JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1525266
J Contemp Med 2024;14(5):280-285

Review / Derleme

Where is the Human Papillomavirus vaccine heading? A Review

Human Papillomavirus aşısı nereye koşuyor? Derleme

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Abstract

DNA oncogenic viruses include Human papillomavirus that causes epithelial proliferation at cutaneous and mucosal surfaces. Human papillomavirus is the most common sexually transmitted infection. It spreads through contact between the skin or mucosa also enters the body through cutaneous or mucosal damage. Vertical transfer from mother to baby during birthing is a possibility but is uncommon. Human papillomavirus infection can result in cancer even though it is usually asymptomatic and readily treated by the immune system. Cancers of the head and neck mucosal regions, cervical, and anogenital areas are examples of malignant lesions associated with Human papillomavirus. It is also linked to non-cancerous disorders such recurrent respiratory papillomatosis and ano-genital warts. Globally, both men and women have an equal chance of contracting the infection at least once in their lifetime. The most important protection methods against Human papillomavirus are education and immunization. It is estimated that within a few decades, countries with effective national HPV vaccination programs will have eliminated cervical cancer. Cervical cancer remains a leading source of morbidity and mortality in underdeveloped countries without systematic screening and HPV immunization programs. In Turkey, cervical cancer screening is a routine procedure, and research is ongoing by the Ministry of Health to include Human papillomavirus vaccine in the national immunization schedule. In addition to discussing some of the challenges faced in achieving universal Human papillomavirus vaccination coverage and, consequently, the eradication of cervical cancer, this review seeks to increase awareness of efficiency, and safety of the Human papillomavirus vaccine.

Keywords: Human papillomavirus, cervical cancer, HPV vaccines

Öz

DNA onkojenik virüsleri arasında kutanöz ve mukozal yüzeylerde epitel proliferasyona neden olan Human papillomavirus bulunur. Human papillomavirus, cinsel yolla bulaşan en yaygın enfeksiyondur. Cilt veya mukoza arasındaki temas yoluyla yayılır, ayrıca kutanöz veya mukozal hasar yoluyla vücuda girer. Doğum sırasında anneden bebeğe dikey geçiş olasılığı vardır ancak, nadirdir. Genellikle asemptomatik olmasına ve bağışıklık sistemi tarafından kolayca bertaraf edilmesine rağmen kansere neden olabilir. Baş ve boyun mukozal bölgeleri, servikal ve anogenital bölgelerin kanserleri Human papillomavirus ile ilişkili kötü huylu lezyonlara örnektir. Ayrıca rekurren respiratuvar papillomatozis ve ano-genital siğiller gibi benign rahatsızlıklarla da bağlantılıdır. Hem erkekler hem de kadınlar yaşamları boyunca en az bir kez enfeksiyona yakalanma konusunda eşit riske sahiptir. Human papillomavirus'e karşı en önemli korunma yöntemleri eğitim ve aşılamadır. Birkaç on yıl içinde, etkili ulusal aşılama programları olan ülkelerin serviks kanserini ortadan kaldıracağı tahmin ediliyor. Serviks kanseri, sistematik tarama ve bağışıklama programları olmayan az gelişmiş ülkelerde önde gelen bir morbidite ve mortalite kaynağı olmaya devam etmektedir. Türkiye'de serviks kanseri taraması rutin bir işlemdir ve Sağlık Bakanlığı tarafından ulusal aşılama takvimine Human papillomavirus aşısını dahil etmek için çalışmalar sürmektedir. Bu inceleme, evrensel Human papillomavirus aşılama kapsamına ulaşmada karşılaşılan zorluklardan bazılarını ve dolayısıyla serviks kanserinin ortadan kaldırılmasını tartışmanın yanı sıra, Human papillomavirus aşısının etkinliği ve güvenliği konusunda farkındalığı artırmayı amaçlamaktadır.

Anahtar Kelimeler: Human papillomavirus, serviks kanseri, HPV aşıları

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Received *(Geliş Tarihi)*: 31.07.2024 **Accepted *(Kabul Tarihi)*:** 11.09.2024

INTRODUCTION

Globally, the most prevalent sexually transmitted infection affecting both sexes is caused by the Human papillomavirus (HPV).[1] According to estimates, the likelihood of contracting the virus during one's lifetime is approximately 90% for men and 80% for women.[1] Humans can readily become infected by skin-to-skin or skin-to-mucosal contact, even though sexual activity is the main way that HPV is spread.[1] Researches have shown that self-inoculation, mouth, fingers, skin contact, and fomites can all be potential routes for HPV infection in children and adults.[2] Warts related to tattoos, for instance, can spread through ink, equipment, etc.[3] An other HPV transmission pathway is vertical transmission from mother to child.[2]

Approximately 311,000 women lose their lives to cervical cancer each year, with 500,000 new cases being diagnosed.[4] Furthermore, in developing nations, 30 children under the age of ten pass away for every 100 moms who pass away from breast and cervical cancer.[5] Every year in our nation, there are 1,245 cervical cancer-related fatalities and 2,532 new cases.[6] About 40% of the general population is thought to be infected with HPV.[1] Compared to men, a significantly higher percentage of women suffer from and pass away from HPV-related illnesses.[1] The group of men with HIV who have intercourse with other men has the greatest frequency of HPV infection among all other groups in terms of males.[7]

Young age at first pregnancy, multiparity, use of hormonal contraceptives, tobacco use, immune system weakened individuals, HIV infection or immunosuppressive therapy, co-infection with other sexually transmitted infections (herpes virus, chlamydia, and gonococcal infections) are among the conditions that increase the risk of cervical cancer.[8]

Human Papillomavirus

HPV is a double-stranded, non-enveloped DNA virus from the Papillomaviridae family.[7] It has major (L1) and minor capsid proteins (L2).[7] There are more than 200 types of HPV.[7] Low-risk forms, such types HPV 6 and 11, are not usually linked to cancer but can cause benign disorders like genital warts.[1] High-risk types, like 16 and 18, are known to be carcinogenic.[1] Up to 92% of cervical cancers are caused by genotypes 16/18/31/33/45/52/58.[9] Viral oncogenesis is caused by the E6 and E7 oncoproteins, which impair the function of the tumor suppressors p53 and pRB after they enter host cells and also APOBEC genes of host contribute to oncogenesis.[10]

Human Papillomavirus Infections

HPV types can be classified into two groups: cutaneous and mucosal.[11] These cutaneous warts are benign and include common skin warts, flat warts, filiform warts, and plantar warts.[2,11,12] (**Figure 1**). The mucosal types are papilloms/warts of mucous membranes, including the upper respiratory tract, oral, anogenital, and conjunctival areas like condylomata acuminata, conjunctival papilloma, recurrent respiratory papillomatosis etc.[2,11,12] The other mucosal types are associated with precancers and cancers of anogenital, cervical, and oropharyngeal regions.[11,12]

It should be mentioned that most infected people are asymptomatic, or they may just have a temporary infection.[14] Mostly infected people are not aware of it.[15] Immunocompromised individuals, such as those infected with HIV, those undergoing chemotherapy, or those undergoing transplants, or with autoimmune diseases have a higher burden of HPV-associated illnesses.[1,11] Human papillomavirus infection can also affect reproductive organs in men, too.[1,15] HPV infection negatively affects sperm parameters, especially spermatozoa motility and number, semen volume, viscosity, so it can cause infertility.[1,15] Furthermore, HPV may have a role in the decreased rates of implantation and pregnancy during assisted reproductive technology operations by adversely affecting the invasiveness of trophoblastic cells.[1,15] Following HPV vaccination, there was an improvement in sperm motility and anti-sperm antibody prevalence, which led to a higher pregnancy rate than in unvaccinated couples recovering from HPV infection.[1]

Human papillomavirus can also cause cancers of the anus, vulva, vagina, penis, oropharynx, and head and neck.[8] HPV is associated with 85% of head and neck cancers, 60-78% of vaginal cancers, 19-48% of vulvar cancers, 80% to 97% of anal cancers, 40-53% of penile cancers, 13–60% of oropharyngeal cancers, and 5-11% of oral cavity.[8,9,16] The typical symptoms of laryngeal papillomas include stridor, poor vocal quality, growing hoarseness, and even severe airway blockage.[17]

Figure 1. A. Penile warts[13], B. Finger wart, C. Face wart.

A rare genetic illness called epidermodysplasia verruciformis is thought to be caused by a lack of cell-mediated immunity, which leads to an aberrant vulnerability to specific kinds of HPV and manifests as skin malignancies and persistent cutaneous lesions.[10]

Cervix Cancer Screening

Every three years, women between the ages of 21 and 29 should get a Papanicolaou (Pap) test. It is advised that women between the ages of 30 and 65 have further HPV/Pap testing every five years.[18] Women with negative HPV DNA are tested again after 5 years.[17] It may be suggested that women over 65 who have undergone repeated testing and received a negative diagnosis should stop getting checked for cervical cancer.[18]

For females thirty years of age or older, cytologic testing should be combined with HPV DNA testing.[18,19] After receiving the HPV vaccine, women should continue to get frequent screenings for cervical cancer.[20] HPV vaccinations can not change the course of infections that already existed prior to vaccination, nor do they offer protection against all HPV strains linked to the development of cervical cancer.[11] Cervical cytologic testing should start at age 21 for all healthy females, regardless of sexual experience, according to recommendations from the American College of Obstetricians and Gynecologists, the American Society for Colposcopy and Cervical Pathology.[11,20] Testing should start at age 25, according to the American Cancer Society.[11] According to the World Health Organisation and Ministry of Health recommendations, cervical cancer can be detected through screening from the age of 30 (from the age of 25 for women living with HIV).[8,19] In sexually active girls, if there is HIV infection, organ transplantation, or long-term corticosteroid treatment, cervical cytological screening should be performed twice at 6-month intervals within the first year and if the results are normal, it should continue to be performed annually thereafter.[11]

HPV vaccination, education, condom use, and male circumcision protect against HPV infections.[21]

Human Papillomavirus Vaccines

The "HeLa cells," an immortalized cancer cell line obtained from Henrietta Lacks's cervical carcinoma in 1951, just before her death, were used to support numerous medical advancements, such as the creation of the vaccination against the human papillomavirus.[22]

The first publicly available HPV vaccine licensed in 2006 for use in preventing illnesses caused by HPV infection in females aged 9 to 45, and and for males 9 to 26 years of age is Gardasil®, a quadrivalent vaccine (4vHPV).[12] Using recombinant DNA technology, the L1 protein is produced in *Saccharomyces cerevisiae* cells.[23] Gardasil® shields against HPV-6 and -11 infections in addition to HPV-16 and 18, which account for 90% of genital warts.[12] An amorphous aluminum hydroxyphosphate sulfate adjuvant is used to adsorber Gardasil®.[22] Approved in our country in 2008.[23]

The European Medicines Agency (EMA) granted a license for Cervarix®, a bivalent vaccine (2vHPV) in 2007.[12] L1 protein was expressed as non-infectious virus-like particles (VLPs) in cells cultured in *Trichoplusia* butterflies through the use of a DNA recombinant Baculovirus production system.[12] It is an inactive vaccine.[12] Cervarix® is formulated in a proprietary AS04 adjuvant containing aluminum hydroxide, 3-O-desacyl-4'-monophosphoryl lipid A (MPL), and is effective in defending against HPV-16 and HPV-18, which are responsible for nearly 70% of cervical cancers.[21] Registered in Turkey in 2007.[24]

With FDA approval in 2014, Gardasil 9® that is a 9-valent vaccine (9vHPV) provides more comprehensive protection against five more HPV strains (HPV-31, 33, 45, 52, and 58), which may be responsible for up to 20% of instances of cervical cancer.[12] Gardasil 9® is recommended for girls between the ages of 9 and 45, and for males 9 to 26 years of age in order to avoid diseases linked to HPV.[23] Gardasil 9® is also recommended for the prevention of dysplastic lesions, warts, anal lesions, oropharyngeal, and neck malignancies.[24] Amorphous aluminum hydroxyphosphate sulfate is used as an adjuvant in the formulation of Gardasil 9®.[12,25] Approved in Turkey on 11/21/2019.[24]

Since the VLP don't contain viral DNA, they can't replicate, infect cells, or cause illness.[25] Information on vaccines are shown in **Table 1**.

Table 1. Comparison of HPV vaccines[21,26]

Vaccine type	Bivalent	Quadrivalent	Nonavalent
Active ingredient	HPV types 16 and 18 L1-capsid virus-like particles	HPV types 6,11,16 and 18 L1-capsid virus-like particles	HPV types 6,11,16,18 31,33,45,52 and 58 L1-capsid virus-like particles
Vaccine type	inactivated recombinant	inactivated recombinant	inactivated recombinant
Production place	cells cultured in Trichoplusia butterflies	*Saccharomyces cerevisiae* cells	*Saccharomyces cerevisiae* cells
Protection	Premalignant lesions and cancers of cervical, vulvar and vaginal, anal	Premalignant lesions and cancers cervix, vulva, vagina, and anus Genital warts (condyloma acuminata)	Premalignant lesions and cancers of cervix, vulva, vagina, and anus Genital warts (condyloma acuminata)
Cross-defence	31, 33	31, 45	Not necessary
Method of administration	Intramuscular injection	Intramuscular injection	Intramuscular injection

For adolescents aged nine to fourteen, it can be administered according to the 2-dose schedule: The second injection should be given between 5 and 13 months after the first injection.[25] If the second dose is administered before 5 months after the first dose, the third dose must be administered.[25] For those aged 15 and over, it can be administered according to the 3-dose schedule: The second injection should be given 2 months after the first injection (not earlier than 1 month after the first dose), the third injection should be given 6 months after the first injection (not earlier than 3 months after the second dose).[11,25] According to current WHO recommendations, girls aged 9 to 20 should receive 1 or 2 doses, after 21 years of age, 2 doses at 6 intervals, and immunosuppressed individuals should receive at least 2 doses, and if possible, 3 doses.[27] A 3-dose HPV vaccination schedule is advised for people with primary or secondary immunocompromising conditions between the ages of 9 and 26, regardless of the age at onset, due to the possibility that immune responses and vaccine efficacy may be lower in immunocompromised people than in immunocompetent people.[11,25] Until the age of 26, the Advisory Committee on Immunization Practices (ACIP) advises males who have sex with men and immunocompromised individuals (including those who are HIV positive) to get vaccinated with 9vHPV or 4vHPV.[28] A series begun with 4vHPV or 2vHPV can be finished with 9vHPV but, for those who have already finished a 4vHPV or 2vHPV vaccination series, there is no suggestion regarding further immunization with 9vHPV.[11,28] The effectiveness of less than three doses of 9vHPV is not well-documented.[28]

The HPV vaccine series should begin at age 9 for children who have had past sexual abuse or assault, as their likelihood of experiencing such behavior again may be increased.[11]

Precautions and Contraindications

Cervarix® should not be administered to individuals who have experienced anaphylactic latex allergy.[28] Prefilled syringe of 2vHPV could contains latex rubber, vial stopper does not latex.[29,30] Those who have experienced acute yeast hypersensitivity in the past should not take 4vHPV or 9vHPV.[28,30] Individuals who have severe allergies to any part of a vaccine should not to get it.[28,30] Those who are suffering from mild to severe acute illnesses shouldn't get vaccinated until their condition has improved.[25,30]

It is also not recommended to administer HPV vaccines to women who are pregnant.[28,30] If a woman becomes pregnant after starting the vaccination series, the remaining three doses should be postponed until the end of her pregnancy.[28] If a vaccine dose has been administered during pregnancy, no action is required.[28,30]

Vaccine Safety

The most often reported adverse events on the Vaccine Adverse Event Reporting System (VAERS) were headache, dizziness, syncope, nausea, and soreness, redness, or swelling in the arm where the vaccine was administered.[31] Of the reports to VAERS, 6% were deemed serious.[31]

A person may, in extremely rare cases, experience a life-threatening allergic reaction (anaphylaxis) to any vaccine, including those for HPV.[30] According to reports, there are three incidences of anaphylaxis in the US for every million doses of vaccine.[31] In November 2015, the European Medicines Agency concluded that there is insufficient evidence to establish a causal relationship between HPV vaccines and either autoimmune disorders, Postural Orthostatic Tachycardia Syndrome (POTS) and Complex Regional Pain Syndrome (CRPS).[25,32]

Vaccine Effectiveness

Clinical trials on females have demonstrated the excellent efficacy of 4vHPV and 2vHPV in preventing cervical precancers associated with HPV strains 16 and 18.[11] Infections with the four HPV varieties that 4vHPV prevents declined 88% among females aged 14–19 and 81% among females aged 20–24 in the United States within 12 years of the vaccine's launch.[31] 4vHPV has been proven in clinical trials to be highly successful in avoiding genital warts associated with HPV types 6 and 11 in both male and female participants aged 16 to 26.[11] Between 2006 and 2014, the prevalence of anogenital warts in females dropped by 61% among those aged 15 to 19 and 44% among those aged 20 to 24.[31] Cervical precancer rates among tested females in 2014–2015 were 36% lower in 21–24-year-olds and 50% lower in 18–20-year-olds compared to 2008–2009.[31] It has also been demonstrated that 4vHPV is very successful in preventing anal precancers in males between the ages of 16 and 26.[11]

Since the introduction of immunization in the United States, Juvenile-onset recurrent respiratory papillomatosis has dramatically decreased.[31] Clinical trials involving female participants aged 16 to 26 have demonstrated that 9vHPV offers 97% protection against the additional 5 HPV types (31, 33, 45, 52, and 58) in the nonavalent product and produces noninferior immunogenicity for the 4 HPV types in the quadrivalent product (6, 11, 16, and 18).[11] Among unvaccinated women, there was a 40.1% reduction in the proportion infected with one or more of the quadrivalent vaccine-type HPV infections alone and a 57.6% reduction in HPV infections with the other five types of the nonavalent vaccine, excluding HPV 6/11/16/18, through herd immunity.[20] Heterosexual men have shown a decline in genital warts of about 82%.[2]

HPV Vaccine Coverage

A total of 144 nations have included HPV vaccines into their national immunization programs, covering girls only in 69 of them and both sexes in 75.[33] Notwithstanding the advantages of HPV vaccination, the global vaccination rate is falling short of what is needed to create herd immunity. Research indicates that a global vaccination rate of 80% is required to eradicate HPV infections.[34] The goal of the WHO's strategy to end cervical cancer as a public health

issue is to achieve 90% in girls, HPV vaccination coverage by 2030.[35] 35 (40%) countries had coverage of 50% or less with the last dose, while just 5 (6%) countries had coverage of 90%.[35] World population coverage is estimated at 15% with the last HPV dose.[36]

One challenge affecting HPV vaccination is vaccine availability and accessibility.[36] Another is vaccine hesitancy due to lack of parental knowledge and education or misinformation about the vaccine.[34] Additionally, noteworthy attitudes and beliefs that support HPV vaccine hesitation include doubt, mistrust of immunization providers, worries about side effects, and worries about vaccine safety.[35]

For the vaccines added to the vaccination schedule, the Expanded Immunization Program is provided with the supply of materials required for its implementation, target strategies are determined, logistic needs are met, work is carried out to train the staff responsible for vaccination services and the community, vaccine and syringe needs are determined, and stock and cold chain monitoring is carried out.[37]

For vaccines that are wanted to be added to the vaccination schedule, vaccine stocks must be kept stable and can be increased to meet rising worldwide demand.[38] Planning specialized trainings for parents and healthcare professionals, battling misinformation, and making responsible and constructive use of the media are all crucial. Transparency must be prioritized in order to establish trust.[39]

CONCLUSION

Increasing HPV vaccination stands out among the precautions that can be used to lower the incidence and death of cancer. Vaccination of all youth, regardless of gender, against HPV has been shown to be effective and safe, and to reduce the incidence of cancer and other diseases associated with HPV. In Turkey, access to the vaccine is difficult for adolescents with low socioeconomic status. It is known that the Ministry of Health is working on adding it to the national immunization schedule. This is is a long-term, highly profitable healthcare undertaking. Maternal and child health, and thus a healthy future, is undoubtedly the goal of all of us. A concentration on expanding the HPV vaccine's coverage and uptake on a worldwide scale will undoubtedly hasten the achievement of this objective.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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