhyay, A. (2013): Cancer of the oral and pharyngeal region - need for sub-site analysis. *Journal of Dental, Oral and Craniofacial Epidemiology* **1**, 1-5.

Chaturvedi, A.K., Engels, E.A., Anderson, W.F. and Gillison, M.L. (2008): Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *Journal of Clinical Oncology* **26**, 612-619.

Chen, H.C., Schiffman, M., Lin, C.Y., Pan, M.H., You, S.L., Chuang, L.C., Hsieh, C.Y., Liaw, K.L., Hsing, A.W., Chen, C.J. and the CBCSP-HPV Study Group (2011). Persistence of type-specific human papillomavirus infection and increased long-term risk of cervical cancer. *Journal of National Cancer Institute* **103**, 1387-1396.

Chesson, H.W., Ekwueme, D.U., Saraiya, M., Dunne, E.F. and Markowitz, L.E. (2011): The cost-effectiveness of male HPV vaccination in the United States. *Vaccine* **29**, 8443-8450.

Chung, H.S., Hahm, C. and Lee, M. (2014): Comparison of the clinical performances of the AdvanSure HPV screening real-time PCR, the Abbott real-time high-risk HPV test, and the hybrid capture high-risk HPV DNA test for cervical cancer screening. *Journal of Virological Methods* **205**, 57–60.

Cleveland, J.L., Junger, M.L., Saraiya, M., Markowitz, L.E., Dunne, E.F. and Epstein, J.B (2011): The connection between human papillomavirus and oropharyngeal squamous cell carcinomas in the United States: implications for dentistry. *Journal of the American Dental Association* **142**, 915-924.

Colgrove, J., Abiola, S. and Mello, M.M. (2010): HPV vaccination mandates - lawmaking amid political and scientific controversy. *New England Journal of Medicine* **363**, 785-791.

Daley, E., Dodd, V., DeBate, R., Vamos, C., Wheldon, C., Kline, N., Smith, S., Chandler, R., Dyer, K., Helmy, H. and Driscoll, A. (2014): Prevention of HPV-related oral cancer: assessing dentists' readiness. *Public Health* **128**, 231-282.

Dochez, C., Bogers, J.J., Verhelst, R. and Rees, H. (2014): HPV vaccines to prevent cervical cancer and genital warts: an update. *Vaccine* **32**, 1595-1601.

D'Souza, G., Agrawal, Y., Halpern, J., Bodison, S. and Gillison, M.L (2009): Oral sexual behaviors associated with prevalent oral human papillomavirus infection. *Journal of Infectious Diseases* **199**, 1263-1269.

Einstein, M.H., Baron, M., Levin, M.J., Chatterjee, A., Edwards, R.P., Zepp, F., Carletti, I., Dessy, F.J., Trofa, A.F., Schuind, A., Dubin, G. and HPV-010 Study Group (2009): Comparison of the immunogenicity and safety of Cervarix®and Gardasil®human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18-45 years. *Human Vaccines*. **5**, 705-719.

Fakhry, C., Westra, W.H., Li, S., Cmelak, A., Ridge, J.A., Pinto, H., Forastiere, A. and Gillison, M.L. (2008): Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *Journal of the National Cancer Institute* **100**, 261-269.

Forman, D., Franceschi, S., Sankaranarayanan, R., Bray, F., Ferlay, J., Dikshit, R., Jha, P. and Wild, C.P. (2012): Do cervical cancer data justify human papillomavirus vaccination in India? Epidemiological data sources and comprehensiveness. *Journal of the Royal Society of Medicine* **105**, 365-366.

Franco, E.L,, Villa, L.L., Sobrinho, J.P., Prado, J.M., Rousseau, M.C., Désy, M. and Rohan, T.E. (1999): Epidemiology of acquisition and clearance of cervical human papillomavirus infection in women from a high-risk area for cervical cancer. *Journal of Infectious Diseases* **180**, 1415-1423.

Gillison, M.L. (2008): Human papillomavirus-related diseases: oropharynx cancers and potential implications for adolescent HPV vaccination. *Journal of Adolescent Health* **43**, S52-60.

Gillison, M.L., Koch, W.M., Capone, R.B., Spafford, M., Westra, W.H., Wu, L., Zahurak, M.L., Daniel, R.W., Viglione, M., Symer, D.E., Shah, K.V. and Sidransky, D. (2000): Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *Journal of the National Cancer Institute* **92**, 709-720.

Gostin, L.O. (2011): Mandatory HPV vaccination and political debate. *Journal of American Medical Association* **306**, 1699-1700

Grce, M. and Mravak-Stipetić, M. (2014): Human papillomavirus-associated diseases. *Clinical Dermatology* **32**, 253-258.

Hariri, S., Dunne, E., Saraiya, M., Unger, E. and Markowitz, L. (2011): Chapter 5: Human Papillomavirus (HPV). In, *VPD Surveillance Manual, 5th edn*; eds Roush, S.W. and Baldy, L.M. Atlanta: CDC. www.cdc.gov/vaccines/pubs/surv-manual/chpt05-hpv.html

Harper, D.M. and Demars, L.R. (2014): Primary Strategies for HPV Infection and Cervical Cancer Prevention. *Clinical Obstetrics and Gynecology* **57**, 256-278.

Harries, J., Moodley, J., Barone, M.A., Mall, S. and Sinanovic, E. (2009): Preparing for HPV vaccination in South Africa: Key challenges and opinions. *Vaccine* **27**, 38-44.

Hernandez, B.Y., Wilkens, L.R., Zhu, X., Thompson, P., McDuffie, K., Shvetsov, Y.B., Kamemoto, L.E., Killeen, J., Ning, L. and Goodman, M.T. (2008): Transmission of human papillomavirus in heterosexual couples. *Emerging Infectious Diseases* **14**, 888-894.

Herrero R., Quint W., Hildesheim A., Gonzalez P., Struijk L., Katki H.A., Porras C., Schiffman M., Rodriguez A.C., Solomon D., Jimenez S., Schiller J.T., Lowy D.R., van Doorn L.J., Wacholder S., Kreimer A.R. and the CVT Vaccine Group. (2013): Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. *PLoS One* **8**, e68329.

Hwang, Y. and Lee, M. (2012): Comparison of the AdvanSure Human Papillomavirus Screening Real-Time PCR, the Abbott RealTime High Risk Human Papillomavirus Test and the Hybrid Capture Human Papillomavirus DNA Test for the Detection of Human Papillomavirus. *Annals of Laboratory Medicine* **32**, 201-205.

IARC (2007): *Monographs on the evaluation of carcinogenic risks to humans. Volume 90: Human Papillomaviruses*. Lyon, France: World Health Organization, International Agency for Research on Cancer.

Insinga, R.P., Dasbach, E.J. and Elbasha, E.H. (2005): Assessing the annual economic burden of preventing and treating anogenital human papillomavirus-related disease in the US: analytic framework and review of the literature. *Pharmacoeconomics* **23**, 1107-1122.

Joura, E. and the V503-001 study team (2013): Efficacy and immunogenicity of a novel 9-valent HPV L1 virus-like particle vaccine in 16-26 year old women. SS8-4 EUROGIN Conference. Florence, Italy. www.eurogin.com/2013/images/pdf/eurogin-2013-abstracts-part-1.pdf

Kaka, A.S., Kumar, B., Kumar, P., Wakely, P.E Jr., Kirsch, C.M., Old, M.O., Ozer, E., Agrawal, A., Carrau, R.E., Schuller, D.E., Siddiqui, F. and Teknos, T.N. (2013): Highly aggressive human papillomavirus-related oropharyngeal cancer: clinical, radiologic, and pathologic characteristics. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology* **116**, 327-335.

Kitchener, H.C., Canfell, K., Gilham, C., Sargent, A., Roberts, C., Desai, M. and Peto, J. (2014): The clinical effectiveness and cost-effectiveness of primary human papillomavirus cervical screening in England: extended follow-up of the ARTISTIC randomised trial cohort through three screening rounds. *Health Technology* Assessment **23**, 1-196.

Koulova, A., Tsui, J., Irwin, K., Van Damme, P., Biellik, R. and Aguado, M.T. (2008): Country recommendations on the inclusion of HPV vaccines in national immunization programmes among high-income countries, June 2006-January 2008. *Vaccine* **26**, 6529-6541.

Kreimer, A.R., Clifford, G.M., Boyle, P. and Franceschi, S. (2005): Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. *Cancer Epidemiology, Biomarkers and Prevention* **14**, 467-475.

Kumar, S. and Butler, D. (2013): Calls in India for legal action against US charity. *Nature News* doi:10.1038/nature.2013.13700

Lambert, R., Sauvaget, C., de Camargo Cancela, M. and Sankaranarayanan, R. (2011): Epidemiology of cancer from the oral cavity and oropharynx. *European Journal of Gastroenterology and Hepatology* **23**, 633-641.

Luxembourg, A. (2013): *An overview of the 9-valent HPV L1 virus-like particle vaccine clinical development program.* Florence, Italy: EUROGIN 2013 congress proceedings.

Machado, J., Reis, P.P., Zhang, T., Simpson, C., Xu W., Perez-Ordonez, B., Goldstein, D.P., Brown, D.H., Gilbert, R.W., Gullane, P.J., Irish, J.C. and Kamel-Reid, S. (2010): Low prevalence of human papillomavirus in oral cavity carcinomas. *Head and Neck Oncology* **2**, 6.

Mah, C.L., Deber, R.B., Guttmann, A., McGeer, A. and Krahn, M. (2011): Another look at the human papillomavirus vaccine experience in Canada. *American Journal of Public Health* **101**, 1850-1857.

Mattheij, I., Pollock, A.M. and Brhlikova, P. (2012): Do cervical cancer data justify HPV vaccination in India? Epidemiological data sources and comprehensiveness. *Journal of the Royal Society of Medicine* **105**, 250-262.

Melkane, A.E., Mirghani, H., Aupérin, A., Saulnier, P., Lacroix, L., Vielh, P., Casiraghi, O., Griscelli, F and Temam, S. (2014): HPV-related oropharyngeal squamous cell carcinomas: a comparison between three diagnostic approaches. *American Journal of Otolaryngology* **35**, 25-32.

Mello, M.M., Abiola, S. and Colgrove, J. (2012): Pharmaceutical companies' role in state vaccination policymaking: the case of human papillomavirus vaccination. *American Journal of Public Health* **102**, 893-898

Meyer, M., Huebbers, C.U., Siefer, O.G., Vent, J., Engbert, I., Eslick, G.D., Valter, M., Klussmann, J.P. and Preuss, S.F. (2014): Prevalence and risk factors for oral human papillomavirus infection in 129 women screened for cervical HPV infection. *Oral Oncology* **50**, 27-31.

Mirghani H., Amen F., Moreau F., Guigay J., Ferchiou M., Melkane A.E., Hartl D.M. and Lacau St Guily, J. (2014): Human papilloma virus testing in oropharyngeal squamous cell carcinoma: what the clinician should know. *Oral Oncology* **50**, 1-9.

Mravak-Stipetić, M., Sabol, I., Kranjčić, J., Kneževic, M. and Grce, M. (2013): Human papillomavirus in the lesions of the oral mucosa according to topography. *PLoS One* **8**, e69736.

Mroz, E.A. and Rocco, J.W. (2012): MATH, a novel measure of intratumor genetic heterogeneity, is high in poor-outcome classes of head and neck squamous cell carcinoma. *Oral Oncology* **49**, 211-215.

NCI (2014): *HPV and cancer*. www.cancer.gov/cancertopics/causes-prevention/risk/infectious-agents/hpv-fact-sheet.

Ndiaye, C., Mena, M., Alemany, L., Arbyn, M., Castellsagué, X., Laporte, L., Bosch, F.X., de Sanjosé, S. and Trottier H. (2014): HPV DNA, E6/E7 mRNA, and p16(INK4a) detection in head and neck cancers: a systematic review and meta-analysis. *Lancet Oncology* **15**, 1319-1331.

Oberg, T.N., Kipp, B.R., Vrana, J.A., Bartholet, M.K., Fales, C.J., Garcia, R., McDonald, A.N., Rosas, B.L., Henry, M.R. and Clayton, A.C. (2010): Comparison of p16INK4a and ProEx C immunostaining on cervical ThinPrep cytology and biopsy specimens. *Diagnostic Cytopathology* **38**, 564-572.

Osazuwa-Peters N. (2013): Human papillomavirus (HPV), HPV-associated oropharyngeal cancer, and HPV vaccine in the United States —do we need a broader vaccine policy? *Vaccine* **31**, 5500-5505.

Pett, M. and Coleman, N. (2007): Integration of high-risk human papillomavirus: a key event in cervical carcinogenesis? *Journal of Pathology* **212**, 356-367.

Polednak, A.P. (2014): Inaccuracies in oral cavity-pharynx cancer coded as the underlying cause of death on U.S. death certificates, and trends in mortality rates (1999-2010). *Oral Oncology* **50**, 732-739.

Radoi, L. and Luce D. (2013): A review of risk factors for oral cavity cancer: the importance of a standardized case definition. *Community Dentistry and Oral Epidemiology* **41**, 97-109.

Ragin, C.C. and Taioli, E. (2007): Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis. *International Journal of Cancer* **121**, 1813-1820.

Rautava, J. and Syrjänen, S. (2011): Human papillomavirus infections in the oral mucosa. *Journal of the American Dental Association* **142**, 905-914.

Ryerson A.B., Peters E.S., Coughlin S.S., Chen V.W., Gillison M.L., Reichman M.E., Wu, X., Chaturvedi, A.K. and Kawaoka, K. (2008): Burden of potentially human papillomavirus-associated cancers of the oropharynx and oral cavity in the US, 1998-2003. *Cancer* **113**(10 Suppl), 2901-2909.

Salazar, C.R., Anayannis, N., Smith, R.V., Wang, Y., Haigentz, M. Jr., Garg, M., Schiff, B.A., Kawachi, N., Elman, J., Belbin, T.J., Prystowsky, M.B., Burk, R.D. and Schlecht, N.F. (2014): Combined P16 and human papillomavirus testing predicts head and neck cancer survival. *International Journal of Cancer* **135**, 2404-2412.

Schiffman, M., Castle, P.E., Jeronimo, J., Rodriguez, A.C. and Wacholder, S. (2007): Human papillomavirus and cervical cancer. *Lancet* **370**, 890-907.

Scudellari, M. (2013): HPV: Sex, cancer and a virus. *Nature* **503**, 330-332.

SEER (2014): *Cancer Statistics Factsheets: Oral Cavity and Pharynx Cancer. National Cancer Institute*. Bethesda, MD, US. http://seer.cancer.gov/statfacts/html/oralcav.html

Shetty, K., Chattopadhyay, A. and Leigh, J. (2005): Detection and typing of human papilloma virus in the oral mucosa of patients infected with human immunodeficiency virus. *Oral Oncology Extra* **41**, 311-315.

Sinanovic, E., Moodley, J., Barone, M.A., Mall, S., Cleary, S. and Harries, J. (2009): The potential cost-effectiveness of adding a human papillomavirus vaccine to the cervical cancer screening programme in South Africa. *Vaccine* **27**, 6196-6202.

Singhi, A.D. and Westra W.H. (2010): Comparison of human papillomavirus in situ hybridization and p16 immunohistochemistry in the detection of human papillomavirus-associated head and neck cancer based on a prospective clinical experience. *Cancer* **116**, 2166-2173.

Sivasithamparam, J., Visk, C.A., Cohen, E.E. and King, A.C. (2013): Modifiable risk behaviors in patients with head and neck cancer. *Cancer* 119, 2419-2426.

Smith, E.M., Swarnavel, S., Ritchie, J.M., Wang, D., Haugen, T.H. and Turek, L.P. (2007): Prevalence of human papillomavirus in the oral cavity/oropharynx in a large population of children and adolescents. *Pediatric Infectious Disease Journal* **26**, 836-840.

Sturgis, E.M. and Cinciripini, P.M. (2007): Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? *Cancer* **110**, 1429-1435.

Summersgill, K.F., Smith, E.M., Levy, B.T., Allen, J.M., Haugen, T.H. and Turek, L.P. (2001): Human papillomavirus in the oral cavities of children and adolescents. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology* **91**, 62-69.

Syrjänen, K.J. (1987): Human papillomavirus (HPV) infections and their associations with squamous cell neoplasia. *Archiv fur Geschwulstforschung* **57**, 417-444.

Syrjänen, S. (2003): Human papillomavirus infections and oral tumors. *Medical Microbiology and Immunology* **192**, 123-128.

Termine, N., Giovannelli, L., Matranga, D., Caleca, M.P., Bellavia, C., Perino, A. and Campisi, G. (2011): Oral human papillomavirus infection in women with cervical HPV infection: new data from an Italian cohort and a metanalysis of the literature. *Oral Oncology* **47**, 244-250.

Toft, L., Storgaard, M., Müller, M., Sehr, P., Bonde, J., Tolstrup, M., Østergaard, L. and Søgaard, O.S. (2014): Comparison of the immunogenicity and reactogenicity of Cervarix®and Gardasil®human papillomavirus vaccines in HIV-infected adults: a randomized, double-blind clinical trial. *Journal of Infectious Diseases* **209**, 1165-1173.

Tomljenovic, L. and Shaw, C.A. (2012): Too fast or not too fast: the FDA's approval of Merck's HPV vaccine Gardasil. *Journal of Law and Medical Ethics* **40**, 673-681.

Tracy, J.K., Schluterman, N.H., Greene, C., Sow, S.O. and Gaff, H.D. (2014): Planning for human papillomavirus (HPV) vaccination in sub-Saharan Africa: A modeling-based approach. *Vaccine* **32**, 3316-3322.

van Bogaert, L.J. (2013): Are the currently existing anti-human papillomavirus vaccines appropriate for the developing world? *Annals of Medical and Health Sciences Research* **3**, 306-312.

Vogt, S.L., Gravitt, P.E., Martinson, N.A., Hoffmann, J. and D'Souza G. (2013): Concordant oral-genital HPV infection in South Africa couples: Evidence for Transmission. *Frontiers of Oncology* **3**, 303.

Walboomers J.M., Jacobs M.V., Manos M.M., Bosch F.X., Kummer J.A., Shah K.V., Snijders P.J., Peto J., Meijer C.J. and Muñoz N. (1999): Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *Journal of Pathology* **189**, 12-19.

Warnakulasuriya, S. (2009): Global epidemiology of oral and oropharyngeal cancer. *Oral Oncology* **45**, 309-316.

WHO (2009): Human papillomavirus vaccines. WHO position paper. *Weekly Epidemiological Record* **84**, 118-131.

WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre) (2010): *Human Papillomavirus and Related Cancers in World. Summary Report 2010*. www.hpvcentre.net/statistics/reports/XWX.pdf

Wu, X., Watson,M., Wilson, R., Saraiya, M., Cleveland, J.L. and Markowitz, L. (2012): Human Papillomavirus-Associated Cancers - United States, 2004-2008. *Morbidity and Mortality Weekly Report* **61**, 258-261.

Xie, X., Piao, L., Bullock, B.N., Smith, A., Su T., Zhang, M., Teknos, T.N., Arora, P.S. and Pan, Q. (2013): Targeting HPV16 E6-p300 interaction reactivates p53 and inhibits the tumorigenicity of HPV-positive head and neck squamous cell carcinoma. *Oncogene* **33**, 1037-1046.