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Etiological Role of Human Papillomavirus Infection in the Genital Organs of Woman

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Abstract: In the analysis of these literatures, the pathogenesis of the Human Papillomavirus (HPV) in recent years (2011-2022), ways of transmission, modern diagnostic methods, widely used vaccinations, importance of serological, molecular biological, immunological methods used in treatment and diagnosis, their possibilities and advantages are presented. For example, the Rapid Fluorescent Focus Inhibition Test (RFFIT), ELISA, viral RNA - RT-PCR, immunofluorescent test (dFAT), mouse inoculation test (MIT), as well as many clinical trials conducted on patients have shown the effectiveness of several vaccines and pharmacological agents and several immune boosters are among them.

Keywords: molecular-biological, PCR, RT-PCR, (CDV), Human Papillomavirus, HPV types.

INTRODUCTION:

Human Papillomavirus (HPV) is a common virus, transmitted through skin to skin sexual contact. Most people will have an HPV infection during their lifetime, even though they do not know they have it and many may not have any signs or symptoms of infection. HPV can infect both women and men. HPV infection usually clears on its own with the body's immune system. However, in some people, HPV infection may persist over time [2, 6 ,7].

There are more than 100 HPV types, and each type is identified by a number. Some HPV types can cause genital or anal warts. Other HPV types can cause cancer, most commonly cervical cancer. HPV infection is also a risk factor for vaginal, penile, anal, mouth and throat cancers. Human papillomavirus (HPV) is a common sexually transmitted infection (STI) and a well-known cause of cervical cancer. Several recent studies have demonstrated that HPV infection may be involved in the development of malignant tumors other than cervical cancer, including oral, pharyngeal, anal, and skin cancers. In fact, it has been estimated that approximately 10% of cancer cases worldwide are associated with HPV infection. Among urogenital malignancies, penile cancer is most likely to be associated with HPV infection, as confirmed by many epidemiological studies [8, 11, 17].

Etiology: Invasive cervical cancer (ICC) is the third most common cancer among women worldwide. In the middle of the 1970s, the hypothesis that cervical cancer may arise from virus infection was established, and in the 1990s, the causal relationship between genital human papilloma virus (HPV) infection and cervical cancer was confirmed. The most

significant etiological factor, HPV in the development of both invasive cervical cancer (ICC) and its precursor lesions (cervical intraepithelial neoplasia, CIN) has been well established. It is now widely recognized that HPV infection is a necessary cause for over 99% of cervical cancer cases, and nearly all invasive cervical cancers are indeed positive in HPV DNA test. HPV is a large of group of epitheliotropic viruses of more than 200 different subtypes. Among them, only 40 HPV subtypes could infect the human being. According to its potential to induce carcinogenesis, HPV types have been classified as low-risk oncogenicity (LR-HPV) and high-risk oncogenicity (HR-HPV). Previous studies showed that HR-HPV plays a crucial role in the etiology of anogenital cancer, especially cervical cancer. Many studies had showed that 13 HR-HPV subtypes were significant connected with cervical cancer, namely HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. Among the high-risk types, infection with HPV16 and 18 are associated with significantly higher risk of disease progression, and consequently these two types together cause approximately 70% of invasive cervical cancer worldwide [13, 16, 27].

The distribution of HPV genotypes in invasive cervical cancer is crucial to guide the introduction of prophylactic vaccines as well. Two prophylactic HPV vaccines are currently available and protect against two carcinogenic HR-HPV types (HPV16 and HPV18). One is a Merck's quadrivalent vaccine preventing infection from 4 HPV types (HPV 6, 11, 16, and 18) (Gardasil), and was approved by FDA in 2006. The second is a bivalent vaccine preventing infection from 2 high-risk oncogenic HPV types (HPV16 and 18) (Cervarix) [18, 20, 32].

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Human papillomavirus (HPV) is a sexually transmit-ted double-stranded DNA virus responsible for the devel-opment of anogenital (cervical, vaginal, vulvar, penile and anal) and oropharyngeal diseases in both women and men. The International Agency for Research on Cancer (IARC) considers it a human carcinogen and classifies HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66 as high-risk (HPV-hr) and HPV 6, 11, 42, 43, 44, 54, 61, 70, 72, 81 as low risk (HPV-lr) types. Some genotypes have an uncertain oncogenic potential. High-risk types 16 and 18 account for almost 70% of all cervical cancers, as well as about 90% of the anal cancers and a variable fraction of vulvar, vaginal, penile and oropharyngeal cancers. HPV genotypes 31, 33, 45, 52 and 58 are the etiological agent for more than 20% of cervical cancers. Low-risk genotypes 6 and 11 mainly cause cervical, vulvar and vaginal low-grade lesions, and are responsible for 90% of the anogenital warts or condy-loma acuminatum [12, 22, 30].

Vaccination represents one of the most cost-effective public health measures. The development of the prophylactic vaccine against HPV, with the aim of preventing the initial infection and subsequent neoplastic transformation, has generated some controversy. Therapeutic vaccines capable of inducing the regression of existing lesions are under development [5, 24, 29].

Currently, three different vaccines are commercialized, varying in the number of HPV genotypes contained. All vac-cines protect against HPV types 16 and 18. The quadriva-lent vaccine also targets types 6 and 11. The nonavalent vaccine, available in Europe since 2015, in addition to the genotypes present in the quadrivalent vaccine, also covers types 31, 33, 45, 52, and 58, predicting 90% efficacy in reducing the overall incidence of cancers associated with HPV infection. In Portugal, this vaccine has been part of the National Immunisation Schedule since 2008. The nonava-lent vaccine in the two-dose scheme replaced the quadriva-

lent vaccine in January 2017, and has been covering girls aged 10 years.2-6 Vaccination in males is recommended by several national and international scientific societies, and its introduction into the immunisation schedule is currently being discussed in Portugal [16, 25, 28].

Clinics: The objective of this article is to review the incidence of non-cervical lesions attributed to HPV genotypes contained in the nonavalent vaccine, and to assess its potential impact in terms of Public Health. Though the incidence of cervical cancer in the Extended Middle East and North Africa (EMENA) shows lower rates compared to the rest of the world [2, 7], the burden of HPV infection still warrants public health interventions. In addition, the age specific HPV prevalence has varied widely across different population and showed two peaks of HPV positivity in younger and older women [8,9]. Among the general population of Arab women with normal or abnor-mal cytology residing in Qatar, we recently estimated an HPV prevalence rate of 6.1% [10]. We also identified the presence of a varied genotypic profile of HPV with a high prevalence of low-risk HPV genotype 81. However, HPV DNA testing cannot differentiate between cur-rent and previous infection and does not reflect the lifetime risk of HPV infection. Moreover, despite much progress, risk factors influencing the epidemiology of HPV infection are not yet fully understood [11].

During HPV infection, both humoral and cellular immune responses are induced, and antibody production against HPV is important for preventing the spread of infection and re-infection [12,13]. Additionally, it has been shown that the cell-mediated immune response cleared the majority of HPV infections within 1–2 year's exposure [14]. Despite the fact that a number of seroprevalence studies have been conducted in resource-rich countries and some in resource-poor countries [15–18], no such data appears to be available from the Arab world. Qatar, a country located in the Arabian Peninsula has in recent years experienced rapid economic growth and globalization resulting in a large influx of foreign expatriates from Western, other Middle Eastern, African and Asian countries. The total population of women of child-bearing age was reported as 447,298; of which 382,067 represent Arabic women (Qatari and non-Qatari) according to the Ministry of Development Planning and Statistics, Qatar [6]. The economic and demographic transition and the resulting dynamic socio-economic and socio-cultural environment, may affect the social and sexual behaviours in the country. How-ever, how these changes affected the behavioral risk factors and impacts on the prevalence of HPV infection among Arab women is yet to be determined. In the present study, the high-risk HPV genotypes 16 and 59 were the most common among women with abnormal cytology, while HPV 35, 33, 39, 59 were found among those with normal cytology. HPV 81, 90, 11 were the most prevalent low-risk genotypes among women with both normal and abnormal cytology, a finding that is consistent with our previ-ous study [10]. HPV 81 was also the most frequent LR genotype among women with normal (34.5%) and abnormal cytology (25%), and this also corroborates our previous findings in this population [10]. The findings on HPV DNA prevalence and genotype distribution, as well as HPV seroprev-alence and potential risk factors for HPV infection, have the clinical potential to improve cervical cancer screening through identifying women at high risk for cervical dysplasia/cancer. Furthermore, they inform the development of genotype-specific vaccines for trials in population-level programs. It has been shown that HPV serology may underestimate infection exposure, as many women do not develop an HPV antibody response [31]. Though, seroprevalence studies has their limitations, such studies, such as the present study, provide a useful tool to understand the dynamics of HPV infection, thereby providing a baseline assessment for the incorporation of HPV vaccination programs in the State of Qatar. In the present study, we found a lower seroprevalence of 4.5% for HPV-IgG antibodies in Arab women than globally [32,33]. This low seroprevalence supports lower intensity of HPV transmission in the Arabfemale population, possibly due to poorly connected and sparse sexual networks, a result of the more conservative sexual norms in this part of the world [28]. Interestingly, none of the women were found positive for HPV IgM antibodies and there was no evidence of an

association between behavioral risk factors and HPV seropositivity. Further-more, it has been reported that once seroconversion occurs, anti-HPV antibody levels remain detectable for years [34, 35], but in the present study, all the HPV DNA positive women were HPV seronegative. The reason could be that these women never seroconverted, despite acquiring HPV infection previously [34, 36]. Additionally, there was no evidence of higher HPV DNA prevalence and seroprevalence among young women in this study, further supporting a flat distribution for HPV prevalence by age. This finding is consistent with our previous findings [10] and those reported in other limited-resource countries in Africa, Asia and globally [32, 37]. This finding how-ever contrasts with the common sharp peak in prevalece of HPV infection among young women following their sexual debut in most studies globally [27, 38]. Lastly, many potential risk factors have been established for HPV infections but none of these (marital status, education level, eco-nomic status, smoking, usage of contraception and awareness of HPV, cervical cancer and HPV vaccine) were associated with HPV DNA positivity or antibody positivity in the present study [39].

The strengths of the present study lie in the use of a standardized and sensitive molecular assay for HPV detection, rendering our findings amenable to a detailed analysis of HPV prevalence, distribution of HPV genotypes, seroprevalence and risk factors among general popula-tion of Arab women residing in the State of Qatar, and comparison to global patterns. In the present study, we aimed for such analysis to be relevant for planning of health service provi-sion and development of appropriate interventions based on the current characteristics of the infection burden and implied future trends for squamous intraepithelial lesions and cervical cancer. The indications that HPV infection burden might be increasing in EMEMNA, adds further importance to this investigation [24].

The limitations of this study include the fact that, because of socio-cultural context, we were unable to collect detailed data on sexual behaviour such as number of sexual partners, age at first sexual intercourse and extramarital relationships. Additionally, the present study was based on a convenient sample from women attending the Women hospital and Gynecology clinic at PHCC. Therefore, it is not known how representative is this sample of the wider Arab women population residing in the State of Qatar [19, 23].

Pathogenesis: HPV consists of a family of small, double-stranded DNA viruses that infect the epithelium. More than 200 distinct types have been identified; they are differentiated by their genomic sequence. Most HPV types infect the cutaneous epithelium and can cause common skin warts. About 40 types infect the mucosal epithelium; these are categorized according to their epidemiologic association with cervical cancer. Infection with low-risk or nononcogenic types, such as types 6 or 11, can cause benign or low-grade cervical cell abnormalities, anogenital warts, and respiratory tract papillomas. More than 90% of cases of anogenital warts are caused by low-risk HPV types 6 or 11. High-risk or oncogenic HPV types act as carcinogens in the development of cervical cancer and other anogenital cancers. High-risk types (including types 16, 18, and others) can cause low-grade cervical cell abnormalities, high-grade cervical cell abnormalities that are precursors to cancer, and anogenital cancers. High-risk HPV types are detected in 99% of cervical precancers. Type 16 is the cause of approximately 50% of cervical cancers worldwide, and types 16 and 18 together account for about 66% of cervical cancers. An additional five high-risk types, 31, 33, 45, 52, and 58, are responsible for another 15% of cervical cancers and 11% of all HPV-associated cancers. Infection with a high-risk HPV type is considered necessary for the development of cervical cancer but, by itself, is not sufficient to cause cancer. The vast majority of women with HPV infection, even those with high-risk HPV types, do not develop cancer. In addition to cervical cancer, high-risk HPV infection is associated with less common anogenital cancers, such as cancer of the vulva, vagina, penis, and anus. These HPV types can also cause oropharyngeal cancers [5, 7, 16].

Genomic organization and gene expression: The HPV has a circular double-stranded DNA as its genetic material. Its genome is comprises of two regions, early (E) and late (L). Early region has the coding regions which are commonly known as open reading frame (ORF) and the late region codes for 2 proteins, L1 and L2. These 2 proteins make its capsid. ORF is the region which codes for proteins or polypeptides. In spite of having two DNA strands, all the ORFs are situated on only one strand. The virus consists of six numbers of ORFs such as E1, E2, E4, E5, E6, and E7. Fig. 2 depicts the genetic organization of a papillomavirus [14].

Promoter site of its gene is activated only after infect the host cell. After doing infection to the host cell, the DNA of the papillomavirus goes into transcription (DNA to RNA). After transcription, primary mRNA is produce which contains all the ORFs. For these characteristics, this mRNA can code more than one protein or polypeptides (because it has six ORFs and all of those are able to do coding for proteins or polypeptides). This type of characterized RNA is generally known as polycistronic RNA [14].

This polycistronic RNA consists of two introns (non-coding sequence of DNA) and three exons (coding sequence of DNA). After the production of this RNA, it undergoes post-transcriptional modification in alteration mechanism more specifically splicing and produces multiple mRNAs. Splicing is a mechanism where the introns are removed. However, in HPV16, an intron of E6 ORF does not remove and endure intact after splicing. This intron codes E6 oncoprotein in translation and also expresses E7 oncoprotein. The viral genome s E2 ORF and enters into host genome, and thus, repression of E2 on both E6 and E7 is prevented. When this viral genome enters into host genome, the expressions obtained by E6 and E7 are increased, which help cells to proliferate and lead to malignancy [15].

Pathogenesis: HPV infection is very common and most people become infected after beginning their sexual life. HPV infection can be prevented by HPV vaccines, recommended for girls aged 9-14 years prior to the age of beginning sexual life. Some country guidelines also recommend HPV vaccination for boys [14, 28].

The incidence of penile squamous cell carcinoma, a rare malignancy of the urogenital system, shows geographic variations. It represents a significant public health hazard in developing countries such as Brazil, Uganda, and Puerto Rico. Phimosis, HPV infection, smoking, HIV infection, and STIs may cause penile cancer. It is currently widely accepted that HPV infection is present in approximately half of all patients with penile cancer [3, 31].

Transitional HPV infections can often be found at genital sites in episomal forms, which are present as simple infections with many viral loads. On the other hand, persistent HPV infection often results in integration of the viral genome into the host genome, which can promote the development of cancer. Therefore, verification of HPV-DNA integration into the host genome is essential to demonstrate an etiological role of HPV infection in penile carcinogenesis. Hence, the objectives of this study were to examine HPV infection status by detecting HPV-DNA locations in tumor tissue and to investigate the expression of certain proteins associated with the oncogenic process, in order to determine a possible role of HPV infection in the development of penile cancer [5, 20].

Patients and methods: Thirty-four patients who had undergone a partial or total penectomy for penile cancer at Kanazawa University Hospital or associated facilities were enrolled in this study. The diagnosis of penile cancer had been made by an experienced pathologist at each institution. Formalin-fixed, paraffin-embedded tumor tissue sam-ples of all participants were collected. Written informed consent for the use of these samples was obtained from all participants, in accordance with a protocol approved by the Ethics Committee of Kanazawa University Graduate School of Medical Science. Penile tumor tissue in the slides was initially identified by hematoxylin–eosin staining. Next, DNA was extracted from each paraffin-embedded tumor tissue sample by micro-dissection using the Pinpoint Slide DNA Isolation

System (Zymo Research, Orange, CA, USA). The DNA quality of all samples was confirmed by amplification of the β-globin gene by PCR analysis [16, 18].

HPV-DNA testing and genotyping were performed using an HPV GenoArray kit (HybriBio; HybriBio Ltd, Hong Kong) according to the manufacturer's protocol. This assay can be optimized to detect 37 different HPV types, including 15 high-risk (HR) HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, and 68), six low-risk (LR) HPV types (6, 11, 42, 43, 44, and CP8304), and 16 probably LR types (26, 34, 40, 54, 55, 57, 61, 67, 69, 70, 71, 72, 73, 82, 83, 84) by flow-through hybridization technique. After specific DNA was amplified by PCR, the amplified DNA samples were heat-denatured and then hybridized with specific HPV probes located on the membrane. The HPV type was determined by visualization of blue spots at the location of each HPV-type probe on the membrane using enzymatic immunoassay methods (Shigehara et al., 2010). The average detection limit of HPV-DNA in this array is around 300 copies/ml of the specific HPV-DNA target. This array has shown good concordance with results obtained by the Qiagen Hybrid Capture II procedure and the Amplicor HPV tests for HPV-type detection [19, 23].

A literature search was conducted in the PubMed data-base between 2013 and 2019 in order to identify papers re-garding non-cervical HPV lesions and vaccine. The search was narrowed to articles written in English and Portuguese and the MeSH terms used included: "HPV", "non-cervical cancer" and "vaccine". Studies were included in this review if they were systematic reviews, meta-analysis or rand-omized controlled trials and were selected on the basis of its the relevance [20, 24].

Vulvar and vaginal cancer: Vulvar and vaginal cancer are rare neoplasias, be-ing associated with HPV infection in a variable fraction of cases, estimated as 29% - 43% and 70%, respectively.13 Considering the subgroup of HPV-related cases, it is pre-sumed that 94.3% of vulvar cancers and 87.1% of vagi-nal cancers are attributed to the genotypes present in the nonavalent vaccine.3 Unlike HPV-negative cancers, virus-associated lesions tend to occur at a younger age, exhibit basaloid instead of keratinizing characteristics, lack p53 mutations and are associated with sexual risk factors. These characteristics are present both in cases of vulvar and vaginal cancers, although vaginal lesions are more fre-quently associated with HPV infection Recurrent respiratory papillomatosis HPV infection has been considered a sexually transmitted disease, but there is increasing evidence pointing to the existence of other transmission routes. Vertical transmis-sion occurs more frequently during vaginal delivery through contact of the fetus with infected maternal cells or during a caesarean section after premature rupture of membranes; ascendant infections have also been described.15 Recurrent respiratory papillomatosis represents the most frequent be-nign laryngeal tumor in children, with 90% to 95% of the cases being caused by HPV genotypes 6 and 11. Although it is a benign condition, it can lead to obstructive symptoms, causing significant morbidity. It also has a potential for ma-lignant transformation, particularly to squamous cell carci-noma about 1% in children and 3% to 7% of adults [22].

Epidemiology

HPV infection is extremely common throughout the world. Most sexually active adults will have an HPV infection at some point during their lives, although they may be unaware of their infection. Humans are the only natural reservoir for HPV. Other viruses in the papillomavirus family affect other species. Transmission HPV is transmitted through intimate, skin-to-skin contact with an infected person. Transmission is most common during vaginal, penile, anal, or oral sex. Studies of newly acquired HPV infection demonstrate that infection typically occurs soon after first sexual activity. In a prospective study of college women, the cumulative incidence of infection was 40% by 24 months after first sexual intercourse, and 10% of infections were caused by HPV 16. Autoinoculation from one body site to another can occur. Very rarely, vertical transmission of HPV from an infected mother to her infant can result in a condition called juvenile-onset recurrent respiratory papillomatosis. The human papillomavirus (HPV) belongs to Papillomaviridae (family of papillomavirus) [1, 2].

Taxonomically, Papillomaviridae is a virus family having the members of non-enveloped DNA viruses, on the whole called as Papillomaviruses [3]. Lots of species of papillomaviruses are there which are traditionally attributed as "types." Papillomaviruses can cause infection in most of the mammals [3] along with some other amniotes such as snakes, birds, and turtles [4-8].

Prevention: Vaccination prevents HPV infection, benefitting both the vaccinated person and their future sex partners by preventing spread of HPV. HPV transmission can be reduced, but not eliminated, with the consistent and correct use of physical barriers such as condoms [20, 23].

Cervical Cancer Screening: Most cases of and deaths from cervical cancer can be prevented through screening and treatment. The Pap test detects precancerous changes in cervical cells collected by a health care provider and placed on a slide (a conventional Pap) or in liquid media (liquid-based cytology). Clinical tests for HPV can be used as a primary screen either alone or in combination with cytology (co-test) or as triage after an equivocal cytology result. Recommendations for cervical cancer screening in the United States are based on systematic evidence reviews by major medical and other organizations including the U.S. Preventive Services Task Force (USPSTF), American Cancer Society (ACS), and the American College of Obstetricians and Gynecologists (ACOG). Annual cervical cancer screening is not recommended for average-risk individuals. Instead, cytology testing is recommended every 3 years from age 21 through 29 years. Between age 30 and 65 years, a choice of a cytology test every 3 years, an HPV test alone every 5 years, or cytology test plus an HPV test (co-test) every 5 years is recommended. Co-testing can be done by either collecting one sample for the cytology test and another for the HPV test or by using the remaining liquid cytology material for the HPV test. Cervical screening programs should screen those who have received HPV vaccination in the same manner as those who are unvaccinated. Screening is not recommended before age 21 years in those at average risk. For those age 30 to 65 years, cytology alone or primary HPV testing are preferred by USPSTF, but co-testing can be used as an alternative approach. USPSTF and ACOG have similar screening recommendations. ACS recommends that screening start at age 25 years for average-risk persons [9, 10].

HPV vaccination does not eliminate the need for continued cervical cancer screening, since up to 30% of cervical cancers are caused by HPV types not prevented by the quadrivalent or bivalent vaccines, and 15% of cervical cancers are caused by HPV types not prevented by the 9-valent vaccine. Human Papillomavirus Vaccines A 9-valent recombinant protein subunit HPV vaccine (9vHPV, Gardasil 9) is licensed for use and is currently distributed in the United States. Two additional HPV vaccines remain licensed in the United States but are not currently distributed: a quadrivalent HPV vaccine (4vHPV, Gardasil), and a bivalent HPV vaccine (2vHPV, Cervarix). All of the vaccines prevent infection with high-risk HPV types 16 and 18, types that cause most cervical and other cancers attributable to HPV; 9vHPV vaccine also prevents infection with five additional high-risk types. In addition, 4vHPV and 9vHPV vaccines prevent infections with HPV types 6 and 11, types that cause anogenital warts [10, 15].

The antigen for HPV vaccines is the L1 major capsid protein of HPV, produced by using recombinant DNA technology. L1 proteins self-assemble into noninfectious, nononcogenic units called virus-like particles (VLPs). The L1 proteins are produced by fermentation using Saccharomyces cerevisiae yeast; 9vHPV vaccine contains yeast protein. 9vHPV vaccine contains VLPs for nine HPV types: two types that cause anogenital warts (HPV types 6 and 11) and seven types that can cause cancers (HPV types 16, 18, 31, 33, 45, 52, and 58). 9vHPV vaccine is administered by intramuscular injection. Each dose of 9vHPV vaccine contains aluminum as an adjuvant. It contains no antibiotic or preservative. Vaccination Schedule and Use HPV vaccination is recommended for females and males at age 11 or 12 years for prevention of HPV infections and HPV-associated diseases, including certain cancers. The

vaccination series can be started at age 9 years. Catch-up HPV vaccination is recommended for all persons through age 26 years who are not adequately vaccinated. Catch-up HPV vaccination is not recommended for all adults older than age 26 years, since the public health benefit of vaccination in this age range is minimal. HPV vaccines are not licensed for use in persons older than age 45 years. HPV vaccines are administered as a 2- or 3-dose series, depending on age at initiation and medical conditions. A 2-dose series is recommended for persons who receive the first valid dose before their 15th birthday (except for persons with certain immunocompromising conditions). The second and final dose should be administered 6 through 12 months after the first dose (0, 6–12 month schedule). If dose 2 is administered at least 5 months after the first dose, it can be counted as valid.

If dose 2 is administered at a shorter interval, an additional dose should be administered at least 12 weeks after dose 2 and at least 6 to 12 months after dose 1.

A 3-dose series is recommended for persons who receive the first valid dose on or after their 15th birthday, and for persons with primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity, such as B lymphocyte antibody deficiencies, T lymphocyte complete or partial defects, human immunodeficiency virus (HIV) infection, malignant neoplasm, transplantation, autoimmune disease, or immunosuppressive therapy, in whom immune response to vaccination may be attenuated. In a 3-dose schedule, dose 2 should be administered 1–2 months after dose 1, and dose 3 should be administered 6 months after dose 1 (0, 1–2, 6 month schedule) [11, 13].

There is no maximum interval between doses. If the HPV vaccination schedule is interrupted, the vaccine series does not need to be restarted. For persons who already received 1 dose of HPV vaccine before their 15th birthday, and now are

age 15 years or older, the 2-dose series is considered adequate. If the series was interrupted after dose 1, dose 2 should be administered as soon as possible. Routine HPV vaccination is recommended beginning at 9 years of age for children with any history of sexual abuse or assault. Ideally, vaccine should be administered before any exposure to HPV through sexual contact. However, persons in theroutine and catch-up age ranges (through age 26 years) should be vaccinated, even if they might have been exposed to HPV in the past. Vaccination will provide less benefit to sexually active persons who have been already infected with one or more HPV vaccine types. However, HPV vaccination can provide protection against HPV vaccine types not already acquired. Recipients may be advised that prophylactic vaccine is not expected to have a therapeutic effect on existing HPV infection, anogenital warts,

or HPV-related lesions [12, 13].

HPV vaccine should be administered at the same visit as other age-appropriate vaccines, such as Tdap and quadrivalent meningococcal conjugate (MenACWY) vaccines. Administering all indicated vaccines at a single visit increases the likelihood that patients will receive each of the vaccines on schedule. Each vaccine should be administered using a separate syringe at a different anatomic site [14, 15].

Conclusion: HPV is a sexually transmitted pathogen responsible for almost all cases of cervical cancer, as well as an important fraction of preinvasive and invasive anogenital and oro-pharyngeal lesions in both sexes. The total fraction of malig-nant and pre-malignant lesions attributed to HPV genotypes contained in the nonavalent vaccine is significant in both women and men, which turns this vaccine into a great asset in terms of Public Health [24].

The overall HPV DNA prevalence and seroprevalence among Arab women in the State of Qatar are rather low in comparison to other countries. Despite the low prevalence, there is a diverse distribution of HPV genotypes among Arab women living in Qatar, and there appears to be an increase in prevalence over the last decade. Our study suggests that these genotypes should also included in future vaccines targeting this specific population. Furthermore, the information about

the molecular and sero-prevalence of HPV infection will be helpful for pol-icy makers in making an informed decision regarding introduction and development of policies, guidelines and implementation of HPV vaccination in the State of Qatar. Contrary to our expectations, no statistically significant association was observed between HPV DNA positivity or antibody positivity and potential risk factors for HPV infection. Though, Arab women in Qatar reported knowledge of cervical cancer, there was limited knowledge of its link to HPV infection and HPV vaccination. Awareness programs of risk associated with HPV infection and HPV vaccination are warranted in Qatar. Finally, further observational studies of HPV infection levels and HPV incidence among different age groups may help elucidate several poorly understood aspects of HPV epidemiology in this part of the world.

Treatment in HPV infection is still not available [27]. Only by giving vaccine, we can prevent HPV infection but the persons already exposed to HPV cannot be cured till now. Recent study shows that HPV-positive oropharyngeal cancers can be cured with the help of surgery as well as adjuvant therapy [28]. Antiretroviral therapy is also found to be helpful in the case of anal and cervical cancers [29].

The HPV infection is one of the major concerns nowadays. The virus can be spread by very common routes such as hand contact, sharing objects, sexual contacts, blood, and most surprisingly through inhalation also [30]. Protection from this virus is available only by vaccination. On the clinical trials (phase II) of CervarixTM, the efficacy of preventing HPV18 and 16 infection was 92% while efficacy in the prevention of obstinate infection was 100%. On the other hand, the efficacy of preventing HPV 6, 11, 16, and 18 with GardasilTM was 90% in Phase II and 100% (for HPV 16 and 18) in phase III clinical trial [31,32]. However, vaccination also associated with many limitations like it should be given within 13– 19 before any kind of sexual exposure though it can be spread through hand contact also. All kind of HPV cannot protect by this vaccines. Only a few can be protected. The use of condoms shows very little protection. Treatment is also unavailable till date. However, recent studies show some hope to as through surgery and adjuvant therapy or antiretroviral therapy is found to cure HPV-positive oropharyngeal, anal, and cervical cancers [25, 39].

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