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Review

Human Papillomavirus (HPV) Vaccines: A Comprehensive Review

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Abstract

Human papillomavirus (HPV) is a double-stranded DNA virus from the Papillomaviridae family that primarily infects basal epithelial cells. This virus is responsible for causing warts, papillomas, and various cancers in both men and women. To date, over 200 HPV types have been identified, which are classified into high-risk and low-risk categories. High-risk types, such as HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 are known to contribute significantly to cancer development. Among these, HPV 16 and 18 are the most common and are strongly associated with the onset of cancer. HPV remains a significant global public health issue, posing substantial social and economic burdens. Despite extensive research, there is currently no approved or proven drug for the effective treatment of HPV infections. However, vaccines play a critical role in the prevention of HPV-related diseases. The U.S. Food and Drug Administration (FDA) has approved three vaccines that provide protection against high-risk HPV types. These vaccines have led to a marked reduction in HPV incidence and associated complications. The World Health Organization (WHO) strongly recommends HPV vaccination as a preventive measure. Furthermore, ongoing research aims to develop next-generation vaccines to enhance protection against HPV. This study underscores the importance of HPV vaccines and highlights their role in mitigating the impact of this pervasive virus.

Keywords: Human Papillomavirus, HPV, HPV Vaccine, Cervical Cancer

INTRODUCTION

Human papillomavirus (HPV) is a non-enveloped, double-stranded DNA virus belonging to the Papillomaviridae family, primarily infecting the mucosal tissues of the cervical and oral tracts (1). The pathological outcomes of HPV infection vary based on the individual's immune status and the specific HPV type involved (2). Certain HPV types cause benign growths such as warts or papillomas, while others are associated with more severe outcomes, including cancer. HPV is one of the most prevalent sexually transmitted infections and poses a significant risk for both men and women. While HPV is the leading cause of cervical cancer in women, cervical cancer remains one of the most common cause of cancer-related mortality in women worldwide. Currently, over 200 different types of HPV have been identified, with types 6, 11, 16, and 18 being particularly noteworthy. Among these, HPV type 16 is the most oncogenic, accounting for a substantial proportion of HPV-related cancers (3). Epidemiological studies suggest that the majority of sexually active individuals are likely to contract an HPV infection at least once during their lifetime (4). HPV vaccines have been developed to address this public health concern. The first HPV vaccine was introduced in 2006. Currently, three prophylactic vaccines are licensed by the U.S. Food and Drug Administration (FDA) for use: Gardasil (Merck & Co., USA/Sanofi Pasteur MSD, France), Cervarix (GlaxoSmithKline Biologicals, Belgium), and Gardasil 9 (Merck & Co., USA) (5).

Implementing preventive measures against HPV can significantly reduce the economic and social burden on society. Consequently, efforts to enhance vaccination

programs and promote early diagnosis are of critical importance. Raising awareness through education and disseminating information about HPV can further contribute to social consciousness. This study aims to examine the development of HPV vaccines over the years and their role in preventing HPV infections and HPV-related cancers.

HUMAN PAPILLOMAVIRUS (HPV)

HPV is a small, non-enveloped, double-stranded DNA virus with a genome of approximately 8000 base pairs (bp). Its structure consists of 72 pentameric capsomeres forming icosahedral (cubic) capsids (6). While sexual transmission is the primary mode of HPV spread, the virus can also be transmitted from mother to infant during childbirth (7).

The HPV genome is composed of eight open reading frames (ORFs): E1, E2, E4, E5, E6, E7, L1, and L2. These ORFs facilitate replication and transcription within the host cell (8). The ORFs are organized into three functional regions: The E (early) region, the L1 and L2 (late) region, and the LCR (long control region). The LCR is a non-coding region responsible for regulating viral replication. The E region encodes proteins involved in the pathogenicity of the virus, particularly its 4-kb non-structural components. Within the E region, the E1 protein functions as a viral DNA helicase, while the E2 protein regulates viral gene transcription. Together, E1 and E2 orchestrate DNA replication by binding to the viral replication origin and forming a complex (9, 10). E5 has been shown to contribute to oncogenicity by expressing growth factors such as EGFR and by synergizing with E6 and E7 (11). The E6 and E7 proteins of HPV target tumor suppressor genes, significantly impacting cell growth and differentiation. These viral oncogenes play a central role in the development of HPV-associated cancers. Blocking the expression of E6 and E7 can halt cell proliferation, trigger apoptosis, and ultimately lead to tumor cell death. Consequently, E6 and E7 have become key targets in research focused on developing treatments for HPV-induced cancers (12). The L region of the HPV genome encodes the L1 and L2 capsid proteins, which are essential for virion assembly. Known collectively as the late region, these genes play a critical role in packaging the replicated viral genome into an icosahedral capsid and facilitating the transmission of infection (9).

HPV infects epithelial cells by interacting with cell surface receptors, including integrin α (13). During HPV infection, the virus initially targets the basal layer of the epithelium, typically gaining access through microlesions. After crossing the basal layer of the epidermis, HPV enters cells through endocytosis. Capsid proteins L1 and L2 facilitate this process, enabling the virus to pass into the basal layer. Additionally, cellular components such as heparan sulfate, proteoglycans, and annexin A2 assist in cellular entry. The differentiation of keratinocytes plays a pivotal role in viral replication. Once the basal cells are infected by virions, cell cycle regulation is disrupted. The infected cells migrate from the basal layer to the upper layers of the epidermis and are eventually shed from the surface (14).

The Relationship Between HPV and Cervical Cancer

HPV is considered the leading cause of cervical cancer (15). In 2022, there were approximately 660,000 cases and 350,000 deaths due to cervical cancer globally. In Türkiye, cervical cancer ranks 12th among cancers in women, and the age-standardized incidence rate of HPV-related cervical cancer cases has been shown to be 4.8 per 100,000 women. The HPV Information Centre informs that 32.8 million women aged 15 and over in Türkiye are at risk of cervical cancer and that 1,245 women die from cervical cancer each year (16,17). If left untreated, HPV infection in the cervix is responsible for 95% of cervical cancers (18). According to a study conducted in 2019, HPV is thought to be responsible for approximately 620,000 new cancer cases in women and 70,000 new cancer cases in men (19).

Cervical cancer is divided into different types according to its location. Squamous cell carcinoma (SCC) accounts for 90% of cervical cases and begins in the ectocervix. The one that begins in the endocervix is called adenocarcinoma (20). Premalignant changes in the squamous cells of the cervical epithelium are referred to as Cervical Intraepithelial Neoplasia (CIN) (21). CIN 1 is characterized as low-grade mild dysplasia, CIN 2 as moderate dysplasia, and CIN 3 as high-grade dysplasia and carcinoma in situ. CIN 1 affects approximately one-third of the epithelial tissue, CIN 2 affects about two-thirds, and CIN 3 involves at least two-thirds of the epithelial tissue (22). Regression of CIN lesions can occur in clinical cases, including CIN 1, CIN 2, and CIN 3 (23).

History of HPV Vaccines

As a result of studies on HPV types, prophylactic vaccines have been developed to prevent HPV infections and related diseases. HPV was first identified in biopsy samples taken from the cervix in 1983 (24). Since then, many reputable international organizations, including the World Health Organization (WHO), FDA, the European Medicines Agency (EMA), and the American College of Obstetricians and Gynecologists (ACOG), have approved various types of HPV vaccines, affirming their safety and efficacy (25). In 2006, the first prophylactic vaccine Gardasil approved by FDA is a quadrivalent vaccine providing protection against HPV types 6, 11, 16, and 18. The marketing authorizations for Gardasil were granted in the European Union on September 20, 2006, for Cervarix on September 20, 2007, and for Gardasil 9 on June 10, 2015, by the European Commission. As of

2024, there are six HPV vaccines globally: Cervarix®, Walrinvax®, Cecolin® bivalent vaccine, Gardasil®, Cervavac® quadrivalent vaccines, and the 9-valent vaccine Gardasil 9® (26). Vaccination is an effective and safe method for preventing HPV infections and related diseases. It is critical in reducing the risk of infection and HPV-related cancers. HPV vaccines are not intended to treat existing infections or diseases caused by HPV but to prevent cancer development. WHO recommends vaccination between the ages of 9-14 as effective against HPV infections, cervical cancer, and other types of cancer. Vaccines should be administered before exposure to HPV to be most effective. Many countries continue to integrate routine HPV vaccination into their immunization programs (27). Table 1 summarize the HPV types covered, approval years, target age groups, and recommended doses of the six vaccines currently in use globally (Table 1).

With the widespread use of HPV vaccines and the global demonstration of their efficacy and safety, vaccination strategies have evolved significantly over time. Initially focused on young women, the CDC (Centers for Disease Control and Prevention), WHO, and Advisory Committee on Immunization Practices (ACIP) now recommend the inclusion of males in vaccination programs and the expansion of target age groups to individuals up to 45 years. These changes reflect the vaccines' demonstrated efficacy and safety in diverse populations (28,29).

EFFECTIVENESS OF VACCINES

The CDC reports that the HPV vaccine has shown positive results and can prevent over 90% of cancers caused by HPV. It has led to a decrease in cases of genital warts among young people and adults. Since the introduction of the vaccine, cervical cancer rates have declined, and the protection conferred by the HPV vaccine has remained effective over time. Additionally, HPV infections among adolescent girls have decreased by 88%, and among young adult women by 81%. The rate of cervical precancers (CIN2 and CIN3) in vaccinated women has also decreased by 40% (30). After the introduction of the quadrivalent vaccine, reductions were observed in infections caused by HPV types 6, 16, and 18, as well as in cytological abnormalities, CIN2 and CIN3, and genital warts. These decreases were more pronounced in the young population. In countries with high vaccination rates, such as Denmark and Australia, decreases in genital warts have been observed. Common HPV types 6 and 11 infections have been reduced by 40–50% in American women and 75–88% in Australian women compared to the pre-vaccination era (31).

Studies highlight varying protection rates among bivalent, quadrivalent, and nonavalent vaccines. Meta-analyses confirm that nonavalent vaccines, such as Gardasil 9, offer the most comprehensive protection against HPV-related diseases. These vaccines provide broader coverage against additional oncogenic HPV types, significantly reducing the incidence of cervical and other cancers (32).

Vaccination Safety and Side Effects

After vaccination with HPV vaccines, as with other vaccines, common side effects such as pain and fever at the injection site, as well as headache and nausea, can occur (33). According to the CDC, in addition to these side effects, dizziness and fainting can also be observed, particularly among adolescents. To mitigate the risk of fainting, it is recommended that individuals sit down during vaccination and rest for 15 minutes afterward (30). A study conducted using data from the Vaccine Adverse Event Reporting System (VAERS) found that side effects such as dizziness, headache, and nausea are frequently reported, but it was concluded that the 9vHPV vaccine is safe (34). Another study reviewed the literature on the safety and efficacy of the Gardasil® vaccine. The results confirmed that the vaccine is both effective and safe (35). An 11-year study conducted in Australia found that the 4vHPV vaccine did not cause any alarming problems and was considered safe (36).

NEW VACCINE STUDIES

HPV is responsible for causing cancers such as anogenital, cervical, and oropharyngeal in both women and men. Cervical cancer is particularly prominent among HPV-related cancer types. Vaccination of young girls and women plays a crucial role in preventing infections and cervical abnormalities. Vaccines are considered one

Table 1. The summary of licensed HPV vaccines.

	GARDASIL; Qadrivalent Vaccine	CERVARIX; Bivalent Vaccine	GARDASIL 9; Nonvalent Vaccine	CECOLIN; Bivalent Vaccine	CERVAVAC; Qadrivalent Vaccine	WALRINVAX; Bivalent Vaccine
Targeted HPV Types	6, 11, 16, 18	16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58	16, 18	6, 11, 16, 18	16, 18
Approval Years	2006	2009	2014	2021	2022	2024
Target Age Groups	-	-	9-45	-	9-26	9-30
Recommended Doses	For people 9-13, 2 or 3 doses For people 14 years and older, 3 doses	For people 9-14, 2 doses For people15 years and older, 3 doses	For people 9-14, 2 or 3 doses For people 15-45, 3 doses	For people 9-14, 2 doses For people 14 years and older, 3 doses	For people 9-14, 2 doses For people 15-26, 3 doses	For people 9-14, 2 or 3 doses For people 15-30, 3 doses

of the greatest achievements of the century, providing life-saving benefits against bacterial and viral infections (37). Vaccines play a crucial role in preventing cancers caused by HPV. Therefore, the development of new vaccines is of great value in terms of cancer prevention.

Researchers are increasingly focusing on the development of therapeutic vaccines rather than prophylactic ones to prevent the development of cervical cancers. Therapeutic vaccines target the E6 and E7 oncogenes and aim to induce a cell-mediated immune response to eliminate infected cells. Unlike prophylactic vaccines, which prevent HPV infection, therapeutic vaccines are designed to target the virus after it has entered the body. For therapeutic vaccines, there are various development strategies, including live vector, bacterial vector, viral vector, peptide, protein-based, and nucleic acid vaccines, depending on their sources (38). An example of a therapeutic vaccine is the RNA virus-based viral vector vaccine Vvax001. Vvax001 consists of SFV (Semliki Forest Virus) particles encoding HPV 16 derivatives E6 and E7. Studies have shown that this vaccine induces HPV 16-specific T cells (39). Vaccines developed to date cannot fully cure cervical cancer. Current HPV vaccines are most effective when administered before infection with the virus. Promising vaccine studies include VGX-3100, which targets high-grade intraepithelial lesions (HSIL) caused by HPV 16 and HPV 18 (40). As of 2024, the recombinant vaccinia vaccine for HPV 16 and HPV 18, which expresses modified forms of E6 and E7 proteins, has completed Phase 2 clinical studies (41).

Cecolin is a bivalent prophylactic vaccine produced in *Escherichia coli*, effective against HPV 16 and HPV 18. Administered intramuscularly, it was approved in China in December 2019 and received prequalification from the WHO in 2021. It is recommended for women aged 9-45 and follows a three-dose schedule, while girls aged 9-14 may receive a two- or three-dose schedule. Cecolin has a similar safety profile to Gardasil as indicated by studies (42). Walrinvax is another prophylactic vaccine that has completed Phase 1 clinical trials in China. This bivalent VLP vaccine targets HPV types 16 and 18 and is expressed in *Pichia pastoris* yeast (43).

Vaccines prevent diseases by activating the body's natural defense mechanisms. Prophylactic HPV vaccines provide immunity against HPV infections, aiming to reduce the global burden of cervical cancer. These vaccines, composed of virus-like particles (VLPs), are highly effective in preventing HPV infections, genital warts, and cervical cancers (4). A study by Lukács et al found that quadrivalent vaccine significantly reduced the occurrence of genital warts after administration to both young men and women (44). A study evaluating the success of HPV vaccination in the United States between 2003 and 2018 demonstrated a decrease in the prevalence of infection. Study results showed that from 2003-2006, when the vaccine was not available, to 2015-2018, the quadrivalent HPV vaccine reduced infection by 88% in people aged 14-19 and by 81% in people aged 20-24. It has also been emphasized that the frequency of infection has decreased significantly even in unvaccinated individuals during the vaccination period. This shows the contribution of increasing HPV vaccination to herd immunity (45).

A study conducted in Costa Rica evaluated the effectiveness of the Cervarix vaccine, focusing on women aged 18–25. In this clinical trial, participants received two doses of the Cervarix vaccine, which targets HPV types 16 and 18. The findings demonstrated that two doses provided strong protection against HPV infections caused by these types. Due to the logistical and cost-related challenges of a three-dose vaccination program, the study also explored the efficacy of one- and two-dose regimens. Statistical data were used to estimate the protective impact of a three-dose schedule. Interestingly, similar protection rates were observed among women receiving one, two, or three doses of the vaccine. Based on these results, the study suggested that reducing the dosage to two doses could effectively lower the incidence of cervical cancer while extending vaccination coverage to a greater number of women (46).

A study conducted on women aged 20–45 evaluated the efficacy and safety profiles of two new four- and nine-valent vaccines compared to Gardasil. The findings showed that these vaccines were as effective as Gardasil and exhibited clinically acceptable safety profiles. Both the four- and nine-valent vaccines demonstrated highly immunogenic properties. Common side effects, such as pain, redness, and swelling at the injection site, were observed in this study as well (47). Research conducted in China revealed that high-risk HPV infections vary by age and region. Incidence rates of high-risk HPV were 24.3% in women under 25, 19.9% in women aged 25–45, and 21.4% in women over 45. These findings emphasize the importance of HPV vaccines, which are effective against common high-risk HPV types. However, the study also highlighted that the characteristics of existing HPV vaccines may not perfectly align with the specific needs of certain populations of China (48). Preventing HPV infections before they occur is more cost-effective in reducing the economic burden. When comparing nonvalent and bivalent vaccines in terms of cost-effectiveness, it was shown that nonvalent vaccine prevents more cases of cervical cancer, but bivalent vaccine, with its cross-protective effect, could be a cost-effective alternative for many low- and middle-income countries (49). Given the significant role of HPV vaccines in alleviating the disease burden, countries should evaluate their available resources, immunization

program goals, and the societal impact of HPV. To enhance global immunization rates, the development of innovative strategies by individual nations is essential (50,51).

Limitations

Despite the comprehensive nature of this review, certain limitations should be acknowledged. First, while we aimed to cover a broad spectrum of literature on HPV vaccines, the rapidly evolving nature of vaccine research may mean that some newly emerging data were not included. Additionally, most studies referenced in this review are based on clinical trials and epidemiological data from specific populations, which may not be fully generalizable to all regions. Another limitation is the lack of long-term real-world data on the effectiveness of newer HPV vaccines in diverse populations. Finally, while we discussed the preventive role of vaccines, the review does not extensively address the challenges in global vaccine accessibility, including economic, political, and social barriers. Future research should focus on these aspects to provide a more comprehensive understanding of HPV vaccine implementation and its long-term impact.

CONCLUSION

HPV is a virus that has affected millions of people throughout history. As one of the most common sexually transmitted infections, HPV can lead to warts as well as cervical, vulvar, and head and neck cancers. Preventing these diseases is possible through immunization, making HPV vaccines crucial in combating infections. Vaccinating individuals before they are exposed to HPV significantly reduces the risk of infection. Currently, three HPV vaccines have been approved by the FDA, with ongoing efforts to develop new ones. Several countries have incorporated these vaccines into their routine immunization programs, though others, including Türkiye, have yet to do so. While vaccination campaigns often focus on girls and women, extending these efforts to include boys and men offers additional protection, benefiting not only individuals but also their partners. Beyond individual health, HPV vaccination reduces the social and economic burden on nations. Therefore, integrating HPV vaccines into routine immunization programs is essential for public health advancement and economic sustainability.

DECLARATIONS

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