Review

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Human papillomavirus vaccination: Review of the current evidence

İnsan papilloma virüs aşısı: Güncel kanıtların gözden geçirilmesi

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Abstract

Human papillomaviruses (HPV) can cause numerous cancers in males and females, including anogenital cancers. Cervical cancer, which is mainly caused by HPV, is one of the most preventable type of cancers. Since the understanding of the etiological association between HPV and cervical cancer, three HPV vaccines have been developed to date. HPV vaccines have been a controversial issue since the first vaccine was recommended to prevent cervical cancer in 2006. Although there are still ongoing controversial topics about HPV vaccines, such as efficacy in HPV-associated cancers, usage in HPV infected individuals and males, these vaccines present an opportunity for HPV-associated precancerous lesions prevention. World Health Organization (WHO) recognizes HPV-associated diseases as global health problems, and recommends that routine HPV vaccination should be included in national immunization programs. While some high-income countries have relatively high uptake of HPV vaccination rates, the low income countries are lagging in the introduction of HPV vaccine. In Turkey, the available vaccines are not in routine immunization schedule. The HPV vaccines are not only need to be more effective, but also be cheap and affordable for everyone in order to increase and sustain introductions of HPV vaccine in low-income and middle-income countries. We need more time to obtain follow-up data for the real-world efficacy, and more research in HPV vaccination.

Key words: *HPV vaccine, human papillomaviruses, vaccination*

Özet

İnsan papilloma virüsleri (HPV), erkeklerde ve kadınlarda, anogenital kanserler dâhil, çok sayıda kansere neden olabilir. Ağırlıklı olarak HPV'nin neden olduğu serviks kanseri, en önlenebilir kanser türlerinden biridir. HPV ve serviks kanseri arasındaki etiyolojik ilişkinin anlaşılmasından bu yana, bugüne kadar üç HPV aşısı geliştirilmiştir. HPV aşıları, 2006'da serviks kanserinin önlenmesi için önerilen ilk aşı ortaya çıktığından beri tartışmalı bir konu olmuştur. Her ne kadar aşıların HPV-ilişkili kanserlerdeki etkinliği, erkeklerde ve HPV ile enfekte bireylerdeki kullanımı gibi konularda tartışmalar hala devam etse de, HPV aşıları, HPV ilişkili prekanseröz lezyonların önlenmesi konusunda bir fırsat sunmaktadır. Dünya Sağlık Örgütü, HPV ile ilişkili hastalıkları küresel sağlık sorunları

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olarak kabul etmekte ve rutin HPV aşılarının ulusal aşılama programlarına dahil edilmesi gerektiğini önermektedir. Bazı yüksek gelirli ülkeler nispeten yüksek oranda HPV aşılama oranlarına sahipken, düşük gelirli ülkeler HPV aşısına ulaşma konusunda gecikmektedir. Türkiye'de mevcut HPV aşıları ulusal aşılama programında değildir. HPV aşılarının, düşük gelirli ve orta gelirli ülkelere ulaşımını artırmak ve sürdürmek için daha etkili olmasının ötesinde herkes için ucuz ve uygun olması da gerekir. Gerçek dünyadaki etkinliği açısından takip verilerine, bunun için de daha fazla zamana ve HPV aşıları ile ilgili daha çok araştırmaya ihtiyacımız vardır.

Anahtar kelimeler: *HPV aşısı, insan papilloma virusleri, aşılama*

Introduction

Human papillomaviruses (HPV) are non-enveloped double-stranded DNA viruses that cause epithelial tumors of the skin and mucous membranes in males and females. There are more than 200 types of HPV, which are classified based upon their genetic material and is assigned a genotype number. Some HPV types are labeled as low or high risk, according to their oncogenic potential. HPV infections are common and cause a wide variety of clinical manifestations such as genital warts, precancerous lesions and carcinomas. Although most infections typically resolve within months, persistent HPV infection, which is caused by high-risk types, may increase the risk of precancerous or cancerous lesions.[1] HPV can cause cervical, vulvar and vaginal cancers in females, penile cancers in males and anal and oropharyngeal cancers in both genders. In one study, HPV was associated with 90.6% of cervical cancers, 75% of vaginal cancers, 68.8% of vulvar cancers, 63.3% of penile cancers, 91.1% of anal cancers, and 70.1% of oropharyngeal cancers.[2] The researchs about HPV vaccines were initiated with an understanding of the etiological association between high-risk types of HPV and cervical cancer. As a result of studies, three different HPV vaccines have been developed. Cervarix® (bivalent, 2vHPV), Gardasil® (quadrivalent, 4vHPV) and Gardasil® 9 (9-valent, 9vHPV) vaccines are licensed HPV vaccines which target various HPV types (Table 1). The Food and Drug Administration (FDA) first approved first-generation Gardasil®, in 2006, which prevented infection of four strains of HPV. Then, Cervarix which is directed against HPV16 and 18, was licensed for use in females in 2009. The recent HPV vaccine, Gardasil® 9, was approved by the FDA in 2014. HPV vaccines present an opportunity for cancer prevention by protecting against acquisition of HPV infection. In this review article, we discuss the updates in HPV vaccination.

Benefits of the vaccines

All three HPV vaccines is a non-infectious, prophylactic, virus-like particle vaccine, designed to prevent infection with HPV and development of subsequent HPV-associated disease. The 4vHPV and 9vHPV vaccines are recommended for use in females and males; the 2vHPV vaccine is recommended for use in females. These vaccines protect against the oncogenic HPV strains that are detected in almost all cases of HPV-related cancers, the 4vHPV and 9vHPV vaccines also protect against almost all cases of genital warts. It is notable that cervical cancer is the most and best studied subject that is about understanding of the etiological association between HPV and cancers. An estimated 24600 HPV-related cancers newly diagnosed each year in the United States are caused by HPV type 16, or 18, and 3800 by the five additional HPV types targeted by 9vHPV.[3] Almost all of the cancers caused by the five additional HPV types occur in females.[3] All three HPV vaccines target HPV 16 and 18 types, which cause approximately 70% of cervical cancers worldwide, the 9vHPV vaccine additionally targets HPV types 31, 33, 45, 52, and 58, which cause an additional 15% to 20% of cervical cancers. In addition, 90% of anal cancers and most of the vulvar, vaginal, penile and oropharyngeal cancers are caused by HPV types 16 and 18, which are typically labeled as high-risk types of HPV. It was shown that women who received the vaccine had a 90% reduction in infection with HPV types 6, 11, 16, and 18 in comparison with women who received placebo in a study that tested a 4vHPV

vaccine in young females who were observed for three years.[4] In another study reported that the 4vHPV vaccine provided substantial protection against cervical abnormalities.[5] HPV 6 and 11 types, which are targeted by the 4vHPV and 9vHPV vaccines, cause 90% of genital warts.[6] A study of 4065 men, which is a randomized, placebo-controlled trial, reported that the 4vHPV vaccine prevents infection with HPV types 6, 11, 16, and 18 and the development of associated genital lesions in males aged 16-26 years.[7]

It appears that the total burden of HPV-related diseases, especially cancers, among males is less than in females. Therefore, vaccinating males appears to be less cost effective than vaccinating females. However, various modeling studies have shown that vaccinating both genders is more advantageous in reducing HPV infection than by vaccinating only females.[8,9] Given the limited resources, especially in low-income countries, it is recommended that efforts mainly focus on vaccinating young females, the group in which the highest benefit and cost-effectiveness of HPV vaccination is expected.

Administration

The American Cancer Society (ACS) published a guideline for the use of prophylactic HPV vaccines in 2007, recommending vaccination for females ages 9 to 26 years.[10] The Advisory Committee on Immunization Practices (ACIP) in the United States has developed recommendations for HPV vaccines since 2006. The ACIP and the Centers for Disease Control and Prevention (CDC) first published recommendations for routine HPV vaccination of females ages 11 to 12 years and catch-up vaccination for females ages 13 to

Table 1. HPV vaccines

Vaccines	Quadrivalent vaccine (4vHPV)	Bivalent vaccine (2vHPV)	9-valent vaccine (9vHPV)
Trade names	Gardasil®	Cervarix®	Gardasil® 9
Targeted HPV types	6, 11, **16, 18**	**16, 18**	6, 11, **16, 18**, 31, 33, 45, 52, 58
Manufacturer	Merck and Co., Inc.	Glaxo Smith Kline	Merck and Co., Inc.
Pharmaceutical form and contents	Suspension for injection 1 vial (0.5 ml)	Suspension for injection 1 vial (0.5 ml)	Suspension for injection 1 vial (0.5 ml)
Method of administration	Intramuscular	Intramuscular	Intramuscular
FDA-approved use			
• Female	Cervical, vulvar, vaginal, anal cancer, genital warts	Cervical cancer, cervical intraepithelial neoplasia	Cervical, vulvar, vaginal, anal cancer, genital warts
• Male	Anal cancer, genital warts	-	Anal cancer, genital warts
• Age	9-26 years	9-25 years	9-45 years
EMA-approved use			
• Female	Cervical, vulvar, vaginal, anal cancer, genital warts, premalignant anogenital lesions	Cervical, anal cancers, premalignant anogenital lesions	Cervical, vulvar, vaginal, anal cancer, genital warts, premalignant anogenital lesions
• Male	Anal cancer, genital warts	-	Anal cancer, genital warts
• Age	>9 years	>9 years	>9 years

EMA, European Medicines Agency; FDA, Food and Drug Administration; HPV, Human papillomaviruses

26 years with the 4vHPV vaccine in 2006. In 2009, the ACIP updated its recommendation for females to include the use of the 2vHPV vaccine and stated that 4vHPV may be given to males aged 9 to 26. In 2015, the ACIP updated their recommendations to include the 9vHPV vaccine.[11] The current ACIP recommendation for HPV vaccination is vaccination of females and males aged 11 to 12 years.[12] Vaccination can be given starting at age 9 years.[12] Children and adolescents aged 15 years and younger need two, not three, doses of the 9vHPV vaccine (Table 2). The administration for older adolescents and young adults aged 15-45 years is three inoculations within 6 months. Catch-up vaccination is recommended for females ages 13 through 26 years, and for males ages 13 through 21 years, who have not been previously vaccinated or who have not completed the three dose series.[12] According to the current ACIP recommendations, males 22 to 26 years old should also be vaccinated if they have sex with men or are immunocompromised because of transplantation, medications, or human immunodeficiency virus (HIV).[11,13]

Optimal time for vaccination

The vaccine works best when it is given before any exposure to HPV. Clinical trials show that preteens have a better immune response to the vaccine than older teens. In other words, HPV vaccination is most effective among individuals who are HPV-naive. Available HPV vaccines do not treat or clear preexisting HPV infections. Individuals who are sexually active should still get the vaccine in accordance with age-specific recommendations.[12] Sexually active individuals should still be vaccinated even if they have a history of an abnormal Papanicolaou (Pap) test, genital warts,

Table 2. Dosing schedules of HPV vaccines

HPV Vaccines	Quadrivalent vaccine (Gardasil®)	Bivalent vaccine (Cervarix®)	9-valent vaccine (Gardasil® 9)
FDA	**9 through 26 years;** 3-dose 0, 2, 6 months	**9 through 25 years;** 3-dose 0, 1, 6 months	**9 through 14 years;** 2-dose 0, 6 to 12 months* 3-dose 0, 2, 6 months **15 through 45 years;** 3-dose 0, 2, 6 months
EMA	**9 through 13 years;** 2-dose 0, 6 to 12 months* **>14 years;** 3-dose 0, 2, 6 months	**9 through 14 years;** 2-dose (The second dose given between 5 and 13 months after the first dose) **>15 years;** 3-dose 0, 2, 6 months	**9 through 14 years;** 2-dose 0, 6 to 12 months* 3-dose 0, 2, 6 months **>15 years;** 3-dose 0, 2, 6 months
Turkey	**9 through 13 years;** 2-dose 0, 6 to 12 months* **>14 years;** 3-dose 0, 2, 6 months	**9 through 14 years;** 2-dose (The second dose given between 5 and 13 months after the first dose) **>15 years;** 3-dose 0, 2, 6 months	-

*If the second dose is administered earlier than 5 months after the first dose, administer a third dose at least 4 months after the second dose.
EMA, European Medicines Agency; FDA, Food and Drug Administration; HPV, Human papillomaviruses

or HPV infection.[13] Beside that, girls and women do not need to get an HPV test or Pap test to find out if they should get the vaccine. However, cervical cancer screening is recommended beginning at age 21 years and continuing through age 65 years for both vaccinated and unvaccinated women.[6] This is important because the vaccine does not protect against all types of cervical cancer.

Choice of vaccine

Not all HPV vaccines are available in all locations in the world. While some countries introduced HPV vaccines into the national routine immunization schedule, some countries have not yet accessed HPV vaccine. Despite of the fact that the 2vHPV and 4vHPV vaccines are available in the country; these vaccines are not in routine immunization schedule in Turkey. The 9vHPV is recommended by the ACIP as one of three HPV vaccines that can be used for routine vaccination of females and one of two HPV vaccines for routine vaccination of males.[11] A randomized trial that compared the efficacy of the 9vHPV and 4vHPV vaccines among 14215 women who were followed for 4.5 years indicated that the efficacy of the 9vHPV vaccine was equivalent to that of the 4vHPV vaccine.[14] If there are not any barriers to get the 9vHPV, it may be recommended the 9vHPV vaccine with the greater HPV-type coverage. The 9vHPV vaccine may also be used to continue or complete a vaccination series started with 4vHPV or 2vHPV.[15] If cost and availability are an issue, it may be administered the 4vHPV or 2vHPV vaccines. Persons vaccinated previously with 9vHPV, 4vHPV, or 2vHPV, and received recommended doses of any HPV vaccine at the recommended dosing schedule, are considered adequately vaccinated.[15] If the vaccination schedule is interrupted, the series do not need to be restarted.[15] The number of recommended doses is based on age at administration of the first dose.[12] There is no ACIP recommendation for additional 9vHPV doses for persons who previously completed a series of 4vHPV or 2vHPV.[12,15]

Special populations

The ACIP recommends routine HPV vaccination beginning at age 9 years for children with a history of sexual abuse or assault.[15] Vaccination is also recommended through age 26 years for men who have sex with men if not vaccinated previously.[15] For transgender persons, the ACIP recommends routine HPV vaccination as for all adolescents, and vaccination through age 26 years for those who were not adequately vaccinated previously.[15] The ACIP recommends vaccination with 3 doses of HPV vaccine for females and males aged 9 through 26 years with primary or secondary immunocompromising conditions, which include B-lymphocyte antibody deficiencies, T-lymphocyte defects, HIV infection, malignant neoplasm, transplantation, autoimmune disease, and immunosuppressive therapy.[15] Administration of any HPV vaccine during pregnancy is not recommended because the safety of the vaccines in pregnancy is unknown.[12] Women who are breastfeeding may be vaccinated.[12]

Immunogenicity and efficacy

Immunogenicity

The researches showed that all HPV vaccines have good antibody responses with seroconversion rates about 95-100%.[11,16-23] Although the seroconversion rates are high in all participants, the younger females (9-15 or 10-14 years of age) have been reported to have higher titers than older females (16-26 or 15-25 years of age).[24-26] The threshold titers for protection have not been defined but higher titers from previous exposure are related to lower re-infection rates with the same HPV type.[27,28]

Efficacy

Cervical, vaginal and vulvar disease: Cervical diseases including cervical intraepithelial neoplasia (CIN 2 or 3) and adenocarcinoma in situ can be prevented by HPV vaccination.[29] A phase III trial compared 4vHPV vaccine with placebo among 5455 women who were followed for an average of three years indicat-

ed that the 4vHPV vaccine significantly reduced the incidence of HPV-associated anogenital diseases in young women.[30] Another trial involving 12167 women between the ages of 15 and 26 years, found that the vaccine group had a significantly lower occurrence of high-grade cervical intraepithelial neoplasia related to HPV than the placebo group.[31] A randomized, international, double-blind study of the 9vHPV vaccine in 14215 women, found that the new vaccine was 96.7% effective for preventing significant dysplasia (CIN 2 or higher) caused by HPV types 31, 33, 45, 52, and 58.[14]

Research shows that HPV vaccination is also effective in preventing HPV-associated disease in older women, but the overall benefit is less than in younger females.[32] Thus, it appears that a prior history of HPV attenuates vaccinate efficacy. In this regard, in 2017, ACS make an additional statement to ACIP recommendations that vaccination in older ages is less effective and the individual must be informed.[33] Besides that, a Cochrane review evaluating bivalent and quadrivalent vaccines have found that vaccines protect against cervical precancer in adolescent girls and young women, however results for the cervical cancer prevention are limited because of the need for long-term follow-up research.[29]

Anal disease: There is limited data informing the impact of HPV vaccine on anal intraepithelial neoplasia (AIN) and anal cancers. However, current researches suggest vaccine efficacy for the prevention. A randomized, double-blind study compared 4vHPV vaccine with placebo among 602 healthy men who have sex with men indicated that vaccination reduced the rate of AIN.[34] There is no direct evidence of efficacy data informing the prevention of AIN in females.

Oral disease: There is no evidence for prevention of oropharyngeal cancers in males or females. However, there is limited data of prevention of oral HPV infection.[35]

Anogenital warts: On the basis of the available evidence, it has been demonstrated the efficacy of 4vHPV vaccine for preventing anogenital warts which are mostly caused by HPV types 6 and 11.[36,37] Since the 9vHPV also targets HPV types 16 and 18, it may be expected to have similar efficacy. A phase III trial, evaluated the efficacy of the quadrivalent vaccine in preventing anogenital diseases associated with HPV types 6, 11, 16, and 18, vaccine efficacy for preventing vulvar and vaginal condylomas was 100% among HPV-naive participants and 70 to 78% among the overall population.[30] A 6 year follow-up study in Sweden reported that the incidence of genital warts was reduced in both women and men despite the low vaccination coverage of 30% in women and no coverage in men.[38] A meta-analysis of 20 studies that were conducted in nine high-income countries reports that in countries that have female vaccination coverage of at least 50% found that HPV type 16/18 infections decreased by 68%, anogenital warts by 61% in 13-19 years of age females. Besides, results suggesting herd effects were reported, such as significant reductions in anogenital warts were reported in boys younger than 20 years of age and women 20-39 years of age. In countries that have female vaccination coverage lower than 50% anogenital warts incidence was also reduced however no herd effect was observed.[39]

Duration of protection: Researches suggest that vaccine protection is long-lasting. On the basis of the available evidence, studies have followed vaccinated individuals for ten years, and show that there is no evidence of weakened protection over time. For instance, continued protection with the quadrivalent vaccine in women has been observed through at least 10 years following vaccination.[40]

Safety

The HPV vaccines appear to be safe. These vaccines that were studied in thousands of people around the world have documented safety in large clinical trials. These studies showed no serious safety concerns. Like any vaccine or medicine, HPV vaccination can cause side effects. Many people who get vaccinated have no side effects at all. Some people report having very mild side effects, such as headache, fever, nausea, dizziness, and injection-site pain, swelling, erythema, pruritus, and bruising.[11,41]

Conclusion

HPV vaccination represents a landmark, not only in the history of vaccination, but in the prevention of HPV-associated infections and cancers. Although the real efficacy of immunization on HPV-related cancers will be evident in the next decades, the HPV vaccines present an opportunity for precancerous lesions prevention by protecting against acquisition of HPV infection. WHO recognizes the importance of cervical cancer and other HPV-related diseases as global health problems. Therefore, they recommend that routine HPV vaccination should be included in national immunization programs. According to WHO, over 80 countries, mostly high income countries, included HPV vaccination into national routine immunization schedule in 2018. While some high-income countries have relatively high uptake of HPV vaccination rates, the low and middle-income countries are lagging in the introduction of HPV vaccine. It is understood that there is considerable need to increase and sustain introductions of HPV vaccine in low-income and middle-income countries, because of carrying the greatest share of disease burden. In order to accomplish this, these vaccines not only need to be more effective, but also cheap and affordable for everyone. In Turkey, the available vaccines are not in routine immunization schedule. It seems that Turkey will not permit the use of HPV vaccines to be included in national routine immunization schedule unless a consensus is made on efficacy, protection rates and safety of HPV vaccination or ongoing controversies about HPV vaccines are over. We need more time to obtain follow-up data for the real-world efficacy, and more researches in HPV vaccination to control over HPV-associated diseases.

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