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REVIEW

HPV, HPV VACCINATION WORLDWIDE AND CURRENT STATUS OF HPV VACCINATION IN TURKEY: A LITERATURE REVIEW

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ABSTRACT

Human papillomavirus is the most common sexually transmitted viral infection in the world. The infection can cause cancers of the anus, vulva, vagina, penis, and oropharynx. There are more than one hundred subtypes of human papillomavirus, of which thirteen are the high-risk types that may cause cancer. Human papillomavirus 16 and 18 are the main types that are noted as high-risk, causing cancer and neoplasia. Cervical cancer is the fourth most frequent cancer among women worldwide, yet it is preventable and treatable when diagnosed early. Almost all cervical cancer cases are linked to infection with high-risk human papillomavirus subtypes, which are extremely common. Cervical cancer occupies a large place in cancer screening, diagnosis, and treatment. It is critical to include the vaccine in national vaccination programs in order to increase herd immunity to human papillomavirus. The human papillomavirus vaccine should be made accessible to everyone, as well as screening tests for human papillomavirus-related diseases. The awareness of human papillomavirus vaccines in immunization programs by health authorities can significantly increase the acceptability of the vaccine in communities. As of May 2022, the human papillomavirus vaccine is not included in the national vaccination program in Turkey. In our study, we have compiled why the human papillomavirus vaccine should be included in the vaccination calendar in Turkey, within the scope of the latest research on this subject.

Keywords: Cervical cancer, vaccination, human papillomavirus, viral infection, public health

INTRODUCTION

Human papillomavirus (HPV) is a group of viruses that are common all over the world. There are more than one hundred subtypes of HPV, of which 13 are high-risk subtypes that can cause cancers of the epithelial mucosal surfaces (1). There is evidence that HPV causes cancers of the anus, vulva, vagina, penis, oropharynx, and cervix (2). Cervical cancers are the fourth most common type of cancer encountered in women worldwide (3). Two types of HPV (HPV16 and 18) are known to cause 70% of cervical cancers and pre-cancerous lesions (3).

Human papillomavirus is transmitted through sexual contact or mucosal contact with an infected area (1). Various methods such as condom use, avoidance of direct contact, testing, and vaccination can be used to prevent the spread of HPV and the risk of cancer (2). Most countries have included the HPV vaccine in their vaccination calendar in order to reduce the economic burden of HPV (4). In our study, we presented general information on HPV and its vaccination, and have compiled why the HPV vaccine should be included in the vaccination calendar in Turkey, within the scope of the latest research on this subject.

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EPIDEMIOLOGY

Human papillomavirus related diseases are the most common sexually transmitted viral infections in the world. It is accepted that most sexually active people are infected with at least one type of HPV at some point in their lives (5-7). The peak prevalence of HPV among young women is at the ages of 20 to 24 (8). However, the prevalence of HPV remains steady among men in all age groups (9, 10). In addition to cervical, penile, anal, vaginal, vulvar, and oropharyngeal cancers, HPV is associated with respiratory papillomatosis and anogenital warts (7). According to a systematic review of thirty-two studies conducted around the world, the annual incidence of anogenital warts ranged from 160 to 289 cases per 100,000 (11). The infection is transmitted through close skin-to-skin contact, most commonly through sexual contact (7). It can be transmitted by skin-mucous contact to the genital areas of the infected area of the person, such as the penis or female external genitalia, or areas such as the mouth and anus (7). Moreover, autoinoculation can occur from one part of the body to another (12).

Eighty-four percent of new cervical cancer cases and 90% of mortalities occur in middle- and low-income countries (13). Almost all cervical cancer cases are linked to infection with high-risk HPV (3). According to the World Health Organization (WHO), cervical cancer was diagnosed in around 570,000 women worldwide in 2018 and about 311,000 women died from the disease (3, 14). While the incidence of cervical cancer is relatively high in Central and Eastern European countries, around 14.9 cases per 100,000, it is lower in Western European countries with 6.9 cases per 100,000 (15). Turkey, on the other hand, has an age-adjusted incidence, which is 4.3 per 100,000 and its mortality is 1.7 per 100,000 (16). In addition, HPV16 and HPV18 are responsible for 75.4% of HPV-positive invasive cervical cancer cases in Turkey (17).

CLINICAL PRESENTATION

Human papillomavirus, a non-enveloped capsid virus with double-stranded DNA, enters the human body through cracks in the epidermis (18). Chronic infection, local infection, or dysplasia are degenerative changes that occur before malignancy (19). Regardless of gender, HPV can cause conditions and diseases in humans (20). HPV exposure can cause benign warts and cancers, though having no evident disease is more common (21). The immune system can recognize HPV and cure HPV infection (7). Therefore, HPV does not lead to the aforementioned conditions every time (7). In some cases, HPV was cleared from the body within two years (22). However, in organ-transplant and immunosuppressed patients, HPV-related diseases present themselves more frequently (e.g., anal cancer ratio of HIV-infected men is greater than HIV-negative men) and more complex due to widespread clinical presentations, creating a much larger burden (7, 23).

HPV-associated Cancers

Human papillomavirus is known to cause two main types of cancer: mucosal and skin (24). HPV is as a risk factor for oropharyngeal, anal, penile, and cervical cancers (25, 26). Benign lesions are more frequent even though high-risk types can also be detected in the head area, such as squamous cell carcinoma being the most common cancer of the oral cavity (27). HPV causes cervical cancers more commonly, though penile cancer rates of 20-60% are not negligible (28).

Cervical cancer is the only one that was admitted to the routine screening among HPV-associated cancers (3, 29). Especially HPV16 and 18 variants have a strong relationship with cervical cancer (19, 22, 30). It is estimated that 96% of cervical cancers are due to HPV (24). After the initial HPV exposure, precancerous lesions followed by cervical invasion create cervical cancer (29). The primary risk factor for cervical cancer is the male partner's sexual behavior (29).

TREATMENT

There is no generally accepted treatment for symptomatic HPV infection, though clinical studies continue to overcome this gap (31). Gene-Eden-VIR/Novirin is among those studies and achieved decreased time for HPV clearance with no adverse effect in one of its clinical trials (31).

Genital warts tend to regress by themselves with or without treatment due to their benign nature (7). Treatment of genital warts includes topical medications (podofilox gel, imiquimod cream, sinecatechins ointment) and only avails presenting symptoms (7, 32). Cryotherapy is another method to deal with warts, but, for widespread cases, surgical approaches are recommended (7, 32).

Radiotherapy, chemotherapy, and surgical removal of the infected tissues/organs are alternatives to manage to treat HPV-related cancers (33). For cervical cancer, different outcomes can be obtained depending on cancer staging, and it is easier to achieve complete resolution in stage 1A, while palliative care is the only option in stage 4B (21, 32). The desire for fertility, size of the tumor, and age of the patient may also affect the treatment plan of cervical cancer (7). Cisplatin is the primary option for chemotherapy, and cetuximab-based treatment could be an alternative for it (21, 34).

Notably, there are studies on therapeutic vaccines aiming to target HPV proteins and create an immune response without needing any further surgeries (35). However, there are still obstacles ahead, and currently, there is no approved therapeutic vaccine in use (35). Targeting E6 and E7 oncoproteins is in development for anal cancer besides many other epithelial neoplasms (36). Also, for penile cancer, studies targeting the HPV pathway with T-cell therapy in addition to chemotherapy are ongoing (28).

PROPHYLACTIC VACCINATION

Vaccines came into use mainly in the 20th century, and their impact on public health and mortality reduction was enormous (37). In general, elimination studies are carried out with vaccines against fourteen main diseases worldwide (38). A standardized vaccination scheme that focused on child vaccination was established within the scope of the Expanded Programme on Immunization (EPI) implemented by WHO in 1977 (38). This scheme has been expanded for different diseases in accordance with endemic countries and developing technology (38). Countries also have immunization programs associated with EPI and these vary depending on regional and country policies. Moreover, the HPV vaccine is included in vaccination programs in some countries (38).

Human papillomavirus vaccines are used for recognizing the natural immunity toward L1 capsid protein and providing antibody protection (39). The vaccines include L1 major capsid proteins that resemble HPV particles (38). There are three licensed vaccines against disease-causing HPVs: divalent Cervarix (HPV16 and 18), a tetravalent Gardasil (HPV6, 11, 16, and 18), and a nine-valent Gardasil 9 (HPV6, 11, 16, 18, 31, 33, 45, 52, and 58) (38, 40). All three contain the two high-risk HPV subtypes (HPV16 and 18). Furthermore, Gardasil prevents infections of HPV6 and 11, which are responsible for 90% of genital warts, and Gardasil 9 inhibits five more HPV subtypes that are responsible for 10% to 20% of cervical cancers (40). HPV vaccines are projected to be a profitable option primarily to reduce the incidence of cervical cancer and anogenital HPV infections (41).

World Health Organization aims to vaccinate 90% of all girls by the age of 15 years, to screen 70% of women aged 35-45 years twice, to ensure that at least 90% of all precancerous lesions detected during screening are cured. Thus, it aims to reduce the age-specific incidence of cervical cancer to less than 4 per 100,000 women worldwide (42). American Cancer Society recommends HPV vaccinations to girls and boys aged 9-14 years and young male adults and suggests HPV vaccines for young female adults aged 14-26 years to be recommended by consulting with healthcare professionals and making a clinical decision after the risks are understood. WHO does not recommend HPV vaccination primarily to males and argues that priority should be given to females at risk of cervical cancer. However, the Centers for Disease Control and Prevention (CDC) suggest the Gardasil vaccine for young males (40). In addition, WHO does not recommend HPV vaccination during pregnancy, especially considering the risk of spontaneous abortion (43).

Global Policies

Human papillomavirus infection constitutes approximately 2% of the total cancer burden in more developed countries and almost 7% in less developed countries (38). Different policies are followed regarding HPV vaccination around the world. HPV vaccines for girls are on the vaccination schedule in forty-five countries, mostly in Europe (38). These HPV vaccines on the vaccination schedule are covered by various insurance systems of the countries (38). Besides, there are licensed HPV vaccines in more than a hundred countries (40). The thirty countries that are a part of the European Economic Area all had the HPV vaccination introduced in their national vaccination programs, except for Romania where it was introduced in 2008 but discontinued after low rates of public acceptance (44, 45). Three HPV vaccines have been licensed in Europe: bivalent, quadrivalent, and nonavalent, publicly known and marketed as Cervarix, Gardasil 4 or Silgard, and Gardasil 9, respectively (46). Poland is the sole country in the European Union that requires full out-of-pocket payment for HPV vaccination (45). In Slovakia, the amount of required payment varies between the types of licensed HPV vaccines (45). In other countries, vaccination is provided free of charge (44). In the United States of America, the Vaccines for Children program funded by the federal government is the main way for children who otherwise do not have access to vaccines, to receive HPV vaccination (47). Although the program provides vaccines at no cost, it only covers children under 18 years of age who are uninsured, Medicaid-eligible, a program that provides health coverage to low-income American citizens, or American Indian/Alaska Native (47, 48). Even though the vaccination can be started at the age of 9 years, the CDC recommended age is 11-12 years (47). The nonavalent vaccine (Gardasil 9) is the only HPV vaccine currently authorized by the federal United States government (49). In Latin America where 64,000 new cases of cervical cancer and 26,000 deaths from it were reported each year, nine countries remain to have introduced the HPV vaccine as of December 2016 (Costa Rica, Cuba, Dominican Republic, El Salvador, Haiti, Guatemala, Martinique, Nicaragua, and Venezuela) (50). China has no HPV vaccination program (51). Bivalent HPV (Cervarix), quadrivalent HPV (Gardasil), and nonavalent HPV (Gardasil 9) are all licensed in China, but they are reported to be expensive and in limited supply (51). In India, similar to China, despite the recommendation by the National Technical Advisory Group on Immunization an HPV vaccination program has not been implemented as of 2018 (52). As of June 2019, nine Sub-Saharan African countries have included HPV vaccination in their National Immunization Programs: Botswana, Lesotho, Rwanda, Sao Tome and Principe, Senegal, Seychelles, South Africa, Uganda, Mauritius, and twenty-two additional countries have HPV vaccine demonstration projects in motion (53). Both of these statistics are in a prime position to increase considerably as international organizations such as the Global Alliance for Vaccines and Immunization and the Program for Appropriate Technology in Health, along with the WHO and United Nations Children's Fund, have generated substantial momentum around HPV vaccination in Sub-Saharan African countries (54).

Global Awareness and Acceptability

Even though its effectiveness is debated, increasing the knowledge of HPV is suggested as one of the methods to improve HPV vaccine uptake (55). Awareness and acceptability of HPV vaccination have been major factors in the success of

individual countries' vaccination programs, one example of this being the Romanian HPV vaccination program falling out due to a low level of public acceptance (44). A major part of the public perception of HPV vaccination is the view of parents (55). Parents of adolescents who had no intention of having their children vaccinated in a 12-month window expressed their reasoning as their child not being at a proper age for vaccination while closely associating it with the age of sexual activity (56).

The emergence of social media and the transition of a new generation into adulthood has shown the potential to positively affect awareness of HPV (57, 58). Although social media creates a more comfortable environment for sharing knowledge on HPV and enables the general public to engage with more information, social media can be used to spread negative content as well (58). Positive content on social media about HPV and HPV vaccination was reported to be associated with greater vaccine coverage, and the negative content on it had adverse effects on its public perception (58). With these in mind, it is important to note that positive content about HPV was able to reach larger audiences compared to its negative counterpart (57, 58).

Evaluation of the Current Status of Turkey

World Health Organization recommends nationwide screening of cervical cancer in all countries (38). According to the national cancer screening standards in Turkey; every woman between 30 to 65 years of age should be screened with HPV-DNA and Pap smear test every five years (38). Screenings are carried out free of charge at Cancer Early Diagnosis, Screening and Training Centers, Family Health Centers, Community Health Centers, and Healthy Life Centers (38). WHO recommends the administration of two doses of vaccination to girls, 6-12 months apart, before sexual intercourse (between 9-14 years of age) (38). However, HPV vaccines are not included in any vaccination program in Turkey. There are two main interventions in the country's policies in the fight against cervical cancer in general (59). First of which screening tests are developed for early diagnosis as a secondary prevention tool, and secondly, vaccination is developed to prevent long-term infection of the agent, which is a primary prevention tool, and its transformation into cancer (59). The decisive factor in including HPV in the vaccination program is whether it is cost-effective. The main argument for cost-effectiveness is the years of life gained by preventing deaths (38). There are not many studies conducted on the cost-effectiveness of the HPV vaccine in Turkey. However, according to Sözmen et al. (60), it was seen that administering two doses of vaccine alone is cost-effective, while vaccination without expanding the current screening program is less so. Additionally, a cost-effectiveness study found that HPV vaccines are very cost-effective to administer in the general population (38). Furthermore, in various survey studies conducted in Turkey, the level of awareness of certain groups about HPV infection, screening, and vaccines was investigated. The general public's knowledge about HPV vaccines was less than their knowledge about cervical cancer and screening, and the most conscious group was found to be health personnel. The group with the least awareness about HPV infection and vaccines is adolescent girls. The results are shown in Table 1 (61-67). In different questionnaires, physicians and students were asked about HPV vaccination-related questions, such as awareness about HPV vaccination, thoughts about their fees, and HPV vaccines being included in the national immunization program was investigated. In general, the results of the surveys with the most supportive responses from students (medical, midwifery, etc.) and physicians are shown in Table 2 where only about 7% of midwifery students are aware of the fact that vaccination may prevent cervical cancer (68-76). Moreover, according to a survey study conducted by Adıgüzel et al. (70), the most common reason for the low HPV vaccination rate in Turkey was that HPV vaccines were not included in the national vaccination program.

It is important to include the HPV vaccine in national vaccination programs to increase herd immunity to HPV (77, 78). This will not only help to eliminate socio-economic inequalities in access to vaccines but also reduce the prevalence of HPV-related diseases. Thus, it will contribute to more efficient use of resources in the health system (77). Early diagnosis of cervical cancer is of great importance for effective treatment (79).

Table 1: A review of several studies conducted in Turkey that examined the general knowledge on HPV.

Study, year	Population	Number of participants	Heard about pap smear (%)	Heard about cervical cancer (%)	Heard about HPV (%)	Heard about HPV vaccination (%)
Pınar et al. (61), 2010	Patients admitted to OB/GYN	471	78.8	92.6	N/A	57.7
Ozan et al. (62), 2011	Patients admitted to OB/GYN	336	51.8	86.6	33.6	44.6
Çetin et al. (63), 2014	Adolescent girls	501	N/A	34.2	22.2	11.7
Görkem et al. (64), 2015	Health personnel in the university hospital	192	97.9	89.1	91.7	85.4
Adıgüzel et al. (65), 2016	Patients admitted to OB/GYN	426	N/A	55.4	39.4	33.1
Kürtüncü et al. (66), 2018	Mothers of 10-15-year-old daughters	100	88	91	53	67
Çelik (67), 2018	Parents of children aged 9-18 years	1000	N/A	64.8	26.9	20.7

HPV: Human papillomavirus, OB/GYN: Obstetrics and gynecology, N/A: Not available

Table 2: The opinions of students and physicians on HPV vaccination-related questions.

Study, year	Population	Number of participants	HPV vaccination prevents cervical cancer (%)	HPV vaccination is expensive (%)	Would recommend HPV vaccination to their patients/ relatives (%)	HPV vaccination should be in the national vaccination program (%)	HPV vaccination is also in use for males (%)
Yıldırım et al. (68), 2009	Pediatricians	438	76.9	76.9*	91.1	N/A	77.4
Çeşmeci et al. (69), 2015	Intern doctors	208	67.3	41.8*	N/A	82.7	90.4
Adıgüzel et al. (70), 2018	Pediatricians	90	N/A	17.8*	38.9	N/A	45.6
Kızılca Çakaloz et al. (71), 2018	Midwifery students	257	6.6	N/A	78.4	85.2	N/A
Aydın (72), 2019	Family physicians	247	57.9	24.7*	35.2	51	42.5
Başlı et al. (73), 2019	Nursing, midwifery, nutrition-dietetics students	287	N/A	9.8*	N/A	87.1	49.1
Erdem et al. (74), 2020	Medical students	85	100	93	98	94	98
Emre et al. (75), 2020	Medical students	780	N/A	25.9*	74.2	69	79.7
Taşar et al. (76), 2021	Pediatricians	98	N/A	7.1*	60.2	N/A	84.7

HPV: Human papillomavirus, N/A: Not available
*The reason for not recommending/getting HPV vaccination is that the patients/participants could not afford it due to the price of the vaccine.
**The percentages indicate/show the group of participants who agrees with the given statements.

Early diagnosis of HPV-positive individuals by popularizing screening tests may alleviate the problems associated with HPV-related diseases, but it is clear that it is not a sufficient strategy alone for the formation of herd immunity.

According to a statement made by the Turkish Medical Association in 2019, in cancer screening programs in Turkey, it is seen that the resources and labor spent are not used appropriately, as there are data losses and monitoring problems (80). In another statement by the Turkish Medical Association in October 2021, it was requested that HPV vaccines be added to the national vaccination program free of charge, in addition to national screening, to prevent avoidable diseases and deaths (81). As the spread of the vaccine will reduce HPV-related diseases, it may create an opportunity for more efficient resources and workforce management (82). However, data losses and monitoring problems are a concern for future research and public health. To prevent future cases and reduce the prevalence of HPV-related diseases, the HPV vaccines should be made accessible to everyone, as well as screening tests.

Studies conducted with different populations in different regions of Turkey reveal that participants' awareness of HPV, cervical cancer, and HPV vaccines is not at a sufficient level, and the prevalence of HPV is similar to other studies in the literature (83-85). A study conducted in Denmark revealed that although there is free access to the vaccine, vaccination rates are affected by the socioeconomic and educational levels of the families (86). This indicates that free access to the vaccine is not a sufficient factor on its own, thus it is also important to work on raising social awareness. As of May 2022, the HPV vaccine is not included in the national vaccination program in Turkey and it is not a vaccine that can be accessed by everyone due to its cost. Although there are requests from time to time to increase awareness of HPV and to include HPV in the national vaccination program with the support of non-governmental organizations and social media campaigns, there has been no development in this direction yet.

CONCLUSION

Due to its carcinogenic types, HPV occupies a large place in cancer screening, diagnosis, and treatment and creates a demand for prevention methods worldwide (25). The wide spectrum of genital cancers, various clinical presentations, the possibility of malignancy, and the vaccine still not being available to the entire population make it an important issue to deal with, especially in low-income countries (21, 35).

In conclusion, the inclusion of HPV vaccines in vaccination programs by health authorities and policies can encourage community acceptance of HPV vaccines. Especially, the participation of countries that do not have HPV vaccines in their national vaccination programs will be an important initiative in terms of protecting public health. In this context, the inclusion of the HPV vaccine in the national vaccination program of Turkey will contribute to the protection of public health with more efficient resource management.

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