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REVIEW

Human Papillomavirus (HPV): Therapeutic Vaccines and Vaccination Strategies

Virus del Papiloma Humano (VPH): Vacunas terapéuticas y estrategias de Vacunación

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ABSTRACT

Background: The human papillomavirus (HPV) has been studied for over a century. Although human warts have been described since ancient times, the presence of HPV in this type of skin and genital lesions was only recognized in the mid-20th century. Currently, HPV is recognized as the most common sexually transmitted infection worldwide. More than 200 genotypes have been identified, with high-risk types being strongly associated with anogenital and oropharyngeal cancers. New therapeutic vaccines currently under study aim to treat established HPV infections in patients with neoplastic lesions at various stages of development. Methods: This study is a descriptive, qualitative, and retrospective study. It was conducted through a systematic bibliographic review of the scientific literature on human papillomavirus (HPV), therapeutic vaccines, and vaccination strategies. Results: Although no therapeutic vaccine has yet been approved for use in humans, preliminary results are encouraging and suggest a potential impact in reducing the progression to invasive cancer. Based on the results obtained by the authors included in this review, we can conclude that therapeutic vaccines are emerging not only as a medical necessity, but as one of the most promising tools in the evolution of treatment for HPV and its related pathologies. Conclusión: Therapeutic vaccines have the potential to become a central pillar of clinical management for high-grade intraepithelial lesions (CIN 2/3) and early cervical cancer, as they not only provide a less invasive strategy than traditional surgical treatments but could also help reduce disease recurrence and improve patients' quality of life.

Keywords: HPV; Therapeutic vaccines; Neoplasms; Prophylactic vaccines.

RESUMEN

Introducción: El virus del papiloma humano (VPH) ha sido objeto de estudio desde hace más de un siglo. Si bien las verrugas humanas fueron descritas desde tiempos antiguos, a mediados del siglo XX se logró reconocer la presencia de HPV en este tipo de lesiones cutáneas y genitales. Actualmente, el VPH es reconocido como el agente de la infección de transmisión sexual más frecuente a nivel mundial. Se han identificado más de 200 genotipos, los tipos de alto riesgo están fuertemente asociados con cánceres anogenitales y orofaríngeos.las nuevas vacunas terapéuticas, actualmente en estudio tienen como objetivo tratar infecciones por VPH ya establecidas en pacientes con lesiones neoplásicas en sus distintos estadios de evolución. Métodos: El presente trabajo corresponde a un estudio de tipo descriptivo, cualitativo y retrospectivo. Se realizó mediante una revisión bibliográfica sistemática de la literatura científica sobre el Virus del Papiloma Humano; Vacunas terapéuticas y estrategias de Vacunación. Resultados: Aunque aún no se ha aprobado ninguna vacuna terapéutica para su uso en humanos, los resultados preliminares son alentadores y sugieren un potencial impacto en la reducción de la progresión a cáncer invasivo. En base a los resultados obtenidos por los autores incluidos en esta revisión podríamos concluir que las vacunas terapéuticas emergen no sólo como una necesidad médica, sino como una de las herramientas más prometedoras en la evolución del tratamiento del VPH y sus patologías derivadas. Conclusión: Las vacunas terapéuticas tendrían el potencial de convertirse en un pilar central del manejo clínico de las lesiones intraepiteliales de alto grado (NIC 2/3) y del cáncer de cuello uterino en sus fases tempranas, ya que no solo aportan una estrategia menos invasiva que los tratamientos quirúrgicos tradicionales, sino que también podrían contribuir a reducir la recurrencia de la enfermedad y mejorar la calidad de vida de los pacientes.

Palabras clave: HPV; Vacunas terapéuticas; Neoplasias; Vacunas profilácticas.

INTRODUCTION

The human papillomavirus (HPV) has been the subject of study for over a century. Although human warts were described in ancient times, it was not until the mid-20th century that the presence of HPV in these types of skin and genital lesions was recognized. The decisive breakthrough occurred around 1970, when virologist Harald zur Hausen proposed that certain HPV genotypes were linked to the development of cervical cancer. This hypothesis, which was initially controversial, was validated by molecular studies that identified genotypes 16 and 18 in more than 70% of cervical cancer cases. (4) These discoveries transformed our understanding of virus-induced carcinogenesis and led to Zur Hausen receiving the Nobel Prize in Medicine in 2008. (11) Currently, HPV is recognized as the most common sexually transmitted infection worldwide. Its global prevalence among women of reproductive age is estimated at 11%. It is estimated that more than 80% of sexually active people will become infected at some point in their lives (1). More than 200 HPV genotypes have been identified; these are divided into low-risk types (e.g., 6 and 11), which cause genital warts, and high-risk types (e.g., 16, 18, 31), which are strongly associated with anogenital and oropharyngeal cancers (6). Infection with high-risk genotypes is present in nearly 100% of cervical cancer cases. Although the immune system can spontaneously clear the infection within one or two years, persistence of the oncogenic virus is the primary risk factor for the development of high-grade cervical intraepithelial neoplasia (CIN) and eventually invasive cancer. CIN represents a spectrum of cellular changes that can be classified into grades 1, 2, and 3, with the latter two having the highest potential for progression to cancer (9).

The geographic distribution of the virus is believed to be highest in regions such as sub-Saharan Africa, Latin America, and Southeast Asia, where prevention and health promotion programs are reportedly insufficient. In the field of prevention, prophylactic vaccines represent a significant advance in public health. These vaccines consist of virus-like particles (VLPs) based on the L1 protein, and their use has demonstrated over 90% efficacy in preventing infections caused by genotypes 16 and 18. The implementation of mass vaccination campaigns has resulted in a marked decrease in the rates of CIN and cervical cancer. This type of vaccine was incorporated into the National Vaccination Schedule of the Argentine Republic in 2017. This initiative significantly reduced HPV infection in both men and women, who have the option to receive the vaccine before the age of 11. (3)

On the other hand, new therapeutic vaccines currently under study aim to treat established HPV infections in patients with neoplastic lesions at various stages of progression. Although no therapeutic vaccine has yet been approved for use in humans, preliminary results are encouraging and suggest a potential impact on reducing progression to invasive cancer. (7) The World Health Organization (WHO) is currently promoting its development and recognizes it as a key tool in the eradication of cervical cancer. (10)

MATERIALS AND METHODS

This study is a descriptive, qualitative, and retrospective study. A systematic review of the scientific literature was conducted, with the study's research objective in mind.

An exhaustive search was conducted for scientific articles published between 2003 and 2024 across recognized biomedical databases, including PubMed, Scopus, ScienceDirect, and Google Scholar. To identify the documents, MeSH terms were used in conjunction with keywords in English and Spanish, including: "Human Papillomavirus," "HPV," "HPV therapeutic vaccines," "cervical intraepithelial neoplasia," "HPV epidemiology," "HPV and cancer," and "HPV vaccine clinical trials."

Original articles, systematic reviews, meta-analyses, clinical trials (phases I–III), and documents from international organizations (WHO) were selected.

Inclusion criteria:

Publications available in full text.

Articles published between 2002 and 2004

Articles written in English or Spanish.

The information was extracted, organized, and analyzed manually. Special attention was paid to efficacy, immunogenicity, mechanism of action, and the current state of development of therapeutic vaccines in clinical trials, as well as to epidemiological and molecular data on HPV reported in recent literature. All sources used were cited in accordance with Vancouver guidelines.

RESULTS

In recent decades, the prevention of human papillomavirus (HPV)-associated cancer has been marked by the introduction and widespread use of prophylactic vaccines, whose efficacy in reducing new infections with high-risk genotypes has been extensively documented. Despite this progress, the persistence of established infections and the progression of precursor lesions to more severe stages remain significant clinical problems. This limitation of prophylactic vaccines has directed a growing share of research toward therapeutic vaccines, designed to induce a specific cellular immune response against HPV-infected or transformed cells. The body of reviewed studies reveals a line of development focused primarily on the E6 and E7 antigens, considered priority targets due to their role in virus-induced carcinogenesis.

Based on the selected studies, a general pattern emerged: therapeutic vaccines show promising immunological effects and, in some clinical contexts, achieve favorable effects on lesion regression and viral clearance. Despite this, the magnitude of the clinical benefit does not yet justify their being positioned as substitutes for conventional treatments in all scenarios. The available evidence comes primarily from narrative reviews, systematic reviews, meta-analyses, and phase I, II, and III clinical trials, which allow for a comprehensive understanding of their development, limitations, and prospects for application.

The study by Garbuglia, Lapa, Sias, Capobianchi, and Del Porto comparatively examined the immunological and clinical bases of prophylactic and therapeutic vaccines for human papillomavirus disease. The authors describe that prophylactic vaccines induce a humoral response based on neutralizing antibodies against the L1 protein, with a high capacity to prevent new infections. In contrast, therapeutic vaccines aim to activate cytotoxic T lymphocytes targeting the E6 and E7 oncoproteins. This distinction is central to understanding the biological rationale of both strategies. The review describes several therapeutic platforms, including DNA vaccines, peptide vaccines, and viral and bacterial vector formulations. The results presented in this study show that, although none of these vaccines had achieved regulatory approval at the time of publication, there was a considerable body of preclinical research and Phase I/II clinical trials supporting their development. A particular point of interest in this review was the consideration of the potential adjuvant role of prophylactic vaccines in patients undergoing surgical treatment, suggesting that their administration after the procedure could help reduce recurrences. This observation introduces a complementary perspective: HPV vaccination should not only be considered from the standpoint of primary prevention but also through combined regimens in patients with a history of treated lesions.

Mo, Ma, Zhang, Shen, Chen, Hong, and colleagues expanded this perspective by reviewing both prophylactic and therapeutic vaccines and presenting a detailed classification of their mechanisms of action and clinical effects. Their analysis confirms that the available prophylactic vaccines—bivalent, quadrivalent, and nonavalent—have achieved protection levels exceeding 90% against new infections by genotypes included in their composition. Nevertheless, the authors emphasize that this efficacy is limited to new infections and does not affect already established persistent infections. This finding clearly delineates the scope of each vaccine strategy. Regarding therapeutic vaccines, the review identifies multiple platforms under investigation, including live vectors, recombinant proteins, and DNA vaccines. The cited clinical studies demonstrate specific immune responses, particularly cellular responses, although translating these responses into sustained clinical benefits remains inconsistent. The analysis argues that the superior performance observed in preclinical models has not been replicated with the same clarity in the clinical phase. The authors attribute this difference to several factors: biological heterogeneity of the lesions, complexity of the tumor microenvironment, limitations in antigen selection, and difficulties with industrial scaling. This study also suggests that future efficacy could be improved by studying in situ tumor models, using combination therapies, and incorporating new antigenic targets, such as E1 and E5 (Figures 1 and 2 and Table 1).

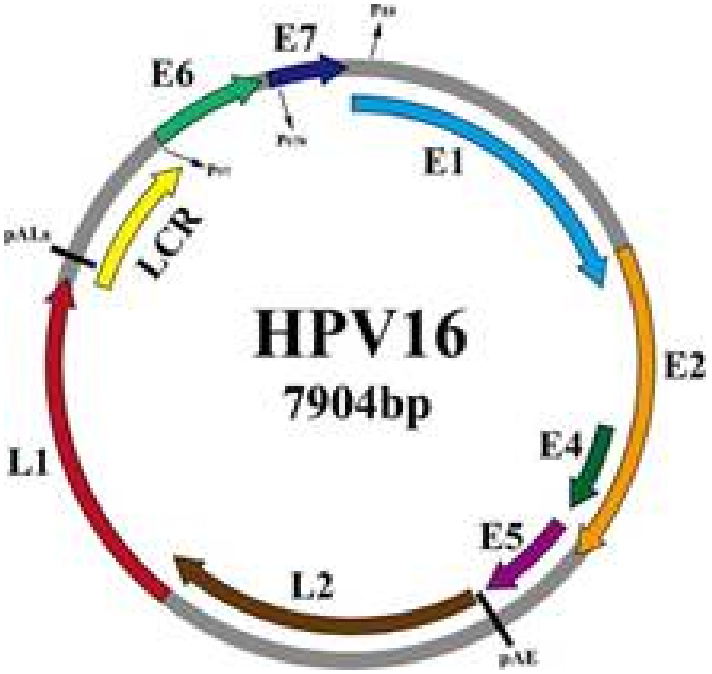

Figure 1 Schematic representation of the dsHPV16 genome (gray circles; other HPV subtypes are similar), with the virus's open reading frames (ORFs) indicated by colored arcs on the genome. Promoters are indicated by P (P97, P670, PE8), and the pAE and pAL sites (polyadenylation sites) are indicated by short straight lines.

Mo Y, Ma J, Zhang H, Shen J, Chen J, Hong J, et al. "Prophylactic and therapeutic HPV vaccines: Current scenario and perspectives". Front Cell Infect Microbiol.

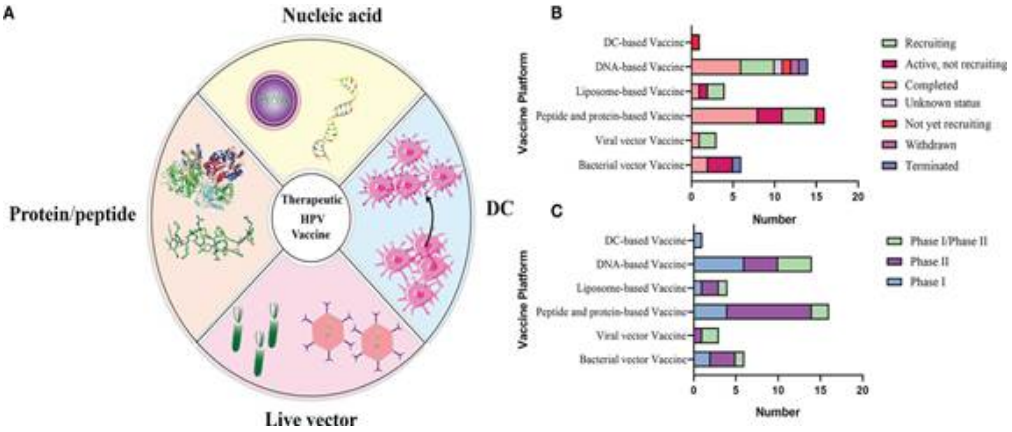

Figure 2. Schematic diagram of several major types of therapeutic vaccines. (B, C) Status and phase of therapeutic vaccines (Data from ClinicalTrials.gov). Most of the clinical trials we found were in Phase I/II, and few of the completed clinical trials have advanced to the next phase, resulting in no therapeutic vaccines being available at this time.

Mo Y, Ma J, Zhang H, Shen J, Chen J, Hong J, et al. "Prophylactic and therapeutic HPV vaccines: Current scenario and perspectives". Front Cell Infect Microbiol.

Table 1. Summary of clinical therapeutic HPV vaccines.

Mo Y, Ma J, Zhang H, Shen J, Chen J, Hong J, et al. “Prophylactic and therapeutic HPV vaccines: Current scenario and perspectives”. Front Cell Infect Microbiol.

Vaccine Platform	Vaccine	Antigen	Conditions	Phase/NCT Number	Study Start	Status
Bacterial vector Vaccine	ADXS11-001	HPV16 E7	EAs,UCC	Phase II/ NCT01266460	May 23,2011	Completed
			OC	Phase II NCT01598792	February 2012	Terminated
			AC,RC	Phase II/ NCT02399813	September 2015	Completed
			UCC,SCCHN	Phase I/Phase II NCT02291055	April 2015	Active, not recruiting
			SCCHN	Phase II/ NCT02002182	December 2013	Active, not recruiting
	Ad/MG1-E6E7	HPV16/18 E6/E7	HPV-Associated Cancers	Phase I/ NCT03618953	June 21,2018	Active, not recruiting
Viral vector Vaccine	TG4001	HPV16 E6/ E7	UCC,ASCC	Phase I/Phase II NCT03260023	September 11,2017	Recruiting
	TA-HPV	HPV16/18 E6/E7	UCC	Phase II/ NCT00002916	November 1996	Completed
	PRGN-2009	HPV16/18 E6/E7	UCC,OC,RC,AC	Phase I/Phase II NCT04432597	August 11,2020	Recruiting
Peptide and protein-based Vaccine	TVGV-1	HPV16 E7	HSIL	Phase II/ NCT02576561	November 2015	Unknown status
	TA-CIN	HPV16 L2/ E6/E7	UCC	Phase I/ NCT02405221	April 4,2019	Recruiting
	ProCervix	HPV16/18 E7	Genital Infection Viral	Phase II/ NCT01957878	December 2013	Completed
	PepCan	HPV16 E6	SCCHN	Phase I/Phase II NCT03821272	November 13,2019	Recruiting
			HSIL	Phase II/ NCT02481414	November 30,2015	Active, not recruiting
	ISA101b	HPV16 E6/ E7	UCC	Phase I/Phase II NCT02128126	September 2013	Completed
			SCC,SCCHN	Phase II NCT04369937	July 6,2020	Recruiting
			UCC	Phase II NCT04946005	June 28,2021	Recruiting
	ISA 101	HPV16 E6/ E7	Malignant Neoplasms of Lip Oral Cavity and Pharynx Solid Tumors	Phase II NCT03258008	April 4,2018	Active, not recruiting
				Phase II/ NCT02426892	December 23,2015	Active, not recruiting
	human papillomavirus 16 E7 peptide	HPV16 E7	UCC	Phase II/ NCT00003977	November 1999	Completed
	human papillomavirus 16 E6/E7 peptide	HPV16 E6/ E7	AC,UCC,EC	Phase I/ NCT00019110	November 1995	Completed
	SGN-00101	HPV16 E7	RRP	Phase II/ NCT00029874	November 2001	Completed
			UCC,CIN III	Phase II/ NCT00075569	March 2004	Completed
			UCC,CIN III	Phase II/ NCT00004041	June 2004	Completed
	Hespecta	HPV16 E6	Tumors or Premalignant Lesions	Phase I/ NCT02821494	March 2015	Completed
Liposome-based Vaccine	PDS0101	HPV16 E6/ E7	SCCHN,OPSCC	Phase II/ NCT04260126	March 29,2021	Recruiting
			UCC IB3/II	Phase II/ NCT04580771	October 14,2020	Recruiting
			CIN I	Phase I/ NCT02065973	February 2014	Completed
	DPX-E7	HPV16 E7	SCCHN,UCC,AC	Phase I/Phase II NCT02865135	December 2016	Active, not recruiting
DNA-based Vaccine/Viral vector Vaccine	pNGVL4a-Sig/E7(detox)/HSP70 with TA-HPV	HPV16/18 E6/E7	UCC,CIN III	Phase I/ NCT00788164	November 2008	Recruiting
DNA-based Vaccine/ Peptide and protein-based Vaccine	pNGVL4a-Sig/E7(detox)/HSP70 with TA-CIN	HPV16 L2/ E6/E7	ASC-US,ASC-H,LSIL	Phase II/ NCT03911076	May 22,2019	Recruiting
	pNGVL4aCRTE6E7L2 with TA-CIN	HPV16 L2/ E6/E7	ASC-US,LSIL	Phase I/ NCT03913117	December 31,2021	Not yet recruiting
DNA-based Vaccine	VGX-3100	HPV16/18 E6/E7	CIN II/III	Phase I/ NCT01304524	April 2011	Completed
	pNGVL4a-Sig/E7(detox)/HSP70	HPV16 E7	UCC,CIN II/III	Phase I/Phase II NCT00121173	November 2003	Completed
	pNGVL4aCRTE6E7L2	HPV16 L2/ E6/E7	CIN II/III	Phase I/ NCT04131413	September 14,2020	Recruiting
	pNGVL4a-CRT/E7(Detox)	HPV16 E7	SCCHN	Phase I/ NCT01493154	April 2012	Terminated
			CIN II/III	Phase I/ NCT00988559	September 2009	Completed
	INO-3112	HPV16/18 E6/E7	SCCHN	Phase I/Phase II NCT02163057	August 13,2014	Completed
			UCC	Phase I/Phase II NCT02172911	June 6,2014	Completed
			UCC	Phase II/ NCT02501278	May 2016	Withdrawn
	GX-188E	HPV16/18 E6/E7	UCC	Phase I/Phase II NCT03444376	May 23,2018	Recruiting
			CIN I	Phase II/ NCT02596243	August 2015	Unknown status
			CIN I	Phase II/ NCT02139267	July 2014	Completed
DC-based Vaccine	DC Vaccines Targeting HPV E6/ E7 Protein	HPV16/18 E6/E7	CIN I/II	Phase I/ NCT03870113	April 1,2019	Not yet recruiting

One of the most significant quantitative contributions comes from the meta-analysis by Ventura, Luís, Soares, Venuti, Paolini, Pereira, and colleagues, which focused on the efficacy of therapeutic vaccines for cervical intraepithelial neoplasia grade 3 (CIN3). This study pooled eight clinical trials and examined variables of direct clinical interest: histological regression of the lesion, viral DNA clearance, and immune response. The study population consisted of women with a confirmed diagnosis of CIN3, a group of high clinical interest due to their risk of progression to invasive disease. The results showed that therapeutic vaccines significantly increased lesion regression rates and HPV DNA clearance rates compared to placebo, with an estimated efficacy of 23.6%. This figure suggests a real clinical benefit, albeit of moderate magnitude. From an interpretive standpoint, the value of this finding lies in demonstrating that active immunotherapy can induce histopathological regression in high-grade lesions, a particularly relevant objective in patients who are candidates for invasive procedures. In this regard, therapeutic vaccines are emerging as an option with the potential to reduce surgical procedures in certain contexts, especially if future research improves response rates and better defines which patient profiles derive the greatest benefit.

Akhmatova, Chan, Azizan, and Aimagambetova conducted a systematic review specifically focused on therapeutic DNA vaccines that express the HPV oncoproteins E6 and E7. This review included six studies conducted between 2003 and 2007, involving centers in the United States, Korea, Estonia, South Africa, India, Canada, Australia, and Georgia. The geographic scope adds value to the analysis by reflecting international interest in this type of formulation. Five vaccines were evaluated in young and middle-aged women with precancerous cervical lesions, primarily CIN2 and CIN3: GX-188E, VGX-3100, MEDI0457, and pNGVL4a-CRT/E7. The results described were consistent in three aspects: immunogenicity, tolerability, and moderate therapeutic effect. All vaccines generated measurable immune responses and exhibited an acceptable safety profile. From a pharmacotechnical perspective, the authors highlight the advantages of DNA vaccines, such as relatively low cost, stability, and biological safety. The observed clinical effect, although favorable, was classified as moderate, indicating that this platform still requires optimization to increase its therapeutic performance. Nevertheless, the data suggest that DNA vaccines occupy a prominent place among the strategies with the greatest potential for integration into combination approaches (Table 2).

Table 2. Comparison of trial results.

Akhmatova A, Chan CK, Azizan A, Aimagambetova G. “The efficacy of therapeutic DNA vaccines expressing the Human Papillomavirus E6 and E7 oncoproteins for treatment of cervical cancer: Systematic review”

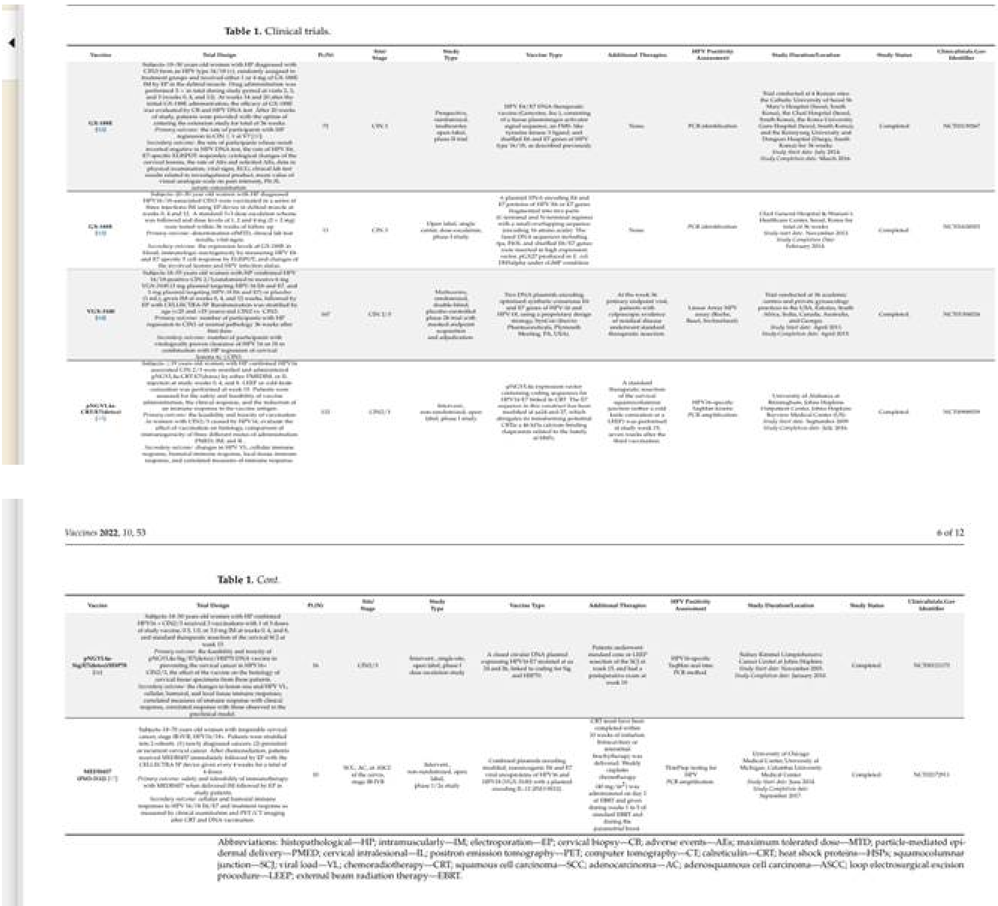

Table 1. Clinical trials.

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Table 1. Cont.

Abbreviations: histopathological—HP; intramuscularly—IM; electroporation—EP; cervical biopsy—CB; adverse events—AEs; maximum tolerated dose—MTD; particle-mediated epidermal delivery—PMED; cervical intralesional—IL; positron emission tomography—PET; computer tomography—CT; calreticulin—CRT; heat shock proteins—HSPs; squamocolumnar junction—SCJ; viral load—VL; chemoradiotherapy—CRT; squamous cell carcinoma—SCC; adenocarcinoma—AC; adenosquamous cell carcinoma—ASCC; loop electrosurgical excision procedure—LEEP; external beam radiation therapy—EBRT.

Morand, Cardona, Cruz, Mynarek, Hier, Alaoui-Jamali, and colleagues focused on HPV-associated oropharyngeal squamous cell carcinoma, a condition whose epidemiology has changed markedly in recent years, particularly among young, non-smoking men in developed countries. The value of this review lies in extending the analysis of therapeutic vaccines beyond cervical cancer to consider their potential in HPV-associated head and neck tumors. The authors compare the biology of HPV-related oropharyngeal carcinoma with that of cervical cancer, identifying similarities in the involvement of viral antigens and differences in the tissue microenvironment, natural history, and therapeutic response. Based on this comparison, they propose that therapeutic vaccines could be incorporated as tools for de-intensifying cancer treatment. Under this approach, the goal is not only to improve tumor control but also to reduce the toxic burden of intensive chemotherapy or radiation therapy. The review presents ongoing studies evaluating therapeutic vaccines alone or in combination with immune checkpoint inhibitors. The central premise is that a vaccination-induced antitumor immune response could allow for less aggressive regimens without compromising oncological outcomes. Although definitive data are still limited, this field opens up a possibility of great clinical interest, especially in patients with a good baseline prognosis and high life expectancy (Table 3).

Table 3. "Therapeutic vaccines for HPV-associated oropharyngeal and cervical cancer: The next DE-intensification strategy?". Int J Mol Sci

Morand GB, Cardona I, Cruz SBSC, Mynarek AM, Hier MP, Alaoui-Jamali MA, et al.

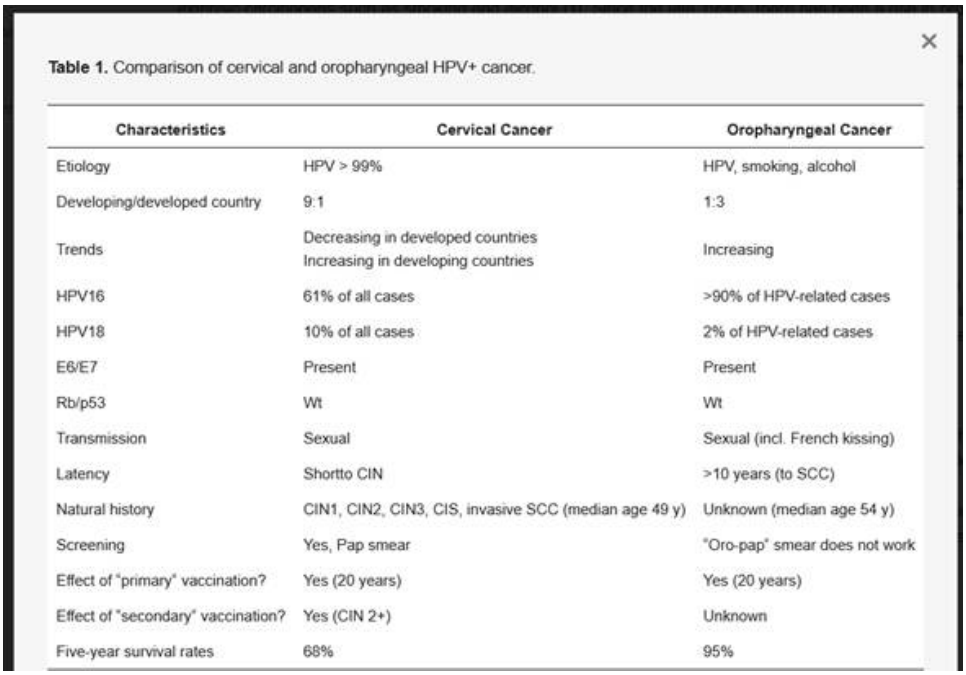

Table 1. Comparison of cervical and oropharyngeal HPV+ cancer.

Characteristics	Cervical Cancer	Oropharyngeal Cancer
Etiology	HPV > 99%	HPV, smoking, alcohol
Developing/developed country	9:1	1:3
Trends	Decreasing in developed countries Increasing in developing countries	Increasing
HPV16	61% of all cases	>90% of HPV-related cases
HPV18	10% of all cases	2% of HPV-related cases
E6/E7	Present	Present
Rb/p53	Wt	Wt
Transmission	Sexual	Sexual (incl. French kissing)
Latency	Shortto CIN	>10 years (to SCC)
Natural history	CIN1, CIN2, CIN3, CIS, invasive SCC (median age 49 y)	Unknown (median age 54 y)
Screening	Yes, Pap smear	"Oro-pap" smear does not work
Effect of "primary" vaccination?	Yes (20 years)	Yes (20 years)
Effect of "secondary" vaccination?	Yes (CIN 2+)	Unknown
Five-year survival rates	68%	95%

Wang, Pan, Jin, Huang, Li, Wu, and colleagues presented a comprehensive review of the opportunities and challenges of HPV vaccines in the context of cervical cancer. The authors reaffirm that prophylactic vaccines have high preventive efficacy, although they do not eradicate preexisting infections. They also note that these vaccines lack therapeutic effect in women who already have lesions, underscoring the need for interventions aimed at eliminating infected cells. An interesting observation in this review is that some of the current therapeutic limitations stem from an incomplete understanding of the immunological mechanisms that allow for the control and elimination of HPV-infected cells in the host. This idea has direct implications for vaccine design, since clinical efficacy depends not only on the selected antigen but also on the immunological context in which it is presented, the type of adjuvant, and the ability to overcome local immunosuppressive mechanisms. The study suggests that, as these mechanisms become better understood, it will be possible to design more effective formulations. It also highlights the development of therapeutic vaccines as a particularly relevant need in regions where prophylactic vaccination coverage is still insufficient (Table 4).

Table 4. HPV vaccines currently in clinical trials.

Características de tres vacunas contra el HPV disponibles comercialmente.

Empty Cell	**Cervarix**	**Gardasil**	**Gardasil 9**
Antígeno	L1 VLP of HPV-16 and 18	L1 VLP of HPV-6, 11, 16 and 18	L1 VLP of HPV-6, 11, 16, 18, 31, 33, 45, 52 and 58
Sistema de expresión	Baculovirus sistema de expresión vectorial	*S. cerevisiae*	*S. cerevisiae*
Adyuvante (µg)	AS04: MPL (50); Hidróxido de Aluminio salt (500)	AAHS (225)	AAHS (500)
Indicaciones	Mujeres entre 9 y 25 años	Mujeres y hombres entre 9 y 26 años	Mujeres y hombres entre 9 y 45 años
Manufactura	GlaxoSmithKline Biologicals	Merck & Co., Inc.	Merck & Co., Inc.

VLP: particular similar a virus; *S. cerevisiae*: *Saccharomyces cerevisiae*; AS04: Sistema adyuvante 04; AAHS: Sulfato de hidroxifosfato de Aluminio amorfo

Wang R, Pan W, Jin L, Huang W, Li Y, Wu D, et al. "Human papillomavirus vaccine against cervical cancer: Opportunity and challenge". Cancer Lett [Internet]. 2020;471:88–102

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The study by Boilesen, Nielsen, and Holst raised a key issue for the future development of therapeutic vaccines: the selection of antigenic targets. Most formulations currently in clinical evaluation target E6 and E7, as these proteins are directly involved in malignant transformation and their expression is maintained in tumor cells. Despite this, the authors believe that focusing the strategy solely on these two antigens could limit the therapeutic scope. In their review, they examine patterns of viral protein expression, immunogenicity, and immune exhaustion at different stages of infection and lesion progression. Based on this analysis, they propose incorporating other antigens, particularly E1 and E2, whose presence at specific stages of the viral cycle could offer new therapeutic opportunities. The argument is that a multi-epitope vaccine, tailored to the stage of lesion progression and the diversity of expressed antigens, could induce a broader and more effective response. In women with persistent infections caused by high-risk genotypes, particularly HPV 16 and 18, this approach could have significant clinical relevance. The value of this review lies not in providing immediate efficacy figures, but in redefining the conceptual framework of vaccine design, shifting it from a narrow focus toward a more complex antigenic vision aligned with the biology of the virus (Table 5).

Table 5. Summary of recent clinical trials of therapeutic vaccines against HPV-positive infections.

Boilesen DR, Nielsen KN, Holst PJ.

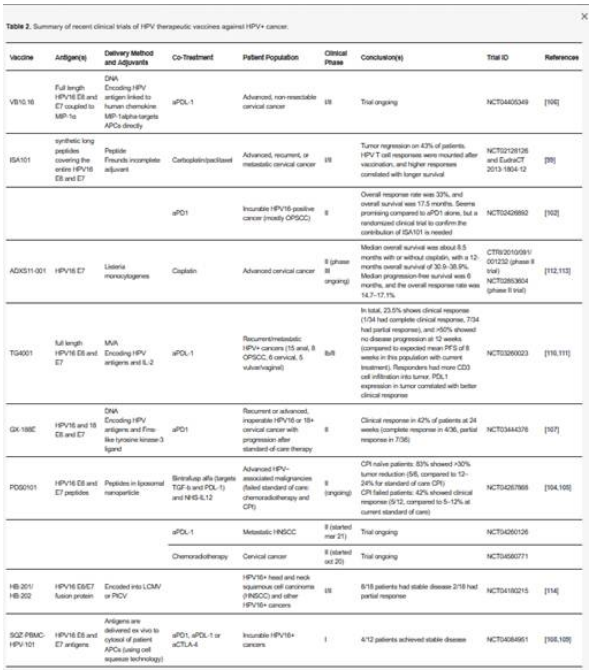


Table 2. Summary of recent clinical trials of HPV therapeutic vaccines against HPV+ cancer.

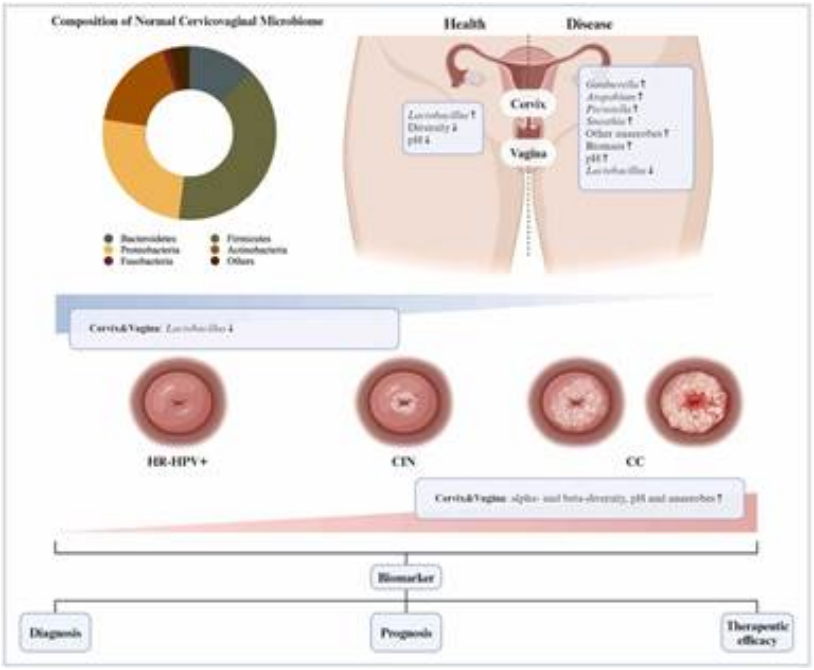
Vaccine	Antigen(s)	Delivery Method and Adjuvants	Co-Treatment	Patient Population	Clinical Phase	Conclusion(s)	Trial ID	References
VB10.16	Full length HPV16 E6 and E7 coupled to MIP-1α	DNA Encoding HPV antigen linked to human chemokine MIP-1alpha targets APCs directly	aPDL-1	Advanced, non-resectable cervical cancer	I/II	Trial ongoing	NCT04405349	[106]
ISA101	synthetic long peptides covering the entire HPV16 E6 and E7	Peptide Freunds incomplete adjuvant	Carboplatin/paclitaxel	Advanced, recurrent, or metastatic cervical cancer	I/II	Tumor regression on 43% of patients. HPV T cell responses were mounted after vaccination, and higher responses correlated with longer survival	NCT01125126 and EudraCT 2013-1804-12	[99]
			aPD1	Incurable HPV16 positive cancer (mostly OPSCC)	II	Overall response rate was 33%, and overall survival was 17.5 months. Seems promising compared to aPD1 alone, but a randomized clinical trial to confirm the contribution of ISA101 is needed	NCT03428893	[102]
ADXS11-001	HPV16 E7	Listeria monocytogenes	Cisplatin	Advanced cervical cancer	II (phase III ongoing)	Median overall survival was about 8.5 months with or without cisplatin, with a 12-months overall survival of 30.9–38.9%. Median progression-free survival was 6 months, and the overall response rate was 14.7–17.1%	CTRI/2010/091/001252 (phase II trial) NCT02853604 (phase III trial)	[112,113]
TG4001	full length HPV16 E6 and E7	MVA Encoding HPV antigens and IL-2	aPDL-1	Recurrent/metastatic HPV+ cancers (15 anal, 8 OPSCC, 6 cervical, 5 vulvar/vaginal)	Ib/II	In total, 23.5% shows clinical response (1/34 had complete clinical response, 7/34 had partial response), and >50% showed no disease progression at 12 weeks (compared to expected mean PFS of 8 weeks in this population with current treatment). Responders had more CD3 cell infiltration into tumor. PDL1 expression in tumor correlated with better clinical response	NCT03260023	[110,111]
GX-188E	HPV16 and 18 E6 and E7	DNA Encoding HPV antigens and Fms-like tyrosine kinase-3 ligand	aPD1	Recurrent or advanced, inoperable HPV16 or 18+ cervical cancer with progression after standard-of-care therapy	II	Clinical response in 42% of patients at 24 weeks (complete response in 4/36, partial response in 7/36)	NCT03444376	[107]
PDS0101	HPV16 E6 and E7 peptides	Peptides in liposomal nanoparticle	Bintrafusp alfa (targets TGF-ß and PDL-1) and NHS-IL12	Advanced HPV+ associated malignancies (failed standard of care: chemoradiotherapy and CPI)	II (ongoing)	CPI naïve patients: 83% showed >30% tumor reduction (5/6, compared to 12–24% for standard of care CPI) CPI failed patients: 42% showed clinical response (5/12, compared to 5–12% at current standard of care)	NCT04287868	[104,105]
			aPDL-1	Metastatic HNSCC	II (started mar 21)	Trial ongoing	NCT04260126	
			Chemoradiotherapy	Cervical cancer	II (started oct 20)	Trial ongoing	NCT04560771	
HB-201/ HB-202	HPV16 E6/E7 fusion protein	Encoded into LCMV or PICV		HPV16+ head and neck squamous cell carcinoma (HNSCC) and other (HPV16+ cancers	I/II	6/18 patients had stable disease 2/18 had partial response	NCT04180215	[114]
SQZ-PBMC-HPV-101	HPV16 E6 and E7 antigens	Antigens are delivered ex vivo to cytosol of patient APCs (using cell squeeze technology)	aPD1, aPDL-1 or aCTLA-4	Incurable HPV16+ cancers	I	4/12 patients achieved stable disease	NCT04084951	[108,109]

Figure 3. Characteristics of the cervicovaginal microbiota in healthy individuals and patients with HPV-AR/CIN/CC. The cervicovaginal microbiota, dominated by Lactobacillus, maintains a local acidic environment. In pathological states, the microbiota becomes imbalanced, characterized by increased pH and microbial diversity, as well as a significant increase in the abundance of harmful anaerobic bacteria, such as Gardnerella and others. The figure illustrates the microbial changes during the progression of high-risk HPV infection to CIN and cervical cancer. These alterations in the microbiota have potential as biomarkers for the diagnosis, prognosis, and treatment efficacy of HPV-associated cervical cancer.

The systematic review and meta-analysis by Ibrahim Khalil, Zhang, Muwonge, Sauvaget, and Basu provides some of the strongest evidence in the analyzed group, both in its methodological structure and in its presentation of concrete quantitative results. The study gathered data from 734 women with high-grade precancerous cervical lesions, infected with high-risk HPV, and participating in phase II and III clinical trials. The results showed that 54% of vaccinated women experienced regression of their CIN2/3 lesions to CIN1 or lower, compared with 27% in the control group. The absolute difference between the two groups was 27 percentage points. Clearance of high-risk HPV DNA was also observed in 42% of the vaccinated group and in 17% of the controls, with an absolute difference of 25 percentage points. These figures confirm a statistically and clinically relevant therapeutic advantage.

Nevertheless, the fact that nearly half of the patients did not achieve complete regression and that viral clearance did not occur in the majority of cases indicates that the efficacy remains partial. In terms of safety, no serious adverse events were consistently reported, supporting the clinical acceptability of these interventions. This study positions therapeutic vaccines as a complementary tool with a solid empirical basis, although still below the threshold required to replace standard management.

Huang, Liu, Sun, and Zhu introduce a biological component into the analysis that may alter the interpretation of the therapeutic response: the cervicovaginal microbiome. Their review is based on the premise that HPV persistence and progression to high-grade lesions do not depend exclusively on the virus and the systemic immune system, but also on the local microbial environment. In women with persistent infections and alterations in the vaginal microbiota, the effect of therapeutic vaccines could be limited if this biological context is not first corrected. The authors describe dysbiosis as a state characterized by the loss of Lactobacillus dominance and an increase in anaerobic bacteria, a situation associated with chronic inflammation, altered local immunity, and greater viral persistence. Based on preclinical evidence, they propose regimens combining therapeutic vaccines with probiotics or bacterial vectors to modulate the cervicovaginal immune microenvironment. This line of work suggests that the clinical response to vaccination may depend, at least in part, on the restoration of a more favorable microbial ecosystem. The review does not present conclusive clinical trials on this integrated strategy, although it does offer a consistent mechanistic basis for future research (Figure 3).



Huang R, Liu Z, Sun T, Zhu L. Cervicovaginal microbiome, high-risk HPV infection, and cervical cancer: Mechanisms and therapeutic potential. Microbiol Res.

The work by Kamolratanakul and Pitisuttithum, while focused on prophylactic vaccines, plays an important role within the reviewed body of work, as it allows for the precise delineation of the therapeutic space that therapeutic vaccines aim to occupy. The authors analyze the efficacy, safety, and reach of prophylactic vaccines in adolescents and young women without prior infection, documenting significant reductions in the prevalence of HPV 16 and 18 and in the incidence of cervical intraepithelial lesions in vaccinated populations. They also describe cross-protection against other high-risk genotypes and favorable safety profiles in mass immunization campaigns. The central message of the study is clear: prophylactic vaccines are highly effective as a primary prevention tool, although they have no therapeutic effect in women with persistent infection. From the perspective of this review of results, this finding is not a minor limitation but rather the main argument justifying research into therapeutic vaccines targeting individuals who are already infected or have established lesions.

Taken together, the studies reviewed show a coherent sequence of findings. First, there is consensus that prophylactic vaccines have favorably altered the epidemiology of HPV infection, although their scope is limited to primary prevention. Second, therapeutic vaccines have demonstrated the ability to induce cellular immune responses directed against viral antigens, particularly E6 and E7. Third, this immunogenicity has translated into measurable clinical benefits in precancerous cervical lesions, including histological regression and viral clearance, albeit of moderate magnitude. Fourth, it is recognized that clinical efficacy is still insufficient to establish them as the sole treatment for high-grade lesions or invasive cancer.

Integrating the results also allows for the identification of several avenues for improvement. One of these is a combination with other treatments, such as immune inhibitors, pharmacological therapies, and post-surgical approaches. Another involves selecting new antigens or multi-epitope combinations that include proteins other than E6 and E7. A third avenue relates to the tumor and mucosal microenvironment, including factors such as the cervicovaginal microbiota. All of this indicates that the efficacy of a therapeutic vaccine depends not only on inducing an immune response, but on ensuring that this response is functional, sustained, and capable of acting in an environment where the virus has developed mechanisms of persistence.

From a clinical perspective, the most consistent finding is that therapeutic vaccines are promising as adjuncts to conventional treatment, particularly in precancerous cervical lesions. The benefit observed in meta-analyses and systematic reviews supports their potential to reduce lesion burden and promote viral clearance. Even so, the available data do not justify the conclusion that these vaccines have achieved sufficient efficacy to replace established procedures. In HPV-associated cancers outside the cervix, such as oropharyngeal carcinoma, the role of these vaccines is more closely linked, for now, to de-intensification strategies and to combination regimens currently under evaluation.

Overall, the reviewed body of evidence indicates that the development of therapeutic vaccines against HPV has moved beyond a theoretical possibility to become a field with measurable, albeit still incomplete, results. The induced immune response is real, the safety profile is acceptable, and clinical benefits in precancerous lesions have been demonstrated in several studies. The gap between this progress and routine clinical adoption stems from the need to improve efficacy, better select candidate patients, optimize delivery platforms, and more accurately understand the interactions among the virus, the host, and the local microenvironment. Within this framework, the results of this review show that therapeutic vaccination represents a treatment pathway with a solid biological basis and growing, strong clinical evidence, particularly relevant for women with persistent high-risk HPV infection and high-grade cervical intraepithelial lesions.

DISCUSSION

The studies examined in this review allow us to situate therapeutic vaccines against human papillomavirus (HPV) within a transitional scenario in the management of persistent infection and associated lesions. The available evidence clearly shows that prophylactic vaccination has transformed the field of primary prevention by markedly reducing the incidence of new infections with high-risk genotypes and, consequently, the frequency of cervical cancer precursor lesions. Despite this progress, the preventive benefit of these vaccines does not extend to individuals with persistent infection, viral integration, or high-grade intraepithelial lesions. This therapeutic limitation explains the growing interest in strategies that induce a cellular immune response to eliminate infected or transformed cells. From this perspective, therapeutic vaccines should not be interpreted as an extension of prophylactic vaccines, but rather as an intervention with biological foundations, clinical objectives, and its own challenges.

One of the central findings from the included studies is the general consistency between the immunological basis of these vaccines and the effects observed in clinical trials. Therapeutic formulations are primarily designed to generate cytotoxic T lymphocytes specific against the E6 and E7 oncoproteins, key antigens in viral persistence and malignant transformation. This approach has a strong biological rationale, as both proteins are stably expressed in precancerous lesions and HPV-associated tumors. The reviewed literature suggests that this strategy induces measurable immune responses in a significant proportion of patients. The main problem, then, does not lie in the total absence of immunogenicity, but rather in the gap that persists between laboratory-documented immune activation and the achievement of consistent, lasting clinical benefits in practice.

This point warrants special consideration. In the development of immunotherapies, the induction of a detectable response does not always translate into lesion regression or complete viral clearance. In therapeutic HPV vaccines, this dissociation occurs repeatedly. Several formulations, particularly those based on DNA, peptides, or vectors, demonstrated good tolerability and the ability to activate cellular immunity. However, the effects on CIN2/3 regression or viral DNA clearance were moderate. This behavior suggests that persistent HPV infection and associated lesions do not depend exclusively on the presence of the antigen, but also on host factors, the local microenvironment, and the biological stage of the lesion. A complex interaction between viral persistence, immune evasion, and chronic inflammation conditions the therapeutic response.

Based on the included meta-analyses, therapeutic vaccines have achieved a clinically relevant level of efficacy, although this is still insufficient to replace standard treatments. The data showing greater lesion regression and greater viral clearance in vaccinated women compared to control groups are particularly valuable because they go beyond the theoretical level and demonstrate a real therapeutic effect. When a study reports lesion regression in 54% of vaccinated women versus 27% of controls, or when another estimates an efficacy of 23.6% in CIN3, these are not marginal variations. These are differences that could have concrete clinical implications, especially in selected patients and in settings where the goal is to avoid invasive procedures. In any case, these figures also show that the response is not universal. A considerable proportion of treated women do not achieve complete regression or viral clearance, which prevents these vaccines from being considered full substitutes for surgical excision or current conventional management.

From a clinical perspective, this scenario calls for a balanced interpretation. Therapeutic vaccines should not be dismissed as failed technologies simply because they have not yet replaced surgery or ablation. Their most realistic contribution, according to the reviewed evidence, lies in their integration as complementary tools within a tiered care model. In high-grade intraepithelial lesions, they could play a role in selected patients, either to induce pre-treatment regression, reduce subsequent recurrences, or decrease the need for repeat procedures. This possibility is particularly important in young women, where excisional treatment may be associated with adverse reproductive and obstetric effects, such as cervical incompetence or preterm delivery. From this perspective, even partial efficacy can be clinically relevant if it reduces exposure to invasive interventions and better preserves quality of life.

The notion of quality of life, although not always quantified across all the studies analyzed, runs implicitly through the discussion. Conventional treatment of high-grade cervical lesions is usually effective, though it is not without physical and emotional costs. The possibility of an immunological strategy that enables lesion regression, reduced recurrences, or less aggressive therapy represents a shift in approach. Rather than intervening solely on the established lesion, therapeutic vaccines aim to modify the biological process that sustains its persistence. This conceptual shift is significant, as it introduces a logic of active immune control against a persistent oncoviral infection. Its importance lies not only in curing a specific lesion but in altering the course of the interaction between virus and host.

Another aspect that emerges from the review is the heterogeneity of the platforms under study. The existence of DNA vaccines, viral vectors, synthetic peptides, recombinant proteins, and combination regimens with immunomodulators reflects the fact that the field is still in a phase of technological definition. This characteristic has two implications. On the one hand, it indicates that there is no dominant platform that has demonstrated conclusive superiority over the others. On the other hand, it reflects a significant scientific effort to find formulations that balance immunogenicity, safety, stability, and manufacturability. DNA vaccines have attracted particular interest due to their relatively low cost, stability, and safety profile, although their clinical effects remain moderate. Viral and bacterial vectors offer advantages in antigen presentation, although they may face regulatory and logistical challenges. Peptide formulations offer high specificity, but they depend on appropriate epitope selection and, in many cases, potent adjuvants.

This technological diversity also requires caution when interpreting aggregated results. When studies with different platforms, heterogeneous populations, and variable response criteria are grouped, quantitative synthesis provides guidance, though it does not always allow for direct comparisons between strategies. In other words, the field of therapeutic HPV vaccines shows promising signs, although it is still at a stage where methodological standardization is insufficient. This observation affects the interpretation of efficacy and the comparison between trials. Variability in the selection of antigens, routes of administration, doses, intervals, adjuvants, and clinical outcomes makes it difficult to identify the optimal regimen. In this regard, future progress in the field will require not only new research but also comparable designs and common evaluation criteria.

The reviewed studies agree that antigen selection will be decisive for improving therapeutic performance. Most vaccines under clinical evaluation target E6 and E7, which is reasonable given their central role in carcinogenesis. Even so, some authors argue that this approach may be limited if it fails to account for the lesion's developmental stage and the differential expression of other viral proteins. The incorporation of antigens such as E1 and E2 appears to be a line of interest because it could broaden the vaccine's immunological scope and act on different phases of the viral cycle. This proposal suggests that a truly effective therapeutic vaccine may not need to be based on a single target, but rather on antigenic combinations capable of adapting to different biological contexts. The idea of multi-epitope formulations is thus grounded in the need to address the complexity of the infectious-tumoral process and not just a part of it.

Along with antigen selection, the local immune microenvironment is another major determinant of the response. In this regard, the review linking the cervicovaginal microbiome, persistent HPV infection, and lesion progression adds a dimension of great interest. The fact that local dysbiosis promotes viral persistence and immunological alterations suggests that adverse mucosal conditions could limit the efficacy of therapeutic vaccines. This hypothesis shifts the focus of interpretation from the vaccine in isolation to the biological ecosystem in which it acts. If the cervicovaginal environment promotes chronic inflammation, diminishes protective barriers, and alters immune cell recruitment, an adequate vaccine response may prove insufficient. Under this logic, the combination of active immunotherapy with microbiome restoration strategies is not a secondary approach but rather one with potential implications for future clinical efficacy.

The discussion must also consider the oncological dimension beyond the cervix. The inclusion of studies on HPV-associated oropharyngeal carcinoma broadens the scope of application for these vaccines. It demonstrates that the clinical problem arising from the virus is not limited to the genital tract. In HPV-related head and neck cancers, therapeutic vaccines could be integrated into treatment de-escalation strategies. This perspective is particularly relevant in young patients with a good prognosis, in whom prolonged survival makes the late effects of intensive treatments more apparent. Reducing functional sequelae without compromising tumor control is a highly valuable clinical goal. Although the evidence in this setting is still evolving, the concept remains relevant because it positions therapeutic vaccines not only as treatments for precursor lesions but also as part of personalized oncology programs.

Another key point of discussion is the role these vaccines could play in countries and regions with limited preventive coverage. In many contexts, unequal access to preventive vaccination, screening, and timely treatment contributes to the persistence of a high burden of HPV-associated disease. In such circumstances, an effective therapeutic vaccine would have major public health implications, as it could be effective in populations where primary prevention has not achieved sufficient coverage. This point should not be interpreted as a substitute for prophylactic vaccination or screening, but rather as part of a broader control strategy. The eradication or substantial reduction of cervical cancer depends on integrated programs that include primary prevention, screening, early diagnosis, treatment of lesions, and follow-up. Therapeutic vaccines fit into this continuum of care, particularly to bridge the gap between persistent infection and established disease.

Within this framework, it is reasonable to argue that the progress of therapeutic vaccines will depend as much on biomedical research as on regulatory and organizational decisions. The reviewed evidence indicates that the field has solid biological foundations and favorable clinical signals. Even so, the transition toward approval and clinical adoption requires larger trials, prolonged follow-up, uniform response criteria, and consistent safety documentation. It also requires regulatory frameworks capable of evaluating these therapies using criteria appropriate to their immunological nature. Hasty approval without sufficient evidence would be problematic; excessively slow regulation could also delay access to a potentially valuable option. The balance between rigor and timeliness will be a decisive factor in the coming years.

The limitations of the body of evidence must be part of this discussion. Many of the included studies correspond to early phases of research or to reviews that integrate heterogeneous trials. In several cases, sample sizes are limited, outcomes are not identical, and follow-up does not always allow for determining the actual duration of the benefit. There is also variability within the study population, particularly regarding age, injury type, viral genotype, and immune status. This heterogeneity limits the automatic generalization of the findings. Similarly, the fact that several vaccines are still under development implies that the available information may change as results from later phases are published. These limitations do not invalidate the observed trend, although they require interpreting the results with methodological caution.

Despite these limitations, the overall direction of the evidence is consistent. Therapeutic HPV vaccines demonstrate demonstrable biological activity, acceptable safety, and partial clinical efficacy in high-grade cervical lesions. They also offer prospects for integration with other therapeutic modalities, whether in the gynecological setting or in virus-associated oropharyngeal tumors. This body of findings supports the view that this is not a marginal experimental approach, but rather an emerging component of the clinical management of persistent HPV. Its primary value lies in addressing an unmet need: the specific immunological treatment of established infections and lesions.

From a conceptual standpoint, the main contribution of this review is to demonstrate that the future of HPV control cannot be limited to preventing new infections. In clinical practice, patients continue to present with persistent infection, high-grade intraepithelial lesions, and, in some cases, early-stage cancer. For this group, the existence of a therapeutic technology capable of inducing lesion regression and viral clearance would be of great significance. The development of therapeutic vaccines responds precisely to this need. The evidence gathered indicates that the path has already begun, although it has not yet reached full clinical maturity.

Conclusions

The conclusions drawn from this analysis can be summarized in several points. First, prophylactic vaccines are a fundamental tool in primary prevention, although they do not resolve the problem of persistent infection or established lesions. Second, therapeutic vaccines represent a strategy with a solid immunological basis and favorable clinical outcomes, especially in CIN2/3. Third, their current efficacy is significant, though partial, positioning them today as a complement rather than a replacement for conventional treatment. Fourth, future improvement will depend on optimizing antigens, platforms, adjuvants, patient selection, and control of the local microenvironment. Fifth, integrating these vaccines into public health programs will require stronger clinical evidence, appropriate regulation, and coordination with prevention, screening, and treatment.

In light of the reviewed results, it can be argued that therapeutic HPV vaccines occupy an increasingly well-defined place within translational and clinical research. The current landscape does not justify excessive expectations, though it also does not warrant downplaying them. They are no longer a remote hypothesis and have become an option with real potential to alter the management of certain precancerous lesions and, eventually, some HPV-associated tumors. Their future development should focus on consolidating efficacy, identifying precise indications, and establishing their role within integrated therapeutic regimens.

In conclusion, a review of the evidence suggests that therapeutic vaccines could become a relevant component of the treatment of persistent HPV and its clinical manifestations, particularly in high-grade cervical intraepithelial lesions and early stages of disease. Their greatest strength lies in addressing a need not covered by prophylactic vaccination. Their main challenge remains translating the immune response into broader, sustained, and reproducible clinical benefits. From this perspective, the future of cervical cancer management and its precursor lesions will likely be shaped by integrated strategies where prevention, immunotherapy, early diagnosis, and follow-up act in a complementary manner. Within this framework, therapeutic vaccines already occupy a legitimate and scientifically grounded place.

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