



## **Human Papillomavirus and Cervical Cancer: Prevention Strategies and Vaccine Impact**

*Papilomavírus Humano e Câncer do Colo do Útero: Estratégias de Prevenção e Impacto da Vacina*

*Virus del Papiloma Humano y Cáncer de Cuello Uterino: Estrategias de Prevención e Impacto de la Vacuna*



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**Luiz Felipe Rodrigues Silva**

*Graduado em Odontologia*

*Universidade de São Paulo, São Paulo, São Paulo, Brasil*

*e-mail: [dds.felipe@outlook.com](mailto:dds.felipe@outlook.com)*

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### **ABSTRACT**

Human papillomavirus (HPV) is the central etiological agent of cervical cancer, representing a major global public health problem. Prophylactic vaccination has emerged as the primary preventive strategy. This narrative review synthesizes the available evidence on cervical cancer prevention strategies, focusing on the impact and effectiveness of HPV vaccines, based exclusively on the provided literature. This is a narrative literature review constructed from the analysis and synthesis of seven provided scientific article abstracts, including review studies, systematic reviews, and population-based cohort studies. Persistent infection with high-risk HPV, particularly HPV-16, is causally associated with cervical cancer. Licensed prophylactic vaccines (bivalent, quadrivalent, and nonavalent), based on the L1 protein, are highly immunogenic. Vaccine effectiveness is greatest when administered to young individuals (<20 years), with up to an 86% reduction in cervical cancer risk among those vaccinated before age 17. Vaccination at older ages (20–30 years) has not demonstrated the same immediate protective effect in population-based studies. Challenges remain in achieving global vaccination



coverage, especially among vulnerable populations and people living with HIV. Therapeutic vaccines are under development to induce cellular immunity against transformed cells. Early prophylactic HPV vaccination is a highly effective and safe strategy for cervical cancer prevention. Expanding vaccination coverage and developing new formulations are crucial to maximizing the reduction of morbidity and mortality from this neoplasm.

**Keywords:** Papillomavirus Infections; Papillomavirus Vaccines; Uterine Cervical Neoplasms; Immunization Programs; Effectiveness.

### RESUMO

O papilomavírus humano (HPV) é o agente etiológico central do câncer cervical, representando um problema de saúde pública global. A vacinação profilática surge como a principal estratégia preventiva. Esta revisão narrativa sintetiza a evidência disponível sobre as estratégias de prevenção do câncer cervical, com foco no impacto e na eficácia das vacinas contra o HPV, baseando-se exclusivamente na literatura fornecida. Trata-se de uma revisão narrativa da literatura, construída a partir da análise e síntese de sete resumos de artigos científicos fornecidos, abrangendo estudos de revisão, revisão sistemática e coorte populacional. A infecção persistente por HPV de alto risco, notadamente o HPV-16, é causal para o câncer cervical. As vacinas profiláticas licenciadas (bivalente, quadrivalente e nonavalente), baseadas na proteína L1, são altamente imunogênicas. A efetividade vacinal é máxima quando administrada em jovens (<20 anos), com redução de até 86% no risco de câncer cervical para vacinadas antes dos 17 anos. A vacinação em idades mais avançadas (20–30 anos) não demonstrou o mesmo efeito protetor imediato em estudos populacionais. Desafios persistem na cobertura vacinal global, especialmente em populações vulneráveis e pessoas vivendo com HIV. Vacinas terapêuticas estão em desenvolvimento para induzir imunidade celular contra células transformadas. A vacinação profilática contra o HPV em idade precoce é uma estratégia altamente eficaz e segura para a prevenção do câncer cervical. A expansão da cobertura vacinal e o desenvolvimento de novas formulações são cruciais para maximizar o impacto na redução da morbimortalidade por esta neoplasia.

**Palavras-chave:** Infecções por Papillomavirus; Vacinas contra Papillomavirus; Neoplasias do Colo do Útero; Programas de Imunização; Efetividade.

### RESUMEN

El virus del papiloma humano (VPH) es el agente etiológico central del cáncer cervical, representando un importante problema de salud pública a nivel mundial. La vacunación profiláctica se ha consolidado como la principal estrategia preventiva. Esta revisión narrativa sintetiza la evidencia disponible sobre las estrategias de prevención del cáncer cervical, con énfasis en el impacto y la eficacia de las vacunas contra el VPH, basándose exclusivamente en la literatura proporcionada. Se trata de una revisión narrativa construida a partir del análisis y la síntesis de siete resúmenes de artículos científicos proporcionados, incluyendo estudios de revisión, revisiones sistemáticas y cohortes poblacionales. La infección persistente por VPH de alto riesgo, particularmente el VPH-16, es causal del cáncer cervical. Las vacunas profiláticas autorizadas (bivalente, tetravalente y nonavalente), basadas en la proteína



L1, son altamente inmunogénicas. La efectividad vacunal es mayor cuando se administra en jóvenes (<20 años), con una reducción de hasta el 86% en el riesgo de cáncer cervical en personas vacunadas antes de los 17 años. La vacunación en edades más avanzadas (20–30 años) no ha demostrado el mismo efecto protector inmediato en estudios poblacionales. Persisten desafíos en la cobertura vacunal global, especialmente en poblaciones vulnerables y personas que viven con VIH. Las vacunas terapéuticas se encuentran en desarrollo para inducir inmunidad celular contra células transformadas. La vacunación profiláctica temprana contra el VPH es una estrategia altamente eficaz y segura para la prevención del cáncer cervical. La expansión de la cobertura vacunal y el desarrollo de nuevas formulaciones son fundamentales para maximizar la reducción de la morbilidad por esta neoplasia.

**Palabras clave:** Infecciones por Papillomavirus; Vacunas contra el Papillomavirus; Neoplasias del Cuello Uterino; Programas de Inmunización; Efectividad.

## 1. INTRODUCTION

Human papillomavirus (HPV) is recognized as the most common sexually transmitted infection worldwide, being causally associated with approximately 5% of all cancers, including those of the cervix, penis, vulva, vagina, anus, and oropharynx (Williamson, 2023; Jensen *et al.*, 2024). Cervical cancer, in particular, is among the leading causes of cancer death in women globally, representing a heavy burden for public health, especially in regions with limited resources (Jensen *et al.*, 2024; Liu; Ai, 2024). The pathogenesis of cervical cancer is intrinsically linked to persistent infection with oncogenic HPV types. HPV-16 is the most carcinogenic type, predominating in cancers, but there is robust evidence that types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 also cause cervical cancer (Williamson, 2023).

The immune response against HPV is directed at the L1 protein, which, when self-assembled into virus-like particles (VLPs), induces the production of type-specific neutralizing antibodies, forming the basis of all commercial prophylactic vaccines. Currently, there are six licensed prophylactic vaccines: three bivalent, two quadrivalent, and one nonavalent, which protect against high-risk HPV types 16 and 18, responsible for over 70% of cervical cancers, and, in the case of higher-valency vaccines, against additional types (Yousefi *et al.*, 2022; Williamson, 2023). Cervical cancer screening, through methods such as Pap smear and HPV testing, remains a fundamental tool, but its access is unequal, particularly in low-resource settings (; Liu; Ai, 2024).

Despite the proven success of prophylactic vaccines, which prevent infection with nearly 100% efficacy when administered before the onset of sexual activity, vaccine acceptance and coverage



remain suboptimal globally. Barriers such as lack of access and limited knowledge about HPV and its vaccine hinder disease control (Rosalik; Tarney; Han, 2021. Jensen *et al.*, 2024). Furthermore, HPV infection disproportionately affects people living with HIV, who have lower viral clearance rates, higher cancer development, and increased mortality, requiring specific strategies (Williamson, 2023; Jensen *et al.*, 2024). Vaccination of adults after treatment for cervical lesions or recurrent respiratory papillomatosis has shown an impact on reducing recurrences. Gender-neutral vaccination is pointed out as a strategy to improve herd immunity and prevent infections in men as well (Williamson, 2023).

Given the availability of different vaccines and the need to optimize immunization strategies to maximize population protection against cervical cancer, it becomes crucial to synthesize the evidence on vaccine effectiveness at different ages and contexts. Recent literature offers robust data on the real-world impact of vaccination but also reveals gaps, such as the need for more research on long-term effects in special populations, like people living with HIV, and the determination of the need for booster doses (Williamson, 2023). The objective of this study, therefore, is to produce a narrative literature review, based exclusively on the provided abstracts, to analyze cervical cancer prevention strategies, focusing on the impact, effectiveness, and challenges related to HPV vaccines.

## **2. METHODOLOGY**

This is a narrative literature review, designed to synthesize and discuss current knowledge on cervical cancer prevention strategies and the impact of HPV vaccination, based on a specific set of sources.

The search was conducted exclusively based on the abstracts of scientific articles provided by the user. The primary sources of information are the following articles: Kjaer *et al.* (2021); Rosalik; Tarney; Han (2021); Yousefi *et al.* (2022); Williamson (2023); Ellingson *et al.* (2023); Jensen *et al.* (2024); Liu; Ai (2024). The search strategy consisted of a comprehensive analysis of the content of these pre-selected documents.

All seven provided abstracts were included, which encompass review articles, one systematic review, and one population-based cohort study, published between 2021 and 2024, in the English language. The selection was predetermined by the user, with no other inclusion or exclusion criteria applied by the reviewer.

Data were extracted through careful and in-depth reading of each abstract. Information pertinent



to the review's objectives was identified, organized, and categorized manually, focusing on: HPV epidemiology, oncogenic viral types, vaccine characteristics, vaccine efficacy/effectiveness by age, impact on cervical cancer reduction, implementation challenges, and development of new vaccines.

Data analysis was conducted qualitatively, through narrative and thematic synthesis of the extracted content. The findings were compared and contrasted across the different studies to identify consensus, divergences, and evidence gaps, allowing for the construction of a critical discussion based solely on the information provided.

As this is a narrative literature review, which does not involve the direct participation of human subjects, submission to an Ethics Committee was not required. The conduct of this study respected the principles of academic and scientific integrity, with strict fidelity to the sources consulted.

### **3. RESULTS AND DISCUSSION**

#### **3.1 HPV Carcinogenicity and principles of vaccine prevention**

The analyzed literature is consensual in establishing HPV as the central causal agent for the development of cervical cancer. Williamson (2023) specifies that, in addition to HPV-16, the most carcinogenic, there is sufficient evidence to include types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 as causes of cervical cancer. Jensen *et al.* (2024) corroborate this view, stating that most cases of cervical, anal, and oropharyngeal cancers are due to HPV infection, with persistent infection being the main risk factor for malignant progression.

The molecular basis of prophylactic prevention lies in the viral capsid protein L1, whose self-assembly capacity into virus-like particles (VLPs) induces a robust and type-specific humoral immune response (Williamson, 2023). Yousefi *et al.* (2022) add that existing prophylactic vaccines, produced by recombinant DNA technology, are highly immunogenic and induce the production of neutralizing antibodies, contrasting with the principle of therapeutic vaccines, which aim to induce cell-mediated immunity against already transformed cells.

#### **3.2 Efficacy and Effectiveness of Prophylactic Vaccines: The Crucial Role of Age at Vaccination**

The evidence on the efficacy of prophylactic vaccines is robust. Jensen *et al.* (2024) state that the vaccine prevents cervical cancer with nearly 100% efficacy if given before first sexual activity. However, real-world effectiveness, particularly when vaccination is offered at older ages, was explored



in detail by two central studies. The systematic review by Ellingson *et al.* (2023), covering studies between 2007 and 2022, consistently demonstrated that vaccine effectiveness against outcomes such as vaccine-type infections, anogenital warts, and cervical abnormalities is highest in the youngest age group. Effectiveness estimates ranged from approximately 74% to 93% for adolescents aged 9-14 years, dropping to a range of 12% to 90% among those vaccinated from 15 to 18 years (Ellingson *et al.*, 2023).

This finding is powerfully reinforced by the Danish population-based cohort study by Kjaer *et al.* (2021), which evaluated the effectiveness of vaccination against cervical cancer in 867,689 women. The results demonstrated a drastic reduction in cervical cancer risk for women vaccinated at age 16 or younger (Incidence Rate Ratio [IRR] = 0.14; 95% CI = 0.04 to 0.53) compared to unvaccinated women. For those vaccinated between 17 and 19 years, protection was lower but still substantial (IRR = 0.32; 95% CI = 0.08 to 1.28). Notably, vaccination in women aged 20-30 years showed no immediate benefit (IRR = 1.19; 95% CI = 0.80 to 1.79), although an analysis with a longer latency period (4 years) suggested a possible non-significant risk reduction (IRR = 0.85; 95% CI = 0.55 to 1.32) (Kjaer *et al.*, 2021). Together, these data consolidate the notion that the main benefit of prophylactic vaccination lies in preventing initial infection, with early age being the determining factor for its maximum effectiveness, as also synthesized by Rosalik; Tarney; Han (2021) and Liu; Ai (2024).

### **3.3 Challenges for Global Implementation and Special Populations**

Despite proven efficacy, the global implementation of vaccination faces significant obstacles. Jensen *et al.* (2024) point out that low vaccine uptake worldwide is due to lack of access and limited knowledge about HPV. Rosalik; Tarney; Han (2021) delve deeper into this discussion, highlighting that while vaccination is accessible in more developed countries, there are substantial barriers to worldwide distribution and acceptance. They emphasize that the delay in achieving adequate vaccination coverage requires methods to encourage vaccination, dispel myths, and implement better global distribution processes. Liu; Ai (2024) also mention the ongoing challenges in the field, reinforcing the need for advances in screening and vaccination strategies.

A critical aspect addressed is the disproportionate impact of HPV on vulnerable populations. Jensen *et al.* (2024) and Williamson (2023) agree that people living with HIV are disproportionately affected, showing lower viral clearance, higher risk of developing cancer, and increased mortality.



Williamson (2023) notes that HPV vaccines are immunogenic in this population but emphasizes the need for more research on the long-term impact of vaccination and the possible need for booster doses, an important evidence gap.

### **3.4 Complementary Strategies and Development of New Vaccines**

In addition to childhood vaccination, complementary strategies are mentioned. Williamson (2023) cites catch-up campaigns for adolescents and young adults, and vaccination of adults after treatment for lesions, which showed an impact on reducing recurrences. Gender-neutral vaccination is also proposed as a way to improve herd immunity and prevent infections in men (Williamson, 2023).

On the research horizon, the development of new vaccines continues. Yousefi *et al.* (2022) mention that therapeutic vaccines, with a distinct mechanism of action (cellular immunity), are being developed to treat pre-existing lesions. Additionally, a second generation of prophylactic vaccines, using alternative viral components and more cost-effective production strategies, is undergoing clinical evaluation (Yousefi *et al.*, 2022). Liu; Ai (2024) also discuss the role of predictive biomarkers, such as DNA methylation and non-coding RNAs, which may refine diagnostic and prognostic practices in the future, integrating into cervical cancer prevention and management strategies.

## **4. LIMITATIONS OF THE AVAILABLE EVIDENCE**

The limitations of this review stem primarily from the nature of the analysis, restricted to the content of the provided abstracts, without access to the full texts and their methodological details. Exclusive reliance on abstracts may imply the loss of important nuances regarding study designs, specific populations, and subgroup analyses. Furthermore, the evidence base synthesized in the original articles itself contains limitations. Williamson (2023) explicitly states the need for more research on the long-term impact of vaccination in people living with HIV. The study by Kjaer *et al.* (2021), although robust, is observational and conducted in a single country (Denmark), which may limit the generalizability of the findings to populations with different epidemiological patterns and vaccination coverage. The heterogeneity in effectiveness estimates for the 15-18 age group in the systematic review by Ellingson *et al.* (2023) also suggests that contextual and methodological factors influence the results, not fully captured in this synthesis



#### 4. CONCLUSION

This review, based exclusively on the provided literature, concludes that human papillomavirus (HPV) infection is the necessary cause for the development of cervical cancer, with types 16 and 18 being the main culprits. Current prophylactic vaccines, based on the L1 protein, represent a highly effective and safe tool for the primary prevention of this neoplasm. The analyzed evidence converges to demonstrate that the effectiveness of HPV vaccination is maximal when administered at early ages, ideally before the onset of sexual life, with significantly greater protection in girls vaccinated before age 17. Vaccination at older ages (20-30 years) did not demonstrate the same immediate protective benefit, reinforcing the importance of immunization strategies targeted at pre-adolescents.

The findings of this synthesis reinforce the urgent need to overcome barriers to vaccine access and acceptance on a global scale, including the implementation of gender-neutral vaccination programs to maximize herd immunity. Vaccination combined with screening programs remains the most promising strategy to reduce cervical cancer morbidity and mortality.

For future research, it is recommended to conduct long-term studies evaluating the durability of vaccine protection and the need for booster doses, particularly in special populations such as people living with HIV. Additionally, continued investigation and development of therapeutic vaccines and new generations of prophylactic vaccines with better cost-effectiveness are crucial to expand access and impact on the prevention and control of cervical cancer.



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