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**Review Article**

# Preventing human papilloma virus transmission in the UAE: evidence-based interventions at primordial, primary and secondary prevention levels

**Niyi Awofeso***

Department of Healthcare Management, School of Health and Environmental Studies, Hamdan Bin Mohammed Smart University, P. O. Box 71400, Dubai Academic City, UAE

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***Correspondence:**
Niyi Awofeso,
E-mail: a.awofeso@hbmsu.ac.ae



## ABSTRACT

Oncogenic viruses, exemplified by Human Papilloma Virus (HPV) which causes cervical cancer, are currently linked to about 15% of human cancers globally. Death rates from cervical cancer have declined by 75% in industrialized nations over the past two decades leaving low and middle-income nations with about 90% of the disease burden. Cervical cancer is one of very few cancers that is almost completely vaccine-preventable – timely administration of the nanovalent HPV vaccine could prevent 85% to 92% of all cervical cancers. In the UAE during 2014, there were 93 incident cases of cervical cancer and 23 deaths from the disease, out of 912 incident cancer cases and about 420 deaths from cancer among females in UAE. Cervical cancer is UAE's third most commonly detected cancer among women and third most common cause of cancer-related death among women. Cervical cancer is a culturally sensitive disease in UAE and most Muslim nations where extramarital sex is illegal, given that HPV is generally sexually transmitted and persistent HPV infection is the cause of all cervical cancers. This review examines major cultural, behavioural and health management-related drivers of HPV transmission in UAE, and proposes evidence-based approaches for primordial, primary and secondary cervical cancer prevention.

**Keywords:** Cervical cancer, HPV, Prevention, UAE

## INTRODUCTION

In viral replication, some human viruses' DNA or RNA fragments may disrupt host cells' genes in ways that precipitate cancer. Fortunately, only a small proportion of infections with oncogenic viruses progress to cancer, typically after a decade or two. The causal link between human papilloma virus (HPV) and cervical cancer had been established since 1976, and causal links with oropharyngeal cancers were subsequently established.[1,2] HPV is an oncogenic and common sexually transmissible DNA virus whose high-risk types account for about 5% of all cancers worldwide.[3]

About a million women globally are estimated to have cervical cancer currently, although at least 35% are not currently diagnosed due mainly to low awareness, stigma, and poorly organized cervical cancer screening services. In 2012, 528,000 incident cervical cancer cases were diagnosed with 266,000 deaths – one death every two minutes. Between 85% and 90% of all cervical cancer cases occur in low and middle income nations. About 25% of all cervical cancer cases are registered in India (age-standardised incident rate of 27/100,000 women) and 26.5% of all deaths globally are also reported from India (age-standardized mortality rate of 15.2/100,000 women). In 2014, 122,844 women resident in India were

diagnosed with cervical cancer and 67,477 died from the disease Unlike most cancers which occur after 60 years of age, the peak incidence for cervical cancer globally is between the ages of 35-65 years.[4]

Of at least 150 serotypes of HPV that infect humans, 15 are ascertained to be high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), three as likely high-risk (26, 53, and 66), and 12 regarded as low-risk (6, 11, 40, 42, 43, 44, 54, 61, 70, 72 and 81) for cervical and oropharyngeal cancers.[5] Estimates indicate that 80% of the general population will be infected with at least one genital serotype of HPV in their life-course. Multiple sexual partners increase the risk of HPV infection.[6]

As HPV is essentially a sexually transmissible disease, it may be surmised that in societies with enforced codes of pre-marital chastity and prohibition of extramarital sex such as UAE and other Muslim nations in the Middle East and North Africa. The Islamic legal concept of *Zina* stipulates that not only is illegal sex a punishable sin, but that any act which may lead to illegal sex is also a crime. The punishment for Zina is same for men and women – 100 lashes for the unmarried and death by stoning for the married.[7]

Hence, it is logical to assume that the incidence of HPV infection in Muslim nations will be very low and subsequently the incidence of cervical cancer will be close to zero. However, in conservative Saudi Arabia, current estimate indicate that every year 152 women are diagnosed with cervical cancer and 55 die from the disease. A rare study of the prevalence of HPV genotypes among women with cervical cancer found that 89% were HPV DNA-positive. The most common HPV genotypes documented were 16 (65.2%), 31 (7.9%), 45 (6.7%), 18 (3.4%), and 73 (2.3%).[8] A more recent study comprising 417 Saudi Arabia residents of which 77% were Saudi nationals attending routine gynecological examinations revealed HPV DNA positivity of 9.8%. The prevalence of HPV was higher among non-Saudi nationals who participated in the study, compared with Saudi women participants (16.7% versus 7.8%, P = 0.0234).[9]

The imperfect correlation between established religious and cultural aspects of social structures for prevention of sexually transmissible infections such as HPV in Muslim majority nations and confirmed prevalence of the infection complicates efforts to control HPV spread, and creates tensions between institutions such as the Department of Religious Affairs and public health experts. In Muslim majority Pakistan for example, a study of 60 biopsied lesions of cervical cancer found that 97% were HPV DNA positive.[10] Well-intended efforts to enhance adherence to religious and cultural norms may inadvertently perpetuate stigma related to venereal diseases and hamper public health efforts to enhance awareness, prevention screening and early treatment of HPV-related diseases.[11]

The United Arab Emirates (UAE) was established on 2 December 1971 as a federation of seven Emirates - Abu Dhabi, Ajman, Dubai, Fujairah, Ras Al Khaimah, Sharjah, and Umm Al Quwain. About 87% of the 9.4 million residents are expatriates. The ICO Information Centre on HPV and Cancer reported in February 2016[12] that 1.82 million female residents in the UAE are at risk of developing cervical cancer. The report indicated that, in 2015, there were 93 detected cases of cervical cancer and 28 documented deaths, and that HPV serotype 16 or 18 were found among 72% of all cervical cancer biopsies.

The UAE health systems have been more progressive and conciliatory than other Middle East nations in efforts to prevent HPV infection. Cervical cancer screening was commenced for women aged 30 to 64 years at three years' intervals, in 2003, and by 2009, 40% had ever been screened. HPV vaccination for girls aged 15 to 17 years, and by 2011, 59% of eligible girls had completed a full course of vaccination. Public private partnership in enhancing public awareness about cervical cancer symptoms and screening opportunities is exemplified the "smear don't fear" campaigns in Dubai and Sharjah emirates organized yearly by Zulekha private hospital in partnership with Dubai Health Authority.[13] Nevertheless, significant gaps exist in efforts to prevent cervical cancer in UAE. The fact that HPV infection and subsequent cervical cancer risk are associated with extramarital sexual relations is a major barrier to vaccination uptake and timely screening, even among educated UAE Muslim women.[14] This article provides a critical review of evidence-based interventions for Primordial, Primary and Secondary Prevention of cervical cancer in UAE.

## PRIMORDIAL PREVENTION

The dictionary of epidemiology (2008) defines primordial prevention as 'actions to minimize future hazards to health and hence inhibit the establishment factors (environmental, economic, social, behavioral, and cultural) known to increase the risk of disease'.[15] In relation to cervical cancer prevention at the primordial level, the most important broad primary determinant is preventing teenage pregnancy. Anatomically, the inner cervical canal (endocervix) is lined by columnar epithelium. The outer area of the cervix (ectocervix) it is composed of stratified squamous epithelium extending from the vagina. The zone where the two epithelia join is the squamo-columnar junction (SCJ). The vulnerability of the SCJ to cervical cancer varies with a woman's age, hormonal status, history of birth trauma, HPV and other sexually transmissible diseases, pregnancy status and use of oral contraceptives. In teenage years, a large section of cervical columnar epithelium transform into squamous epithelium.

The cervical transformation zone is highly vulnerable to HPV infection and it's the most common site of cervical squamous cell cancer.[16] The UAE has a minimum legal age of marriage for women of 18 years, compared with

15 years for Kuwait, 10 years in Saudi Arabia and no age limit in Yemen. Setting a minimum legal age of marriage foe females at a stage when the cervical transformation zone is not very vulnerable to HPV infection. Conversely, promiscuity in teenage years, early age of first intercourse and early age at first pregnancy are associated with significantly higher risks of cervical cancer.[17]

Minor contributors to cervical cancer risk include tobacco smoking, male circumcision and chlamydia infection.[18-20] In the UAE tobacco smoking prevalence among women is less than 3%, male circumcision is obligatory for all Muslims, and social, religious and legal mores (particularly for unmarried Emirati females) contributes to efforts to reduce the risk of chlamydia and other sexually transmissible diseases.

## PRIMARY PREVENTION

Primary prevention aims to reduce the risk of specified diseases from developing. While the UAE 2012 estimates for cervical cancer cumulative risk at age 75 years (0.5%) and age standardized mortality rate (4.4/100,000 women) are significantly lower than the global average (0.8% and 6.8/100,000 women, respectively), the rising trend in the number of detected cases of cervical cancer in UAE - which is typically preceded by HPV infection at least a decade earlier – from 46 in 2008 to 93 in 2014 highlights the importance of primary prevention.[12] The most important and most effective primary prevention intervention for cervical cancer is HPV vaccine. Although awareness of the vaccine is improving, the preparatory community sensitization programs prior to vaccine introduction were not nearly as effective compared to countries like Rwanda, whose HPV vaccine uptake three years after the vaccination program commenced reached 93%, double the uptake rate for eligible girls in UAE over the same period.[12,21,22]

To address this deficiency, advocacy, communication and social mobilization activities need to be coordinated with important stakeholders such as parents, opinion leaders, and the Department of Religious Affairs and Family Development Foundations nationwide. A professional public health workforce skilled on health communication issues is required to implement evidence-based behavior change approaches that facilitate active community engagement and promote equity. It is preferable in UAE to refer to the HPV vaccine as a "cancer vaccine", rather than a vaccine against a sexually transmitted infection - if the perceived benefit is to prevent a cancer, the vaccine will probably command more interest and demand.[23]

In the UAE, a mild tension exists between primordial prevention programs and the core primary prevention strategy of HPV vaccination. In Abu Dhabi Emirate high schools for example, 8% to 10% of parents annually sign vaccination refusal forms to prohibit their daughters from receiving HPV vaccination. A few parents believe that the religious and cultural mores of Emirati are sufficient and virtuous safeguards to prevent HPV infection, and as such encouraging young girls to have HPV vaccine implies inadequate confidence in society's long=standing religious and cultural approaches for prevention of HPV and other sexually transmissible infections.[24,25] The later ages for HPV vaccination in UAE (ages 17 to 26) compared with the recommended ages in Western nations (e.g. ages 11 – 12 in USA) perhaps represents a seal of approval in the efficacy of socio-religious mores in maintaining chastity (at least among females) prior to age 18. However, the immune response at ages 11 – 12 is much higher than at the later ages recommended for females in UAE.[26] Sexual ethics may justify teenage males resident in UAE to be vaccinated against HPV for their own protection and to prevent them from transmitting HPV to females.[27]

The tension between socio-cultural issues related to vaccination demands appropriate sensitivity and pragmatism to address. In a study of parental perceptions vis-à-vis HPV vaccination for girls in New Delhi, India, for example, it was found that parents regarded the vaccine as safe but unnecessary for their (chaste) daughters. Some respondents that getting the vaccine will make sex safe, promote risky sexual behavior, precipitate social stigmas and tarnish their families' honour.[28]

Importantly, a study of sexual networking among youth in India ascertained that a study 10 percent of women and 30 percent of men in India engage in premarital sex by or before the age of 25 years, thus weakening the socio-religious counterweight to expanding HPV vaccination. While similar sexual networking trends may be applicable to UAE citizens and residents, evidence collection through research is problematic.[29]

Vaccine cost is another factor that may reduce the primary prevention potential of HPV vaccination. Apart from Abu Dhabi Emirate which provides vaccines to eligible schoolgirls free of charge, other Emirates charge between 400 – 700AED for a full cost of three doses of HPV vaccine. It may not be highly cost-effective for all seven UAE Emirates to provide HPV vaccine free of charge – according to modelling studies every 100,000 eligible females vaccinated against HPV in UAE will prevent about 1250cases of cervical cancer developing – i.e. AED 56,000 for each cervical cancer case averted.[30]

The cost effectiveness of HPV vaccination in UAE may be enhanced if the nanovalent vaccine, which prevents 85% to 92% of invasive cervical cancers replaces the bivalent and quadrivalent vaccines in current use which prevent about 75% of invasive cervical cancers.[31] Furthermore, free vaccination for all eligible Emirati females and reimbursement of at least 90% of the vaccine cost for all expatriate children covered by their parents' health insurance will facilitate equity in HPV prevention.

## SECONDARY PREVENTION

Secondary prevention focuses on early detection for prompt and appropriate treatment and management of HPV prevention and its sequelae. Early detection strongly predicts prognosis of cervical cancer – average 5-year survival for early stage 1A cancers is 93%, dropping steeply to 15% in late stage 4B In keeping with its epidemiological transition, the UAE has revamped and enhanced accessibility of screening services for cancers of the breast, cervix, lung and bowel.[32] Since mid-2015, a National Periodic Health Screening and Cancer Screening initiative for UAE citizens has been in place. Even with the appropriate administration most comprehensive HPV vaccine currently available to eligible females, at least 8% of HPV-related cases in cervical cancer will still occur. In Abu Dhabi, where the coverage is provided free to citizens and expatriates, coverage of eligible females currently approaches 90%, compared with less than 60% coverage in other Emirates.

Papanicolaou test, known as the Pap smear test, is the most commonly used test for screening cervical cancer. It is a cytological test that is used to detect precancerous cells of the cervix. A positive Pap smear test result is further confirmed by a colposcopy and cervical biopsy. The Pap smear test is considered a test of moderate sensitivity, ranging between 20% and 50%, yet with a high specificity exceeding 90%.[33] Since its introduction, Pap smear test has succeeded to reduce incidence of cervical cancer in the United States by 50% since organized screening commenced in 1975. However, managerial inefficiencies in the United states, such as 15% of the pap smear tests performed between 1993 and 2003 occurring among women who previously had hysterectomy and therefore do not need to have this procedure.[34] Visual inspection using acetic acid (VIA) test is an alternative screening test used to detect cervical cancer. VIA test is a sensitive, cheap, non-invasive test that gives instant results and thus is recommended to be used in low-income settings. Saleh compared sensitivity and specificity of VIA test to that of Pap smear and reported a sensitivity of 90% for the VIA test as compared to 50% for the Pap smear test; yet specificity values were 37% and 93% for VIA test and Pap smear test respectively.[35]

In April 2013, Abu Dhabi Emirate launched UAE's first cervical cancer screening program, with the objective of screening 70% of eligible women aged 25-65 years, achieve 60% reduction in cervical cancer incidence and 20% reduction in mortality by 2018. Screening frequency in this program is every three to five years. The implementation process was by invitation and limited to citizens. According to American Society for Clinical Pathology, cervical cancer screening should begin at age 21 years. Women aged younger than 21 years should not be screened regardless of the age of sexual initiation or other risk factors. For women aged 21 to 29 years, screening with cytology alone every 3 years is recommended. Women aged 30 to 65 years should be screened with cytology and HPV testing ("co-testing") every 5 years (preferred) or cytology alone every 3 years (acceptable).[36] Australia recently enacted a new cervical cancer screening policy, effective from 1 May 2017 replacing cervical cancer Pap smear screening with HPV testing. This policy is expected to reduce the already low incidence of cervical cancer by a further 15% annually. The revised National Cervical Screening Program focuses on women aged 25 to 74 years, both HPV vaccinated and unvaccinated, who will be invited to undertake an HPV test every 5 years. This approach should be considered in UAE as HPV test will detect 99% of cervical cancers, expect for rare neuroendocrine cervical cancer which is not also not effectively detectable by Pap smear tests.[37]

Since at least 2011, about 70% of cervical cancer cases in UAE present in late stages of the diseases, with consequent poor prognosis.[38] This may be an underestimate as Emirati women are likely to opt for overseas treatment for advanced cervical cancer symptoms. A 2014 study of 212 sexually active women in Sharjah emirate revealed that although 74.5% had knowledge about the Pap smear test, 37.2% had never ever undertaken a Pap smear test.[39] Despite this sub-optimal situation, UAE is currently the only Gulf Cooperation Council nation with a cervical cancer screening program. Cultural sensitivity and stigma about HPV being sexually transmitted disease hampers the effectiveness of screening programs. A commendable program to address barriers to cervical cancer screening is Abu Dhabi's Live Healthy and simply check campaign, promoting regular screenings and behaviour that reduce cancer risk.

## CONCLUSION

During the 4th World Government Summit in Dubai in February 2016, H.H. Sheikh Mohammad Bin Rashid Al Maktoum, United Arab Emirates Vice President and Prime Minister and Ruler of Dubai, announced major structural changes in the UAE's federal government. One such strategic move is the renaming of the UAE's Ministry of Health as the Ministry of Health and Prevention. H.H. Sheikh Mohammad stated that the Ministry's role will focus more on disease prevention and society's protection from illnesses. Cervical cancer prevention exemplifies a 'best buy' prevention initiative in UAE. Cervical cancer is relatively uncommon in countries that have instituted and maintained national screening programs with adequate support for the following pillars: information, leadership, financing, affordable nanovalent HPV vaccines, quality education, vaccination, screening and treatment services with appropriate call and recall of eligible women at regular intervals, monitoring and evaluation, and a proactive client-centred health workforce. The UAE health authorities may wish to examine the feasibility of making most of the cost of HPV vaccine insurance reimbursable

for eligible daughters of UAE residents with at least basic health insurance. The recently established National Periodic Health Screening and Cancer Screening initiative needs to be equipped to efficiently undertake service delivery, monitoring and evaluation, and a parallel voluntary screening program will be required for non-citizen residents. Finally, HPV DNA testing should be utilized as the standard cervical cancer screening intervention, in place of Pap smear screening approaches, in view of its greater sensitivity and specificity, as well as the reduced screening frequency.

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