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HPV Vaccine: Current Data, Efficacy, and Clinical Implications

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ABSTRACT

Introduction and Purpose: Human papillomavirus (HPV) is a major cause of several cancers, including cervical cancer, and HPV vaccination is an effective method of preventing these diseases, especially before the initiation of sexual activity. The aim of this paper is to review current knowledge regarding HPV vaccines. It seeks to determine their effectiveness and their application in both primary and secondary prevention of HPV-related diseases.

Materials and Methods: The review provides a summary of key information on the effectiveness, clinical aspects, and potential side effects following HPV vaccination. This analysis is based on peer-reviewed studies sourced from scientific databases such as PubMed.

Results: Studies show promising results, with complete remission in most patients with genital warts and a skin cancer cases, such as squamous cell carcinoma (SCC), in patients receiving the Gardasil vaccine. Additionally, the vaccine shows potential effectiveness in treating epidermodysplasia verruciformis (EV), particularly in immunocompromised patients, where

clinical improvement and HPV DNA clearance have been observed. Data from countries such as Thailand, Tanzania, and India suggest that a single dose of the HPV vaccine may offer protection comparable to multiple doses, making vaccination more cost-effective and accessible in resource-limited countries, supporting public health goals to reduce cervical cancer cases. Furthermore, the introduction of new treatment methods and ongoing research into HPV vaccines, including DNA vaccines and PD-L1 blockade, may provide additional therapeutic options in the future.

Conclusion:Vaccinations show a herd effect, reducing the number of cases of genital warts and respiratory papillomatosis, and their widespread implementation in health programs can significantly impact the reduction of HPV-related cancers worldwide.

Keywords: human papilloma virus, cervical cancer, HPV-related oropharyngeal cancer, gardasil, vaccination

Introduction

Human papillomavirus (HPV) is a common pathogen from the Papillomavirus family. It is primarily transmitted through sexual contact, as well as contact and vertical transmission. It is estimated that up to 80% of sexually active individuals are carriers. Its presence predisposes individuals to benign conditions, such as genital warts and recurrent respiratory papillomatosis. Genital warts are usually small, cauliflower-like growths that appear in the urogenital area. While they are benign, they can significantly affect the physical and psychological discomfort of patients. [1] HPV is responsible for 99% of cervical cancer cases, 90% of anal cancer cases, 65% of vaginal cancers, 50% of vulvar cancers, and 45-90% of oropharyngeal cancers. [2]

Cervical cancer is a malignancy largely associated with HPV infection, which can lead to a precancerous condition known as cervical intraepithelial neoplasia (CIN). It is the most common genital cancer worldwide. In 2020, approximately 604,000 new cases of cervical cancer and 342,000 deaths were recorded globally, with nearly 90% of these cases occurring in developing countries.[3] Its incidence can be significantly reduced through vaccination, which is especially important before the initiation of sexual activity, to prevent potential infection. In the diagnosis of cervical cancer, cytological screening is crucial, which, depending on the result,

may be further confirmed with HPV tests and specialized examinations, such as colposcopy, Schiller's test, or biopsy of suspicious tissue.

The main available vaccines are Gardasil® (quadrivalent – HPV6/11/16/18 and nonavalent – HPV6/11/16/18/31/33/45/52/58) and Cervarix® (bivalent – HPV16/18). Gardasil® protects against recurrent respiratory papillomatosis (RRP) caused by subtypes 6,11 as well as several oncogenic subtypes.[4] The most common oncogenic genotypes worldwide are HPV-16 and HPV-18, although their prevalence shows geographic variability.[5] For example, in China, the most common subtypes are HPV-16, 52, and 58.[6]

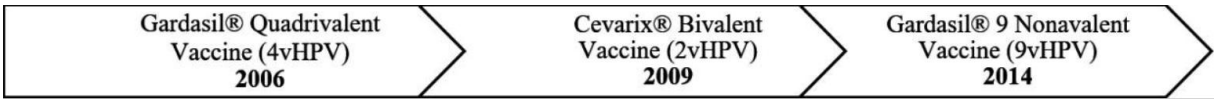

Fig 1. Timeline of the United States Food and Drug Administration (FDA) approval of HPV vaccines currently available on the market [4]

HPV vaccination is currently the only one that belongs to primary cancer prevention. It is commonly referred to as the "anti-cancer vaccine." It significantly reduces both mortality rates and treatment costs for the potential consequences of virus infection. Many countries have decided to subsidize it, with Poland starting from June 1, 2023. Prior to that, since 2006, the vaccine was available and recommended but not publicly funded, which, due to its high cost, limited its accessibility— the cost was about 1500 PLN while the average gross monthly salary was 2,477 PLN. [7]

The Role of Human Papillomavirus Vaccination in the Management and Treatment of HPV-Associated Diseases

1. Cutaneous Warts

   Plantar warts and flat warts are a common reason for patients to visit a dermatologist. These lesions are often difficult to treat, tend to spread locally, and recur frequently. An effective prevention method for these changes, which are caused by HPV infection, is being sought.

   In the study by Nofal et al., a three-dose vaccination (at 0, 1 and 6 months) was administered either intramuscularly or locally to the largest wart every two weeks until the lesion was removed (up to 6 sessions) in 44 patients dealing with these changes. Complete resolution of the lesions was observed in 63.3% of patients in the first trial and 81.8% in the second. Furthermore, no relapses were observed within 6 months.

These effects still require further research to determine their effectiveness and guidelines, but the results of current tests are promising.

2. Genital Warts

   The authors report a study involving a 10-person research group, in which 60% of participants achieved complete remission after receiving the Gardasil vaccine, 10% showed partial improvement, and 30% had no response to the treatment. A case of a 44-year-old man with perianal warts, which did not respond to imiquimod treatment, was also described. Remission was achieved after eight weeks of administering the quadrivalent Gardasil vaccine.

3. Keratinocyte Carcinomas

   Studies suggest that the HPV virus may play a role in the development of squamous cell carcinoma (SCC) of the skin, acting as a co-carcinogen in combination with other risk factors. Nichols et al. assessed the impact of the Gardasil vaccine on patients with multiple skin cancers, observing a significant reduction in the incidence of new cases of SCC and basal cell carcinoma (BCC) after vaccination. In another study, Gardasil-9 was administered to a 90-year-old patient with extensive SCC lesions, with both intramuscular and intralesional injections. After a few months, significant improvement was observed, and after 11 months, complete remission was achieved, which lasted for at least 2 years.

4. Epidermodysplasia Verruciformis

   Epidermodysplasia verruciformis (EV) is a rare genetic disorder associated with mutations in the EVER1 and EVER2 genes, which increase susceptibility to HPV infection and may lead to chronic infections and skin cancers. There is also an acquired form of EV that develops in patients with weakened immune systems. Maor et al. described the case of a 50-year-old woman who had undergone a kidney transplant, in whom EV progressed despite standard treatment. After administering three doses of the Gardasil vaccine over six months, significant clinical improvement was observed, and no HPV DNA was detected in PCR testing, suggesting the potential effectiveness of vaccination in the treatment of EV. [8]

5. Non-small cell lung cancer (NSCLC)

   Research findings suggest that HPV may play a role in the pathogenesis of non-small cell lung cancer (NSCLC), influencing both its development and the effectiveness of immunotherapy. [9]

6. Human Papillomavirus Conjunctival Papilloma

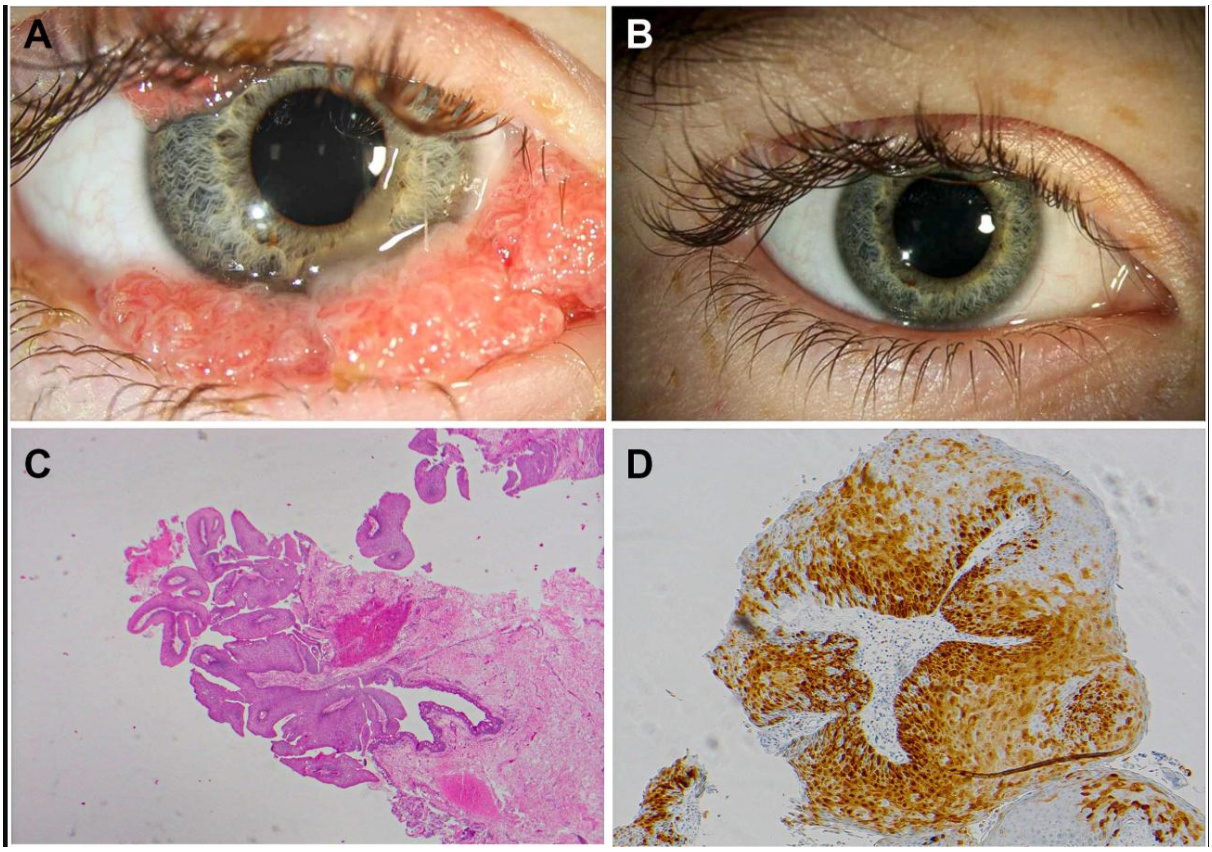

Fig 2. "The authors describe the clinical progression of a 9-year-old boy with unilateral, severe conjunctival papillomatosis (CP; **A**-**B**). Histopathological diagnosis showed squamous cell papilloma (**C**) and evidence of human papillomavirus-6 (HPV-6) infection with polymerase chain reaction, and histopathological immunohistochemistry demonstrated HPV P16 (cyclin-dependent kinase inhibitor p16) focal patchy reactivity (**D**). Over 24 months, he had recurrent CP despite management with surgical excision, cryotherapy, and subconjunctival interferon therapies. Four months after administration of one 9-valent HPV vaccine (Gardasil-9), there was significant regression of size and resolution of bulbar CP when combined with topical interferon therapy." [10]

7. Recurrent Respiratory Papillomatosis

Analysis of data from patients with recurrent respiratory papillomatosis (RRP) has shown that HPV vaccination leads to an extended period between treatments and a reduction in their frequency. Most participants in the study were men with a late-onset form of RRP associated with HPV-6 infection. Previous studies in this area had limited value due to small sample sizes and methodological diversity, with results being inconclusive. However, significant progress has been made in the prevention and treatment of RRP in recent years, and the broader use of the HPV vaccine may contribute to a reduction in the prevalence of this disease. Vaccination may have an immunomodulatory effect, improving the body's response to HPV infection and complementing therapies such as interferon or bevacizumab, as well as secondary vaccinations. The introduction of new systemic treatment methods has increased the ability to control resistant cases of RRP, and ongoing research into DNA vaccines and PD-L1 blockade may provide additional therapeutic options in the future. [11] A key role in limiting RRP lies with doctors, promoting HPV-9 vaccination, which could lead to the elimination of this disease. Although further studies, including randomized clinical trials, are necessary, current results suggest that HPV vaccination may be an effective adjunctive therapy for RRP, positively impacting patients' quality of life and reducing the need for surgical interventions. However, the COVID-19 pandemic has created additional challenges in the care of patients with RRP, requiring the use of appropriate personal protective measures. [12]

HPV Vaccination Strategies: Balancing Efficacy, Immunity, and Cost in Single vs. Multi-dose Approaches

The widespread prevalence of HPV-related diseases, including cancers, has prompted governments to increase the availability of vaccines worldwide. This issue is particularly relevant in underdeveloped countries, where access to healthcare is limited. Studies have been conducted in low- and middle-income countries, including India and Tanzania, to assess the effectiveness of various vaccination delivery methods.

1.1Thailand

The study found that administering two doses of the nine-valent HPV vaccine (9vHPV) to 12-year-old adolescents was the most cost-effective strategy, more effective and cheaper than the current recommendations in Thailand, which involve using the quadrivalent vaccine (4vHPV). The cost-effectiveness analysis (CEA) showed that both one and two doses of 9vHPV led to cost savings compared to no vaccination, but two doses provided greater effectiveness. Despite

some limitations, the results of this study may help shape national health policies regarding cervical cancer and HPV vaccination strategies. [13]

1.2 Tanzania

The DoRIS study was the first to evaluate the immune response and safety of a single dose of the HPV vaccine compared to two and three doses in target group girls in Tanzania. The results suggest that a single dose may provide protection comparable to the full vaccination schedule, supporting WHO recommendations for both single and two-dose regimens for age groups 9–14 and 15–20 years. Both vaccines showed high tolerance and effectiveness in preventing persistent HPV 16 and 18 infections, exceeding 97%, with the bivalent vaccine inducing higher antibody levels than the nine-valent vaccine. The use of a single-dose regimen could simplify the implementation of vaccination programs in resource-limited countries, increasing their accessibility and accelerating the elimination of cervical cancer in line with WHO's 2030 goals.

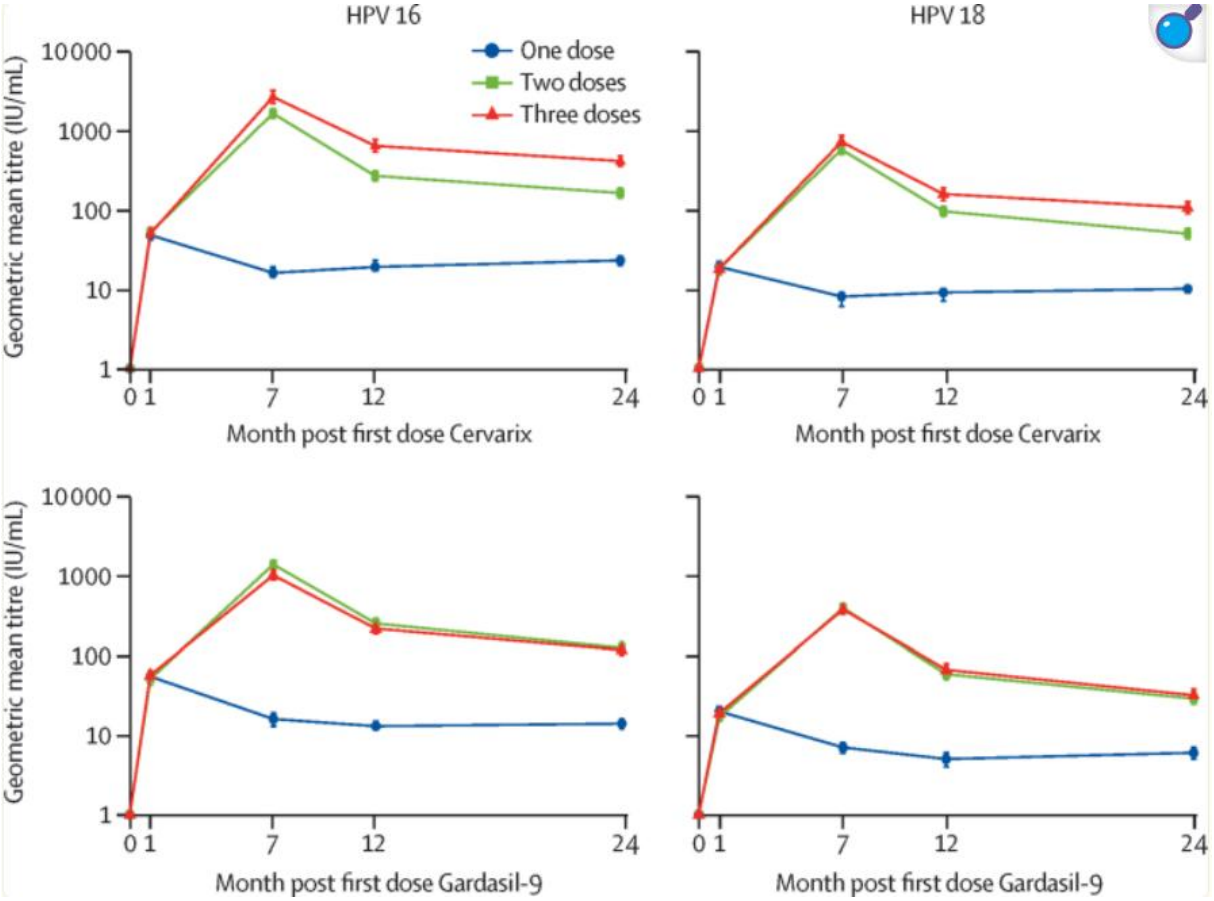

Fig 3. "HPV 16 specific and HPV 18 specific antibody geometric means by number of HPV vaccine doses" [14]

1.3 India

The study found that a single dose of the quadrivalent HPV vaccine against HPV 16/18 provides the same high level of effectiveness as two or three doses, maintaining protection for at least 10 years. According to the decision of IARC experts, protection against persistent cervical infection is sufficient evidence of the effectiveness of a single dose of the vaccine in preventing cervical cancer. [15]

Vaccine effectiveness

HPV vaccines have shown high effectiveness not only in vaccinated girls but also in reducing the number of genital wart cases in unvaccinated men, due to the herd effect. It has been estimated that the Gardasil-9 vaccine in a 3-dose regimen can reduce the infectivity of body fluids in women infected with HPV and prevent the transmission of the virus to sexual partners. [16]

Available HPV vaccines were compared, showing a higher antibody level after the bivalent vaccine than the quadrivalent one, seven years after administration. The nonavalent vaccine demonstrated the highest effectiveness. Interestingly, seropositivity was detected among genotypes not included in the vaccines (HPV31, HPV33, and HPV45). This phenomenon is attributed to cross-protection, caused by the similarity between different HPV genotypes. It is unclear how long this protection will last, but current research results are promising. [17]

Studies have shown that these vaccines induce both innate responses and trained immunity, which modifies responses to Toll-like receptor (TLR) ligands. The Cervarix vaccine induces a stronger cytokine response, while Gardasil, despite weaker cytokine expression, induces trained immunity and increases TNF-α production upon secondary stimulation. [18]

Aluminum-containing adjuvants have been used in vaccines for nearly 100 years, primarily in children and adolescents, and despite some limitations, such as weaker Th1 response induction and sensitivity to freezing, they remain a popular component due to their safety, tolerance, and low cost. Recent advances in the physicochemical characterization of these vaccines and modern screening methods support the development of new formulations and quality control in production. Due to their high adsorptive capacity, aluminum adjuvants will increasingly be used to create new combination adjuvants, ensuring their dominant role in future vaccines. [19]

Thrombosis and thrombocytopenia after HPV vaccination

A case is described of a 25-year-old woman who developed symptoms resembling Vaccine-induced Immune Thrombocytopenia and Thrombosis (VITT) 10 days after vaccination. This is

a rare but serious condition that can occur after vaccination with some adenoviral vector-based vaccines, such as those against COVID-19 (e.g., AstraZeneca). The syndrome is characterized by thrombocytopenia, thrombosis, and elevated D-dimer levels. This phenomenon results from an atypical immune reaction in which the body produces antibodies against platelet factor 4 (PF4), leading to platelet activation and the formation of blood clots. It is a serious condition requiring prompt diagnosis and treatment. This case draws attention to the potential occurrence of VITT after other vaccines, not just those for SARS-CoV-2. [20]

Conclusion

Human papillomavirus (HPV) is a significant health threat, leading to various cancers, including cervical cancer, which is primarily associated with this pathogen. HPV vaccination is an effective preventive method, especially when administered before the initiation of sexual activity, and the availability of vaccines like Gardasil® and Cervarix® is crucial in preventing the development of HPV-related cancers. Recommendations for vaccine use in countries with different income levels highlight their high effectiveness, as confirmed by studies conducted in countries like Thailand, Tanzania, and India.

Vaccination also has a herd effect, reducing the number of cases of genital warts in unvaccinated individuals. Additionally, research results indicate a positive impact of the vaccines on reducing the incidence of respiratory papillomatosis and some skin cancers, such as squamous cell carcinoma. Despite a few cases of serious side effects, such as VITT syndrome, the benefits of HPV vaccination outweigh the risks, especially in the context of global efforts to eliminate cervical cancer.

Introducing HPV vaccination into health programs and ensuring widespread access to these vaccines can significantly reduce the number of HPV-related cancer cases, ultimately improving global public health in the long term. Further research and monitoring of the long-term effects of vaccination will be crucial to ensure optimal protection and safety, particularly in developing countries where access to treatment is limited.

Disclosures

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Investigation – Katarzyna Załuska, Adriana Skuba, Aleksandra Bartoszek

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Writing – review and editing – Julia Adamiuk, Karolina Kopeć, Sylwia Nykiel
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