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Review Article

HPV Vaccines: Types, Effectiveness and Safety: A Comprehensive Review

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ABSTRACT

The development of the HPV vaccine represents a groundbreaking achievement in the history of vaccine research. These vaccines, a pioneering category, effectively prevent infection by sexually transmitted microorganisms that affect mucous membranes. Importantly, they accomplish this without specifically triggering mucosal immunity, signifying a significant shift in preventive medicine. With an estimated efficacy of preventing 70% to 90% of HPV-associated cancers, these vaccines work by intercepting HPV infection before it enters the body, distinguishing them from traditional treatment-focused approaches. It is crucial to emphasize that the Virus-Like Particles (VLPs) used in all approved HPV vaccines are non-infectious and do not contribute to cancer development. The FDA initially recognized Gardasil in 2006, followed by Cervarix in 2008 and Gardasil 9 in 2014. Despite the availability of vaccines for a potentially deadly virus, immunization rates remain low. Factors contributing to this include limited knowledge about HPV among parents and adolescents, lack of awareness among healthcare providers, the cost of immunization and concerns about vaccine-related risks. National immunization programs are being implemented to promote vaccine usage among adolescent boys and girls, as the vaccine is recommended before age 26. Post-licensure studies have confirmed the safety and efficacy of the vaccine, which is consistent with pre-licensure findings.

Keywords: Adolescents, HPV vaccine, Human Papillomavirus, Immunization.

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INTRODUCTION

Human Papillomavirus (HPV), a small double-stranded DNA virus belonging to the Papovaviridae family, poses a significant public health concern due to its predominantly sexually transmitted nature. While sexual contact is a common route of transmission, penetrative intercourse is not a prerequisite, with skin-to-skin genital contact being a prevalent means of infection. With around 200 subtypes, HPV infections can manifest in both skin and epithelial tissues. These vaccines represent a pioneering approach as the first of their kind to prevent infection by a sexually transmitted infectious agent affecting mucous membranes. Estimated to prevent approximately 70% to 90% of cancers associated with HPV, these vaccines operate by intercepting HPV infection before it gains entry into the body, distinguishing them from traditional treatment-focused approaches (Charde and Warbhe, 2022; Castle and Maza, 2016). All officially approved HPV vaccines leverage Virus-Like Particles (VLPs) constructed from the non-infectious L1 major capsid protein. The groundbreaking development of Human Papillomavirus (HPV) vaccines marked a pivotal milestone in preventive medicine, with two leading companies, GlaxoSmithKline Biologics (GSK) and Merck and Co., at the forefront of this transformative endeavour. GSK introduced Cervarix, a bivalent vaccine targeting HPV 16 and HPV 18. In tandem, Merck and Co. pioneered the development of Gardasil, a quadrivalent vaccine with efficacy against HPV 16, 18, 6 and 11. The evolution of HPV vaccines continued with Merck and Co.'s introduction of Gardasil 9 in 2014, a nonavalent vaccine extending its protective reach to include HPV 31, 33, 45, 52 and 58, in addition to the previously targeted subtypes (Markowitz and Schiller, 2021). This review aims to comprehensively explore the current trends in the development of preventive vaccines and their impact on public health.

Vaccination in adolescence

Despite the introduction of the quadrivalent vaccine in 2006 and the bivalent vaccine in 2008, the prevalence of HPV-related diseases remains significant. The primary reasons for not getting vaccinated included concerns about potential side effects, doubts about the vaccine's safety and effectiveness, fear of injections and worries about the vaccine's cost. Additional reasons included a lack of information about the vaccine, some adolescents not yet been sexually active and believing they didn't need the vaccine,

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concerns about vaccine-induced infertility, a belief that infection could still occur despite vaccination and parental (especially maternal) disagreement with vaccination (Iova *et al.*, 2023). It was observed that female students had a higher level of awareness about HPV compared to their male counterparts. Moreover, adolescents from urban areas exhibited greater knowledge about HPV in comparison to those from rural regions. The primary obstacle to successful HPV vaccination appeared to be the lack of information and awareness related to HPV (Zhang *et al.*, 2021).

HPV vaccine types

There are two types of vaccines, one for preventing infections (prophylactic vaccines) and another for treating them (therapeutic vaccines). Vaccines work by triggering either the body's humoral or cell-mediated immune responses (Yousefi *et al.*, 2022).

Therapeutic vaccines

Therapeutic vaccines function differently from prophylactic vaccines. They work by stimulating cell-mediated immunity involving T helper cells and cytotoxic T cells. Their primary focus is on targeting E6 and E7 proteins, which are predominantly present in cancerous tissues (Chabeda *et al.*, 2018). In the initial stages of a viral infection, there are also significant levels of E1 and E2 proteins, which are expressed more abundantly than E6 and E7. An optimal therapeutic vaccine would aim to target these proteins, provoking a robust response from tumour-specific T helper type 1 cells and cytotoxic lymphocytes, ultimately leading to the destruction of cancerous cells (Yousefi *et al.*, 2022). E2 serves as a suppressor of E6 and E7 and its levels are higher in precancerous conditions. Therefore, vaccines designed to target E2 are employed in the treatment of precancerous lesions, genital warts and related ailments. Therapeutic vaccines for HPV come in four categories: live vector vaccines, peptide and protein-based vaccines, nucleic acid-based vaccines and whole-cell vaccines. These vaccines work by introducing the target antigen to Antigen-Presenting Cells (APC) to stimulate a specific immune response involving HPV-specific cytotoxic CD8+T lymphocytes and helper CD4+T cells (Mo *et al.*, 2022).

Peptide-based vaccines

Peptide-based vaccines consist of peptides, which are short chains of amino acids originating from the target organism and are used to trigger an immune response. The immunogenic response of a vaccine is influenced by the length of the peptide chain it contains. Peptide-based vaccines can be categorized into two groups based on their chain length: short peptides, which consist of 8-11 amino acids and long peptides, which consist of 11-30 amino acids. Short peptide vaccines are displayed by MHC class I, while long peptides are presented by MHC class II (Buonaguro and Tagliamonte, 2023). Short peptide-based vaccines can directly attach to Human Leukocyte Antigen (HLA) class I, triggering a CD8+T cell response while avoiding a CD4+T cell response. This elicits an immediate reaction but falls short in generating a long-lasting response. Therefore, short peptide-based vaccines are specific to the patient's MHC and must be compatible with it. Long peptide-based vaccines have the ability to bind to both MHC class I and MHC class II, leading to the activation of CD4+T cells, which in turn support the cytotoxic function of CD8+T cells (Smalley *et al.*, 2020).

Live vector-based vaccines

Live vector-based vaccines use vectors like bacteria or viruses to transport E6 and E7 antigens to Antigen-Presenting Cells (APC) for the activation of CD8+cytotoxic cells and CD4+T helper cells. Live vectors can replicate within the host, amplifying the antigen and triggering an immune reaction. However, in individuals with compromised immune systems, live vectors may cause infections. Another concern is the potential development of resistance due to the generation of specific antibodies against the vector (Kumar *et al.*, 2015).

Whole cell vaccine

Whole cell-based vaccines encompass dendritic cell-based vaccines and tumour cell-based vaccines. Dendritic cell-based vaccines are created by modifying them with E6 or E7 peptides, DNA, or RNA encoding these peptides, or by employing vectors carrying the E6 or E7 genes. The production of these vaccines is quite costly (Lin *et al.*, 2010).

Nucleic acid vaccine

They involve a plasmid containing genes responsible for coding target-specific antigens. Nucleic acid vaccines have the capability to stimulate both humoral and cellular immunity. The DNA vaccine is designed for efficient cell penetration, which triggers the activation of cytotoxic cells and the production of antibodies. Once it enters the cell, it can penetrate the nucleus and undergo transcription and translation in the cytoplasm. This results in the expression of the encoded antigen on Major Histocompatibility Complexes (MHC), leading to the generation of T helper and T cytotoxic cells, which play a role in antibody production as well (de Moura *et al.*, 2022).

Prophylactic vaccines

In the case of HPV infections, the body generates serum antibodies that neutralize the primary capsid protein, L1. However, the quantity of these antibodies isn't sufficient to completely clear the infection. It's uncertain how much protection these antibodies provide and the risk of infections remains high. Consequently, this approach is considered an effective method for prophylactic vaccines and serves as the foundation for all such vaccines. These neutralizing antibodies are specific to L1 proteins and necessitate the presence of structurally similar proteins to stimulate their production. Growing HPV in culture is challenging due to its oncogenic properties. Large quantities of L1 proteins are

manufactured through the use of recombinant baculovirus, which is subsequently assembled into Virus-Like Particles (VLPs) that closely resemble L1 proteins in both structure and function. Immunizing animal models with these VLPs has proven to be effective in generating neutralizing antibodies against L1 proteins (Stanley, 2007).

Available prophylactic vaccines

There are three kinds of prophylactic HPV vaccines accessible: Gardasil 4, which is a quadrivalent vaccine; Cervarix, a bivalent vaccine; and Gardasil 9, a nonavalent vaccine. All of these vaccines contain virus-like particles (VLP) (Mo *et al.*, 2022). Two pharmaceutical companies, GlaxoSmithKline (GSK) and Merck and Co., played pivotal roles in developing HPV vaccines. GSK created a bivalent vaccine called Cervarix, consisting of virus-like particles from HPV 16 and HPV 18. Merck and Co. developed a quadrivalent vaccine called Gardasil, which included virus-like particles from HPV 16, 18, 6 and 11. Later, Merck and Co. introduced Gardasil-9, a nonavalent vaccine launched in 2014. This vaccine targets a broader range of HPV types, including 18, 16, 6, 11, 31, 33, 45, 52 and 58 (Stanley, 2007; Markowit and Schiller, 2021).

Need of HPV vaccination

Human Papillomavirus (HPV) is a small, circular, double-stranded DNA virus with a genome consisting of approximately 8,000 base pairs. It contains Early genes (E1, E2, E4, E5, E6 and E7) and Late genes (L1 and L2). E6 and E7 are known for their oncogenic potential. Initially, when a person acquires an HPV infection, the immune system swiftly eliminates the virus within 12 to 24 hr. This clearance is achieved through the activation of immune components such as CD4+T and CD8+T lymphocytes, macrophages and B cells. T cells specifically target the early genes E6 and E7, while B cells target the late protein L1. Targeting L1 results in the production of Neutralizing Antibodies (Nab) that effectively clear the infection. However, in cases where the immune system fails to clear the infection, HPV can persist within the host's body. This persistence leads to the activation of E6 and E7 proteins, which have the potential to induce cancer. E6 interferes with the function of the apoptosis regulator protein p53, preventing apoptosis and causing cells to survive longer than they should. This disrupted apoptosis leads to the formation of lesions. E7 interferes with the retinoblastoma protein, which normally suppresses tumour formation. Suppression of retinoblastoma protein causes cells to continuously enter the S phase of the cell cycle, resulting in uncontrolled cell division. Prolonged infection can allow the virus to penetrate the basal epithelium, undergo repeated life cycles and increase the risk of Cervical Intraepithelial Neoplasia (CIN), a precursor to cervical cancer. The immune system's inability to clear the infection is often due to insufficient levels of serum neutralizing antibodies. Prophylactic vaccines are designed to address this issue by containing virus-like particles that closely resemble the L1 protein of HPV. Vaccination triggers the production of neutralizing antibodies by activating B cells, which specifically target the L1 protein. This ensures a significant presence of antibodies in the bloodstream, offering protection against future HPV infections (Akhatova *et al.*, 2022).

Schedule of vaccine

The HPV vaccine is administered in a two-dose regimen for kids between 9 and 14 years old, with a six-month gap between doses. In contrast, young women aged 15 to 26 receive it as a three-dose schedule at 0, 2 and 6 months. Children who have weakened immune systems or are infected with HIV should receive three doses of the HPV vaccine. Research was conducted to assess the effectiveness of the HPV vaccine when given in both double and triple doses. Gardasil 9 was given as a two-dose vaccine at 0, 6, or 12 months for individuals aged 9 to 14 and as a three-dose vaccine at 0, 2 and 6 months for women aged 15 to 26 (Salvadori, 2018).

Vaccine efficacy

Research suggests that the effectiveness of the vaccine is notable in young women without prior HPV infection. The bivalent, quadrivalent and nonavalent vaccines exhibit comparable efficacy against HPV 16/18, but the nonavalent vaccine offers broader protection, including HPV types 31, 33, 45, 52 and 58. The substantial decrease in HPV infections involving types 6, 11, 16 and 18 among vaccinated women, as opposed to those who are not vaccinated, demonstrates the effectiveness of the vaccine. The two-dose vaccine regimen is more straightforward and cost-effective than the three-dose alternative and both vaccines exhibit immunogenicity. In males, the quadrivalent vaccine proves more efficacious in preventing genital lesions and persistent infections caused by HPV 16/18/6 or 11, while there is limited information on the effectiveness of the bivalent vaccine in males (Kamolratanakul and Pitisuttithum, 2021). A study was conducted to evaluate the effectiveness of the quadrivalent HPV vaccine in preventing HPV infection and associated diseases in males. The administration of the HPV vaccine was linked to a decrease in the occurrence of external genital lesions in the treatment group compared to the placebo group. Additionally, it was observed that these infections were attributed to HPV types 6, 11, 16 and 18. The treatment group reported experiencing injection site pain in comparison to the placebo group (Giuliano *et al.*, 2011).

The efficacy of the HPV vaccine was also assessed in women who tested positive for HPV, aiming to determine its effectiveness in preventing disease progression. The vaccination proved to be highly effective in preventing cervical intraepithelial neoplasia 2 or 3 and cervical adenocarcinoma caused by the types for which the women tested positive, as well as those types for which they tested negative (Future II Study Group, 2007). Over a 10-year period following the administration of the third dose

of the 9-valent HPV vaccine, a study tracked boys and girls aged 9 to 15. The findings revealed that there were no instances of high-grade intraepithelial neoplasia or condyloma associated with HPV6/11/16/18/31/33/45/52/58 in both males and females. The incidence rates of 6-month persistent infection related to HPV6/11/16/18/31/33/45/52/58 were minimal in both genders. The vaccine exhibited prolonged immunogenicity and effectiveness (Restrepo *et al*., 2023).

Information gathered from multiple studies indicates that administering a double-dose vaccine, whether bivalent or quadrivalent, to adolescents, is as effective and demonstrates comparable immunogenicity when compared to the three-dose HPV vaccine (Kreimer *et al*., 2015). Adolescents who received the bivalent HPV 16/18 vaccine exhibited a reduced occurrence of HPV 16/18 infections. Moreover, there was a notable decrease in the viral load in cases of breakthrough infections (van der *et al*., 2019). The effectiveness of the quadrivalent HPV vaccine was evaluated a decade after vaccination in individuals who had received one, two, or three doses at the age of 16 to 18. Results indicated that the neutralizing antibody levels generated after a single dose were lower than those after the third dose, yet significantly higher compared to the non-vaccinated group. This study suggests that even with a single dose, recipients experience a substantial and enduring protective effect (Joshi *et al*., 2023).

A separate study aimed to elucidate the efficacy variations among single, two-dose and three-dose regimens of the bivalent vaccine. The vaccine efficacy against HPV 16 or HPV 18 remained consistent for the single-dose vaccine and the antibody levels also remained stable throughout the study period (Kreimer *et al*., 2020). The study assessed the impact of a single dose versus a double dose of the vaccine, finding that a single dose can provide similar benefits to a double dose. Administering a single dose not only streamlines the vaccination process but also reduces vaccination costs. The cost-effectiveness of a second dose could be justified under conditions such as a shorter duration of protection from a single dose, more affordable vaccines and delivery strategies and a high burden of cervical cancer (Prem K *et al*., 2023).

Vaccine safety

Vaccine safety pertains to the occurrence of adverse reactions post-vaccination, with severe adverse effects including congenital anomalies, disability, hospitalization, life-threatening conditions, or death. In 97% of cases, HPV vaccines were determined to be safe (Charde and Warbhe, 2022). A research investigation in West Bengal, examining the effectiveness and safety of HPV vaccination in girls aged 9 to 14, found that 98% of the participants successfully received both vaccine doses without encountering any significant adverse reactions (Mandal *et al*., 2021). In the state of Sikkim, a combination of robust political dedication, mandatory school enrolment and cooperation between the education and health departments led to the achievement of over 95% vaccination coverage among the specified group of girls and there were no reports of serious adverse reactions (Ahmed *et al*., 2022). A research study involving Indian girls found that the quadrivalent HPV vaccination led to mild to moderate injection site reactions, including pain and tenderness (Garland *et al*., 2022).

The implementation of the National HPV Vaccination Program in Australia led to a reduction in the prevalence of HPV, particularly the 4-valent HPV types (Patel *et al*., 2018). The safety of the quadrivalent HPV vaccine in Japanese boys was assessed, with the primary identified adverse effect being injection site reactions (Murata *et al*., 2019). The safety of the 9-valent HPV vaccine in adolescent boys and girls was monitored for duration of 7 to 8 years. The study found no instances of high-grade intraepithelial neoplasia or genital warts related to vaccine-type HPV after the administration of three doses of the vaccine. The incidence rate of persistent infection associated with HPV types 6/11/16/18/31/33/45/52/58 was lower in both males and females. Throughout the study period, the 9-valent HPV vaccine demonstrated substantial safety, with no reports of vaccine-related serious adverse effects or deaths (Olsson *et al*., 2020).

The safety of the 9-valent vaccine was assessed in both boys and girls aged 12-13 years. The conclusive findings indicated that none of the reactions could be attributed to the vaccine. Allergic reactions and incidents of syncope were infrequent and were not found to be linked to the vaccine. Importantly, no deaths associated with the vaccine were reported during the follow-up period (Hansen *et al*., 2023). The safety of the 9v vaccine was evaluated for both males and females in the United States post-licensure over a three-year period using the Vaccine Adverse Event Reporting System (VAERS). A higher percentage of Adverse Drug Reactions (ADRs) was reported among females compared to males. The most frequently reported ADRs included dizziness, syncope, headache and injection site reactions, with no discernible difference in common ADRs between the two genders. The post-licensure data aligned with findings from pre-licensure trials (Shimabukuro *et al*., 2019).

Post-marketing surveillance of the HPV vaccine revealed that the predominant Adverse Drug Reaction (ADR) was injection site pain, primarily occurring after the first dose, with mild intensity and subsequent recovery. No severe ADRs necessitating hospitalization or emergency department visits were reported (Eun *et al*., 2023). An investigation was carried out on individuals aged 10-14 who received the AS04-adjuvanted HPV-16/18 vaccine and they were monitored for a duration of 10 years. Throughout the follow-up period, no severe adverse effects or unfavourable pregnancy outcomes linked to the vaccine were observed (Schwarz *et al*., 2019). In contrast to many studies focusing on the long-term safety of vaccines, a specific investigation was conducted to assess the immediate effects following bivalent HPV vaccination. Participants were instructed

to document reactions, including their duration and intensity, for the subsequent 7 days. The most frequently reported reaction was injection site pain, with a higher frequency observed in the vaccine group compared to the placebo. Other local reactions noted included itching, redness, swelling and hardening at the injection site. The predominant systemic side effect was fever, followed by occurrences of headache, fatigue, allergic reactions, nausea, vomiting, muscle pain, or diarrhea. Pregnancies were documented during the study and no association between the vaccine and congenital anomalies was identified (Li *et al*., 2023).

CONCLUSION

HPV vaccines have been established as the sole effective measure for mitigating HPV infections and reducing the associated morbidity and mortality. Despite two decades since FDA approval, the uptake of these vaccines remains disappointingly low. This review identifies several factors contributing to the underutilization of HPV vaccines, including insufficient awareness among healthcare providers, reluctance from patients, limited knowledge about vaccines, the financial burden of vaccination, concerns about potential risks or adverse reactions and the influence of peer opinions. While it is recommended for all adolescents, irrespective of gender, to receive the vaccine, the misconception that it is exclusively for girls contributes to lower vaccination rates among boys.

The proven efficacy and safety of HPV vaccines, as demonstrated in both pre-and post-licensure studies, underscore the need for concerted efforts to address these barriers. Healthcare providers, particularly gynaecologists and paediatricians, should take proactive initiatives to promote vaccination among their patients. Additionally, a national-level movement is imperative to champion immunization, emphasizing the importance of HPV vaccination in preventing a range of diseases.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ABBREVIATIONS

ADR: Adverse Drug Reaction; **APC:** Antigen-Presenting Cell; **AS04:** Adjuvant System 04 (used in vaccines); **B cells:** B Lymphocytes; **CD4+:** Cluster of Differentiation 4 Positive (Helper T cells); **CD8+:** Cluster of Differentiation 8 Positive (Cytotoxic T cells); **CIN:** Cervical Intraepithelial Neoplasia; **DNA:** Deoxyribonucleic Acid; **E1 and E2 protein:** Early Proteins 1 and 2 (regulatory proteins in HPV); **E4 and E5 protein:** Early Proteins 4 and 5 (involved in HPV lifecycle and oncogenesis); **E6 and E7 protein:** Early Proteins 6 and 7 (oncoproteins in HPV); **FDA:** Food and Drug Administration; **GSK:** GlaxoSmithKline (pharmaceutical company); **HPV:** Human Papillomavirus; **L1 protein:** Major Capsid Protein of HPV; **L2 protein:** Minor Capsid Protein of HPV; **MHC Class I and II:** Major Histocompatibility Complex Class I and II; **p53:** Apoptosis regulator protein; **RNA:** Ribonucleic Acid; **T cells:** T Lymphocytes; **VAERS:** Vaccine Adverse Event Reporting System; **VLP:** Virus-Like Particle.

SUMMARY

Despite two decades since FDA approval, HPV vaccine uptake remains low due to factors such as limited awareness, patient reluctance, misconceptions, financial barriers and societal influences. Addressing these challenges requires proactive efforts from healthcare providers and a national-level movement to promote immunization. With proven safety and efficacy, HPV vaccines play a critical role in preventing HPV-related diseases, highlighting the urgency of improving vaccination rates to protect public health.

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