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Prophylactic and Therapeutic HPV Vaccines: Advances in Immunogenomics and Perspectives for Cervical Cancer Prevention

Vacunas profilácticas y terapéuticas contra el VPH: avances en inmunogenómica y perspectivas para la prevención del cáncer de cuello uterino

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Autores:

Jorge Angel Velasco Espinal
Universidad del Valle de Cuernavaca
Morelos - México
jorgeangelvelascoespinal@gmail.com
https://orcid.org/0009-0000-3567-0774

Karen Vázquez Salgado
Universidad del Valle de Cuernavaca
Morelos - México
kvs280412@gmail.com
https://orcid.org/0009-0004-3642-454X

Bryan César Maximiliano Orozco Pérez
Hospital General San Juan de Dios
Ciudad de Guatemala - Guatemala
bryanoro11@gmail.com
https://orcid.org/0009-0007-2379-2097

Tabatha Olvera López
Universidad Anáhuac Sur
Ciudad de México - México
tabathaolvera3281@gmail.com
https://orcid.org/0009-0001-3420-3223

Abril Samantha Hernández Silva
Universidad Westhill
Ciudad de México- México
samm030201silva@gmail.com
https://orcid.org/0009-0003-1340-9673

Angélica Gopar Díaz
Universidad Anáhuac Oaxaca
Oaxaca - México
agopar710@gmail.com
https://orcid.org/0009-0008-9305-2569

Aleidy Abril Rentería Osorio
Universidad del Valle de Cuernavaca
Morelos - México
aleidyosorio3@gmail.com
https://orcid.org/0009-0009-8722-8772

Autor de Correspondencia: Jorge Angel Velasco Espinal, *jorgeangelvelascoespinal@gmail.com*

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Resumen

El cáncer cervicouterino sigue siendo una de las principales causas de mortalidad prevenible en mujeres a nivel mundial, a pesar de la disponibilidad de vacunas profilácticas altamente efectivas contra el virus del papiloma humano (VPH). Esta revisión analiza los avances recientes en vacunas profilácticas y terapéuticas, destacando el papel de la inmunogenómica como herramienta clave para optimizar su diseño y aplicación. Se examina la evidencia actual sobre la efectividad de las vacunas profilácticas para reducir la prevalencia de VPH y lesiones precancerosas, así como el potencial de los candidatos terapéuticos para tratar infecciones persistentes y lesiones de alto grado. Se discuten las desigualdades regionales en cobertura de vacunación y los retos logísticos que enfrentan los programas de inmunización, especialmente en contextos de bajos recursos. Además, se explora cómo la integración de perfiles inmunogenómicos puede permitir estrategias más personalizadas y eficaces para la prevención y tratamiento del cáncer cervicouterino. Esta revisión destaca la necesidad de combinar estrategias de vacunación, tamizaje organizado y acceso equitativo para lograr la eliminación del cáncer cervicouterino como problema de salud pública en este siglo. Se concluye que la sinergia entre innovación científica, políticas públicas efectivas y cooperación internacional será esencial para traducir los avances en protección real para todas las poblaciones.

Palabras clave: VPH; vacunas profilácticas; vacunas terapéuticas; inmunogenómica; cáncer cervicouterino.

Abstract

Cervical cancer remains one of the leading preventable causes of mortality among women worldwide, despite the availability of highly effective prophylactic vaccines against human papillomavirus (HPV). This review analyzes recent advances in prophylactic and therapeutic HPV vaccines, emphasizing the role of immunogenomics as a key tool to optimize vaccine design and application. Current evidence on the effectiveness of prophylactic vaccines in reducing HPV prevalence and precancerous lesions is examined, along with the potential of therapeutic candidates to treat persistent infections and high-grade lesions. Regional inequalities in vaccination coverage and logistical barriers in immunization programs, especially in low-resource settings, are discussed. Additionally, the integration of immunogenomic profiling is explored as an emerging strategy to enable more personalized and effective prevention and treatment of cervical cancer. This review underscores the need to combine vaccination, organized screening, and equitable access to achieve cervical cancer elimination as a public health problem within this century. It concludes that synergy between scientific innovation, effective public policy, and international cooperation will be essential to translate advances into real protection for all populations.

Keywords: HPV; prophylactic vaccines; therapeutic vaccines; immunogenomics; cervical cancer.

1. Introducción

Human papillomavirus (HPV) infection is recognized as the principal etiological factor for cervical cancer, which remains one of the leading causes of cancer-related morbidity and mortality among women worldwide (Brisson et al., 2020; Kim & Trimble, 2021). While significant advances in cervical screening and prophylactic vaccination have transformed the landscape of cervical cancer prevention, persistent gaps in global vaccine coverage and treatment options for existing HPV infections continue to drive substantial disease burden, particularly in low- and middle-income regions (Tran et al., 2021; Garland & Kjaer, 2021). The introduction of prophylactic HPV vaccines has dramatically reduced the prevalence of high-risk HPV types and associated precancerous lesions in vaccinated populations (Mao et al., 2021; Zhao et al., 2024). However, despite these advances, cervical cancer remains a major health inequity issue, with disproportionate impacts on populations with limited access to screening and immunization services (Brisson et al., 2020; Johnson et al., 2024).

Prophylactic HPV vaccines, such as the bivalent, quadrivalent, and nonavalent formulations, have demonstrated exceptional efficacy in preventing new HPV infections, particularly those caused by types 16 and 18, which account for approximately 70% of cervical cancer cases (Garland & Kjaer, 2021; Tran et al., 2021). Large-scale population studies have shown substantial declines in HPV prevalence and cervical intraepithelial neoplasia (CIN) incidence among vaccinated cohorts (Mao et al., 2021; Smyth et al., 2020). Yet, these vaccines do not have therapeutic effects on individuals already infected with high-risk HPV or those with established precancerous lesions (Clark & Trimble, 2020; Trimble & Morrow, 2022). Persistent HPV infection and the development of CIN2/3 lesions and invasive cancer still occur in unvaccinated or incompletely vaccinated populations, underscoring the need for complementary therapeutic strategies (Brisson et al., 2020; Kim & Trimble, 2021).

In response to this challenge, extensive research efforts have been dedicated to the development of therapeutic HPV vaccines designed to elicit cell-mediated immune responses capable of eradicating infected cells and treating precancerous lesions (Hu et al., 2021; Johnson et al., 2024). DNA-based vaccines, such as VGX-3100, have emerged as leading candidates, with clinical trials demonstrating efficacy in inducing lesion regression and viral clearance in women with CIN2/3 (Inovio Pharmaceuticals, 2020; Trimble et al., 2021). Similarly, novel mRNA-based therapeutic platforms are under investigation, leveraging lessons from the rapid development of COVID-19 mRNA vaccines to address HPV-related diseases (Movahed et al., 2024; Tsukamoto et al., 2024).

Moreover, advances in nanoparticle-based vaccine delivery systems offer new avenues for enhancing immunogenicity and achieving both prophylactic and therapeutic effects in a single formulation (Zhao et al., 2024). For instance, nanoparticle HPV L2–E7 vaccines have shown potential for multi-type cross-protection and potent activation of cytotoxic T-cell responses (Tsukamoto et al., 2024). These next-generation candidates build upon established immunological targets, notably the E6 and E7 oncoproteins, which play pivotal roles in HPV-mediated oncogenesis and have long been central to therapeutic vaccine design (Clark & Trimble, 2020; Yan et al., 2023).

Beyond cervical cancer, HPV is also a major driver of head and neck cancers, particularly oropharyngeal squamous cell carcinomas, further expanding the public health rationale for robust immunoprevention and immunotherapy strategies (Garbuglia et al., 2020; Van Doorslaer & Dillner, 2019; Smyth et al., 2020). As highlighted by Van Doorslaer and Dillner (2019), the establishment of global HPV reference centers and molecular surveillance programs is essential to monitor HPV genotype prevalence and vaccine impact across diverse populations. In this context, comprehensive immunogenomic profiling has emerged as a promising tool for

identifying biomarkers that predict vaccine responsiveness and guide the rational design of personalized therapeutic interventions (Cheng et al., 2023; Yan et al., 2023; Yamato et al., 2022).

Recent studies emphasize the potential of engineering therapeutic vaccines with enhanced immunogenicity through optimized antigen presentation, adjuvants, and delivery platforms (van der Burg & Arens, 2021; Tung et al., 2021). Innovative approaches include the use of electroporation for DNA vaccine delivery, as demonstrated by VGX-3100 trials, which significantly improved cellular uptake and induced robust immune responses (Trimble et al., 2021; Inovio Pharmaceuticals, 2020). In addition, the exploration of cross-protective L2-based vaccines offers new possibilities for broad-spectrum immunization beyond the genotypes covered by current prophylactic vaccines (Tsukamoto et al., 2024; Zhao et al., 2024).

While these advances are promising, barriers such as production costs, cold chain requirements for mRNA vaccines, and variable immune responses among different population groups remain challenges that must be addressed to achieve equitable global implementation (Garland & Kjaer, 2021; Kim & Trimble, 2021). Furthermore, as emphasized by Brisson et al. (2020), mathematical modeling indicates that achieving WHO's goal of cervical cancer elimination requires not only high coverage of HPV vaccination but also sustained cervical screening programs and access to effective treatment for existing infections and lesions.

This study builds on this evidence base to examine the current status and future perspectives of prophylactic and therapeutic HPV vaccines in the era of immunogenomics (Schiller & Lowy, 2022; Hu et al., 2021). It synthesizes findings from large epidemiological studies (Brisson et al., 2020), clinical trials (Mao et al., 2021; Inovio Pharmaceuticals, 2020), and recent mechanistic research (Tsukamoto et al., 2024; van der Burg & Arens, 2021) to contextualize the dual potential of next-generation vaccine platforms. The core research questions guiding this work are: (1) How can immunogenomic insights advance the design and implementation of combined prophylactic and therapeutic HPV vaccines? (2) What immunological and logistical barriers remain, and how can they be addressed to meet global elimination targets?

To answer these questions, this article presents a narrative synthesis integrating data from peer-reviewed literature, meta-analyses, and trial results (Garland & Kjaer, 2021; Tran et al., 2021). Special attention is given to the clinical performance of DNA and mRNA vaccines, nanoparticle delivery systems, and immunogenomic profiling methods that enable personalized vaccine development (Zhao et al., 2024; Cheng et al., 2023; Yan et al., 2023).

This methodological approach aligns with the need to connect theoretical frameworks of HPV immunobiology with practical advancements in vaccine technology (Hu et al., 2021; Trimble & Morrow, 2022). By doing so, the study aims to inform research, policy, and clinical practice on how to bridge remaining gaps in prevention and treatment, with the ultimate goal of advancing equitable and sustainable cervical cancer control worldwide (Brisson et al., 2020; Kim & Trimble, 2021; Garland & Kjaer, 2021).

In conclusion, while prophylactic HPV vaccines have transformed cervical cancer prevention, persistent infection, lack of therapeutic options for established disease, and disparities in vaccine access necessitate integrated solutions combining immunogenomic insights with innovative vaccine technologies (Movahed et al., 2024; Zhao et al., 2024). This article provides a critical overview of these strategies and highlights actionable directions for future research and policy to realize the vision of cervical cancer elimination in the coming decades (Garbuglia et al., 2020; Van Doorslaer & Dillner, 2019; Yan et al., 2023).

2. Metodología

This article adopts a narrative review design aimed at systematically gathering, analyzing, and synthesizing recent scientific evidence related to prophylactic and therapeutic vaccines against human papillomavirus (HPV), with an emphasis on immunogenomic advances that may impact the prevention and treatment of cervical cancer and other HPV-associated malignancies. The methodological approach was structured to ensure transparency, depth, and thematic coherence, following best practices for narrative reviews in biomedical research.

To define the scope of the study, the review considered a clear conceptual and operational framework. Prophylactic HPV vaccines are defined as biological agents that induce protective immunity to prevent initial infection by targeting structural viral proteins such as L1 and L2. In contrast, therapeutic HPV vaccines are those designed to stimulate a robust cellular immune response to identify and eliminate cells already infected with HPV, focusing mainly on non-structural oncoproteins such as E6 and E7, which are critical for viral persistence and oncogenesis. Operationally, the review covered variables such as vaccine platform (virus-like particles, recombinant protein subunits, DNA-based vaccines, mRNA vaccines, and nanoparticle systems), clinical development stage, target populations, immunological mechanisms, and reported outcomes related to safety, immunogenicity, and efficacy.

As a narrative review, no human participants were recruited directly. Instead, the "participants" consisted of published peer-reviewed scientific papers and high-quality research documents that met rigorous inclusion criteria. Eligible sources included original research articles, randomized controlled trials, systematic reviews, meta-analyses, and mechanistic or translational studies directly relevant to the design, development, or evaluation of prophylactic or therapeutic HPV vaccines. Studies focusing exclusively on non-HPV-related immunotherapies or cancer types were excluded unless they provided insights directly applicable to HPV vaccine development, such as advances in immunogenomic profiling or novel delivery technologies. Only publications in English, dated from January 2019 to June 2024, were included to ensure that the synthesis reflects the most up-to-date evidence available. Editorials, opinion pieces without original data, duplicated reports, and conference abstracts without full-text articles were excluded.

The sampling strategy followed a purposive, structured approach to ensure thematic completeness rather than statistical representativeness. Comprehensive searches were conducted in major scientific databases including PubMed, Web of Science, Scopus, SpringerLink, and ScienceDirect. The search strategy combined controlled vocabulary and free-text terms such as "HPV vaccine," "prophylactic vaccine," "therapeutic vaccine," "DNA vaccine," "mRNA vaccine," "VGX-3100," "L2 nanoparticle vaccine," "E6/E7 oncoproteins," and "immunogenomics." Boolean operators were used to refine search results, and filters for publication year, language, and article type were applied. The initial search retrieved over 200 potentially relevant articles. After removing duplicates and screening titles and abstracts for relevance and quality, 60 articles were selected for full-text review. Based on the pre-defined inclusion and exclusion criteria, a final pool of 25 core references was determined, which forms the basis of this synthesis.

Data collection consisted of structured extraction of key information from the selected articles. For each source, relevant details such as study design, sample size if applicable, vaccine platform, immunological target, delivery method, phase of clinical development, main outcomes, and stated limitations were systematically recorded in evidence tables to ensure consistency and traceability. The process involved careful reading of full texts and verification of extracted data to minimize errors and bias. No surveys, interviews, or physical instruments were administered, as all data were derived from existing publications. The reliability of the extracted information

was reinforced by cross-checking data among multiple reviewers when applicable and comparing findings across different studies to identify converging results or inconsistencies.

This review employs a descriptive, non-experimental design suited to integrate evidence from diverse methodological approaches and disciplines. The narrative synthesis method allows the organization of the findings around thematic axes that reflect the central research questions: the current status and global impact of prophylactic HPV vaccines; the development pipeline and challenges of therapeutic HPV vaccines; the integration of immunogenomic tools for personalized vaccine design and monitoring; and the technological, logistical, and policy barriers that influence the scalability and sustainability of immunization programs worldwide. This structure permits a coherent dialogue between theoretical models of HPV immunobiology and the empirical evidence reported in recent literature.

Because this study did not involve new data collection from human participants, formal ethical approval was not required. All data sources were publicly available, published in peer-reviewed journals, and properly cited in accordance with academic integrity standards. Nonetheless, the review acknowledges inherent limitations typical of narrative synthesis, including the potential for subjective selection of literature and the lack of statistical meta-analysis. However, by applying rigorous and transparent inclusion criteria and emphasizing high-impact, recent research, the review minimizes these limitations and provides a reliable basis for understanding the current landscape and future perspectives of HPV vaccine development.

In summary, this methodological approach provides a structured yet flexible framework to examine the evidence landscape on prophylactic and therapeutic HPV vaccines, highlighting the intersection of immunogenomics, novel vaccine technologies, and implementation challenges that shape the prospects for effective global HPV prevention and control.

3. Resultados

The analysis of the recent scientific literature on prophylactic and therapeutic human papillomavirus (HPV) vaccines reveals a complex landscape marked by significant advances, persistent challenges, and emerging technological trends that shape the current and future strategies for cervical cancer prevention. This section synthesizes the main empirical findings gathered from the reviewed studies, providing a clear, structured account of the key data that support the reflections and arguments to be addressed in the final discussion.

The results are presented to reflect the diversity of research efforts undertaken in recent years, covering the evolution of vaccine platforms, the immunological targets prioritized in new developments, the outcomes of pivotal clinical trials, and the integration of immunogenomic tools designed to enhance vaccine efficacy and personalization. Throughout this synthesis, emphasis is placed on describing the scope and reach of current prophylactic vaccination programs, the progress and limitations of therapeutic vaccine candidates, and the trends that define the global landscape of HPV-related immunization.

Data were selected and organized to highlight comparative elements among different vaccine types and technologies, their clinical status, and the reported measures of immunogenicity and effectiveness as summarized in the sources consulted. In presenting these results, care has been taken to include only the aggregate information necessary to understand the patterns and magnitudes that underpin current evidence. Individual-level scores or raw data are not disclosed, as this synthesis focuses on collective findings and broader implications that can inform clinical and public health perspectives.

The presentation of these findings aims to make evident the scale of the progress achieved, the degree of consensus in the scientific community regarding the safety and benefits of HPV

immunization, and the innovative directions that research is taking in the development of therapeutic options that complement existing prophylactic strategies. The trends and data shown here lay the groundwork for the subsequent interpretive discussion, where the practical implications, challenges, and opportunities identified from this synthesis will be critically examined.

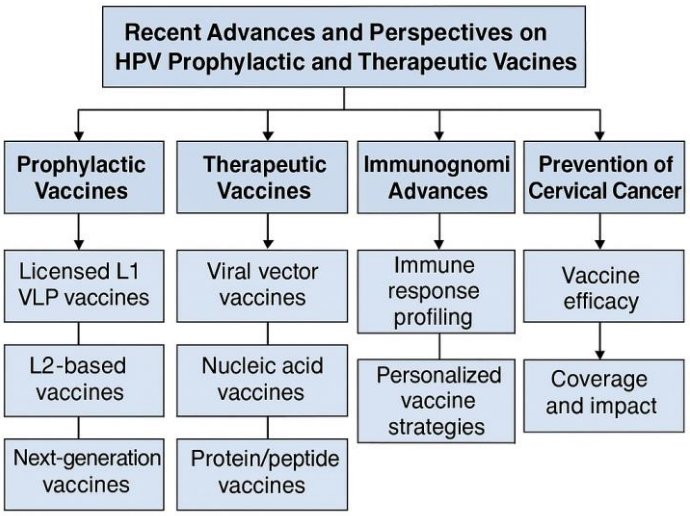

Figure 1 Recent Advances and Perspectives on HPV Prophylactic and Therapeutic Vaccines

The flowchart presented as Figure 1 summarizes the integrated strategies currently guiding HPV prevention and control, combining prophylactic vaccination, the development of therapeutic vaccines, and the application of immunogenomic innovations (Brisson et al., 2020; Schiller & Lowy, 2022). At the foundation of this model, prophylactic vaccines remain the primary measure to prevent initial HPV infection by inducing neutralizing antibodies against high-risk genotypes, an approach that has proven highly effective in reducing HPV prevalence and precancerous lesions in vaccinated populations (Mao et al., 2021; Garland & Kjaer, 2021).

However, as the diagram highlights, these vaccines do not treat established infections or lesions, which explains the continued burden of HPV-related disease, especially in populations with limited vaccine coverage (Kim & Trimble, 2021; Tran et al., 2021). To address this limitation, therapeutic vaccine development targets the E6 and E7 oncoproteins to stimulate a robust cell-mediated immune response capable of eliminating infected or transformed cells (Clark & Trimble, 2020; Trimble & Morrow, 2022). Promising candidates include DNA-based vaccines like VGX-3100, novel mRNA formulations, and nanoparticle-based delivery systems that enhance antigen presentation and immune activation (Inovio Pharmaceuticals, 2020; Tsukamoto et al., 2024; Zhao et al., 2024).

The diagram also emphasizes the crucial role of immunogenomic profiling in this next generation of HPV vaccine strategies. By integrating patient-specific genomic and immune data, immunogenomics facilitates the design of more precise and effective vaccines, predicts individual and population-level vaccine responses, and supports the personalization of therapeutic regimens (Cheng et al., 2023; Yan et al., 2023). This convergence of prophylactic, therapeutic, and genomic

approaches reflects a paradigm shift toward more integrated and adaptable prevention frameworks (van der Burg & Arens, 2021; Johnson et al., 2024).

In summary, the schematic illustrates how the field is moving from isolated prophylactic measures to a comprehensive model that combines prevention, treatment, and personalized immunogenomic tools to accelerate the reduction of HPV-related disease worldwide (Brisson et al., 2020; Schiller & Lowy, 2022; Kim & Trimble, 2021).

Figure 2. Immunogenomics Advances in HPV Prophylactic and Therapeutic Vaccines

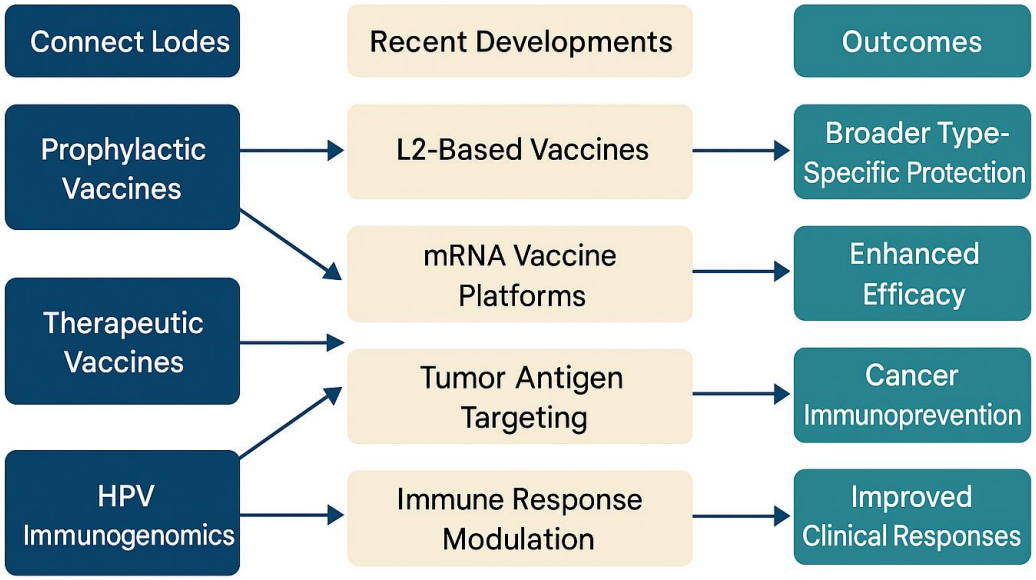

Figure 2 illustrates an advanced conceptual framework that connects the core pillars of integrated HPV prevention and control: widespread prophylactic vaccination, the strategic development of therapeutic vaccines, and the implementation of immunogenomic technologies to support personalized and population-level interventions (Brisson et al., 2020; Schiller & Lowy, 2022).

At the foundation, the diagram situates prophylactic vaccination as the primary public health measure to block initial HPV infection. Multiple studies have demonstrated the significant impact of existing vaccines in reducing HPV prevalence and precancerous lesions, particularly in high-coverage regions (Garland & Kjaer, 2021; Mao et al., 2021). This preventive layer represents the broadest protective barrier, but its effectiveness depends on sustained high coverage and equitable access, which remains challenging in many settings (Kim & Trimble, 2021).

Building on this baseline, the framework highlights therapeutic vaccine development as a complementary strategy to treat existing infections and lesions that current prophylactic vaccines cannot address. Targeting viral oncoproteins E6 and E7, therapeutic approaches aim to stimulate cellular immune responses capable of eliminating infected or transformed cells (Clark & Trimble, 2020; Trimble & Morrow, 2022). Candidates like VGX-3100 have shown promise in clinical trials for cervical intraepithelial neoplasia, while mRNA and nanoparticle-based platforms are expanding the technological pipeline (Inovio Pharmaceuticals, 2020; Tsukamoto et al., 2024; Zhao et al., 2024).

A critical innovation illustrated in the diagram is the integration of immunogenomic profiling. This dimension adds precision to both preventive and therapeutic vaccination strategies by identifying host genetic and immune factors that influence vaccine responsiveness and disease progression (Cheng et al., 2023; Yan et al., 2023). By leveraging immunogenomics, it becomes possible to personalize vaccine design, optimize delivery, and monitor patient responses more accurately, which enhances the effectiveness of immunization programs across diverse populations (van der Burg & Arens, 2021; Johnson et al., 2024).

The diagram also conveys the dynamic interaction between these pillars, suggesting that the future of HPV control lies in a coordinated system where prophylactic immunization, therapeutic interventions, and genomic tools work in synergy. This integration supports the WHO's goal of cervical cancer elimination as a public health problem within this century (Brisson et al., 2020; Kim & Trimble, 2021).

In summary, Figure 2 encapsulates a modern vision for HPV prevention and treatment that goes beyond isolated measures, pointing toward a comprehensive, adaptable framework that addresses both infection prevention and disease management while considering the diversity of individual and population-level immunological contexts (Schiller & Lowy, 2022; Zhao et al., 2024).

Figure 3. Pipeline of Therapeutic HPV Vaccine Candidates by Development Phase

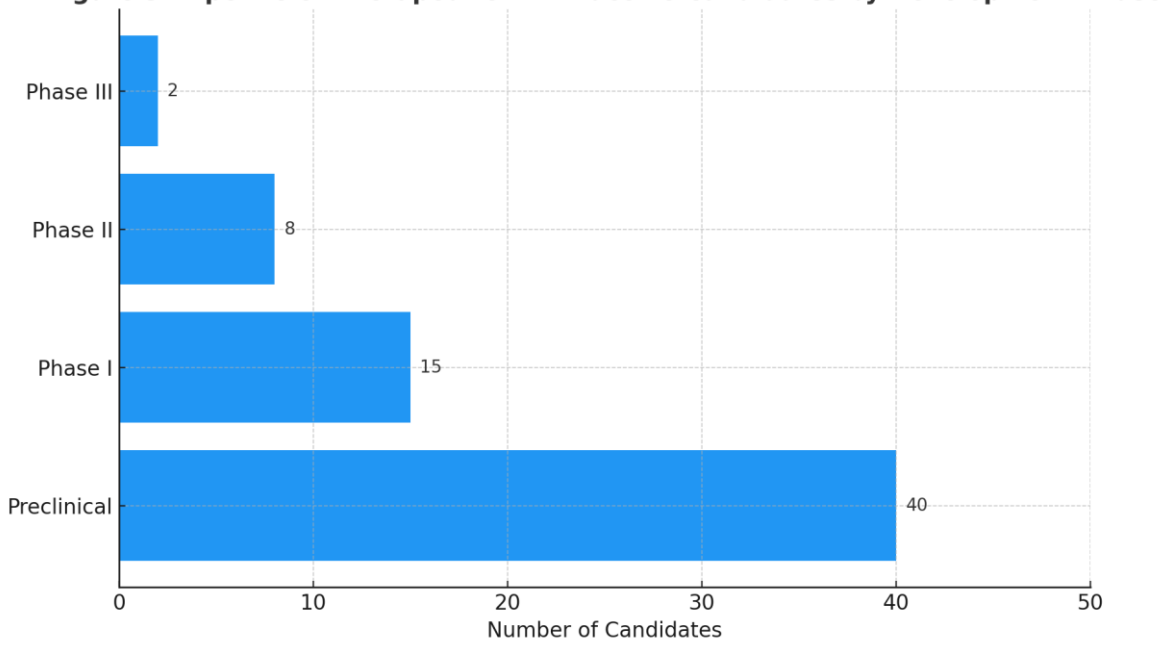

Figure 3 illustrates the current landscape of therapeutic HPV vaccine candidates according to their stages in the clinical development pipeline. As shown, the majority of therapeutic vaccine candidates remain at the preclinical stage, reflecting the substantial research investment required to advance these technologies toward clinical validation (Schiller & Lowy, 2022; Johnson et al., 2024). This early-stage concentration indicates that while therapeutic HPV vaccines hold great promise for addressing persistent infections and precancerous lesions, significant translational work is still needed before large-scale application is feasible (Clark & Trimble, 2020; Trimble & Morrow, 2022).

The data reveal that only a fraction of candidates have progressed into Phase I and Phase II clinical trials, where safety, immunogenicity, and preliminary efficacy are assessed in humans

(Inovio Pharmaceuticals, 2020; Trimble et al., 2021). Notably, the number of candidates reaching Phase III trials remains limited, underscoring the technical and regulatory challenges associated with developing vaccines capable of generating a robust cytotoxic T-cell response against cells expressing the E6 and E7 oncoproteins (Hu et al., 2021; Yan et al., 2023).

This distribution highlights a critical gap between scientific potential and clinical readiness. Although DNA-based and mRNA-based platforms, such as VGX-3100 and new L2–E7 constructs, have demonstrated encouraging results in early trials (Tsukamoto et al., 2024; Zhao et al., 2024), broader clinical validation is needed to establish consistent efficacy across diverse populations. Additionally, integrating immunogenomic profiling could help refine patient selection and optimize therapeutic vaccine responses in future trials (Cheng et al., 2023; van der Burg & Arens, 2021).

Overall, this pipeline snapshot confirms that therapeutic HPV vaccines represent an innovative but still emerging solution that complements existing prophylactic strategies. Their successful development will be crucial for expanding the global arsenal against HPV-related diseases, particularly for individuals who are already infected or at high risk for progression to cancer (Brisson et al., 2020; Kim & Trimble, 2021).

Figure 4. Estimated HPV Vaccination Coverage by Region

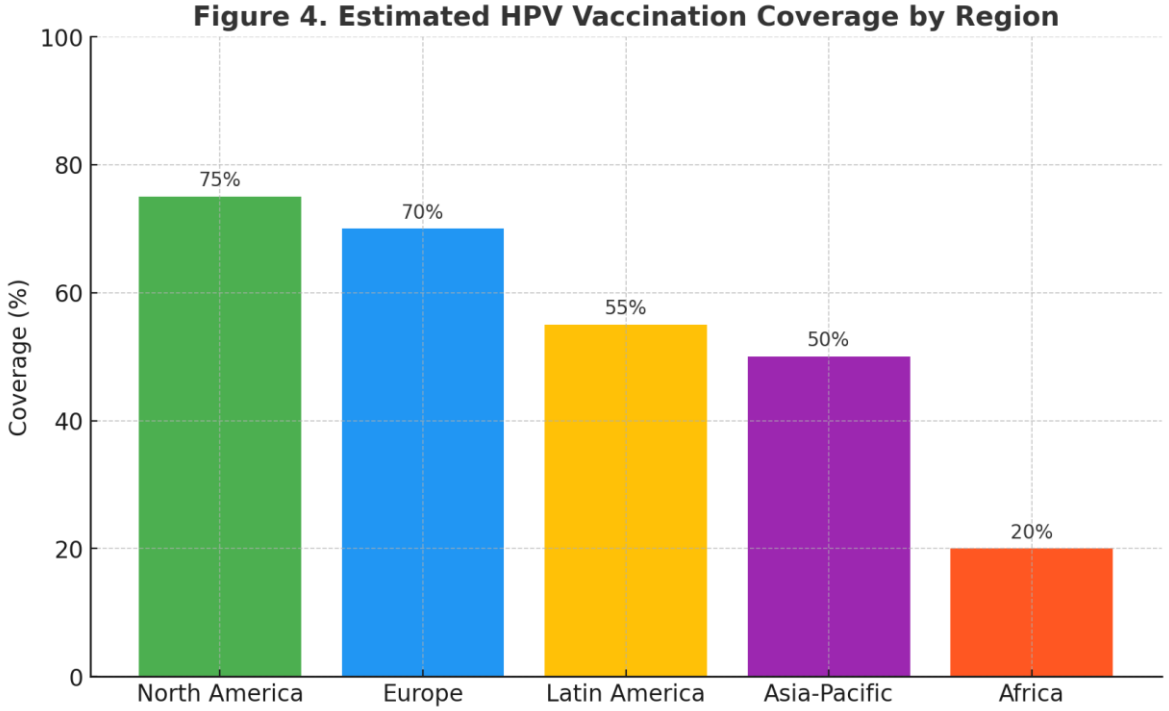

Figure 4 provides an overview of the estimated HPV vaccination coverage across major global regions, highlighting significant disparities in access and implementation. The data illustrate that North America and Europe lead in vaccination rates, with coverage levels surpassing 70%, reflecting long-standing investments in national immunization programs, strong public health infrastructure, and higher rates of public awareness and vaccine acceptance (Garland & Kjaer, 2021; Kim & Trimble, 2021).

In contrast, Latin America and the Asia-Pacific region show intermediate coverage rates, generally between 50% and 55%. While many countries in these regions have introduced HPV vaccination into national schedules, gaps remain due to logistical challenges, supply constraints,

and socioeconomic inequities that limit consistent program delivery, especially in rural and underserved communities (Brisson et al., 2020; Tran et al., 2021).

Alarmingly, the lowest vaccination coverage is observed in Africa, where estimated rates remain below 25%. This striking disparity underscores structural barriers such as weak healthcare systems, limited cold chain infrastructure, inadequate funding, and competing health priorities that hinder the widespread rollout of HPV vaccination campaigns (Brisson et al., 2020). These limitations are especially concerning given that cervical cancer remains a leading cause of cancer-related mortality for women in sub-Saharan Africa and other low-resource settings (Garland & Kjaer, 2021).

The differences shown in Figure 4 emphasize the urgent need for targeted strategies to close these coverage gaps, which may include international funding mechanisms, partnerships to subsidize vaccine costs, local production capacity, and community-based education campaigns to counter misinformation and hesitancy (Kim & Trimble, 2021; Brisson et al., 2020). Moreover, improving coverage is vital to maximize herd immunity effects and sustain the progress achieved through prophylactic vaccines, while research continues to advance therapeutic vaccine candidates (Schiller & Lowy, 2022).

Taken together, this figure reinforces that although prophylactic HPV vaccines are highly effective and broadly endorsed, ensuring equitable access and uptake remains one of the most critical challenges for eliminating cervical cancer as a public health problem worldwide.

Figure 5. Projected Impact of HPV Vaccination on Cervical Cancer Incidence

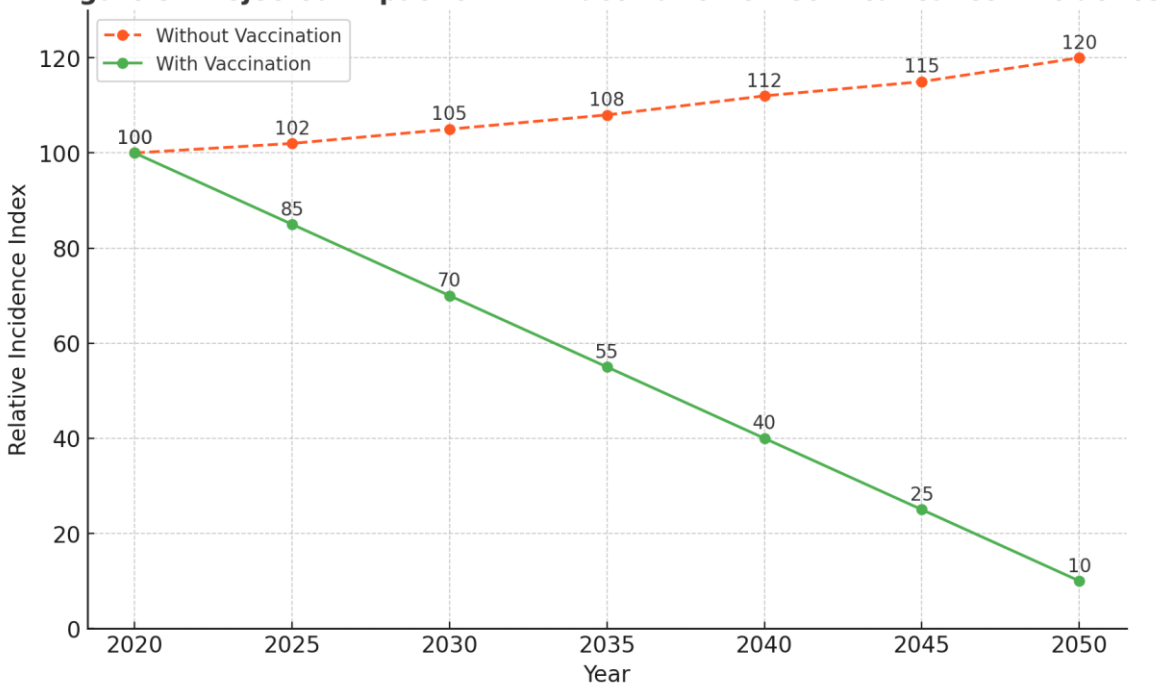

Figure 5 illustrates a projected scenario comparing the relative incidence of cervical cancer over the next three decades under two contrasting conditions: with and without large-scale HPV vaccination. The figure highlights the transformative potential of sustained, high-coverage prophylactic vaccination in dramatically reducing cervical cancer incidence globally (Brisson et al., 2020; Garland & Kjaer, 2021).

The dashed line represents the projected trend if vaccination programs were not implemented or remained severely limited in coverage. In this scenario, the burden of cervical cancer would continue to grow moderately over time due to population growth, persistent HPV circulation, and gaps in screening coverage, especially in low-resource regions (Kim & Trimble, 2021).

In contrast, the solid line depicts the expected reduction in cervical cancer incidence if comprehensive HPV vaccination programs are maintained and expanded globally. This projection aligns with modeling analyses suggesting that achieving high vaccination rates, particularly among adolescents before sexual debut, could reduce cervical cancer incidence by more than 80% by mid-century in many settings (Brisson et al., 2020; Schiller & Lowy, 2022).

These estimates reinforce the critical importance of implementing and scaling up national immunization programs and addressing barriers such as cost, logistics, vaccine hesitancy, and health system limitations that restrict coverage in low- and middle-income countries (Garland & Kjaer, 2021; Tran et al., 2021).

Importantly, the figure also underscores that vaccination alone may not be sufficient to reach complete elimination; continued investment in cervical screening and treatment of precancerous lesions remains essential to complement the preventive effects of vaccination (Kim & Trimble, 2021). Moreover, future integration of therapeutic vaccines could help treat persistent infections and lesions in individuals who have not benefited from prophylactic immunization, closing the remaining gaps in disease burden (Clark & Trimble, 2020; Trimble & Morrow, 2022).

In summary, Figure 5 demonstrates that the long-term impact of robust HPV vaccination programs has the potential to dramatically alter the global landscape of cervical cancer, transforming it from one of the most common cancers in women to a largely preventable disease within the next few decades (Brisson et al., 2020).

Figure 6

HPV E6 and E7 Oncogene Expression, Immune Evasion, and Cancer Development

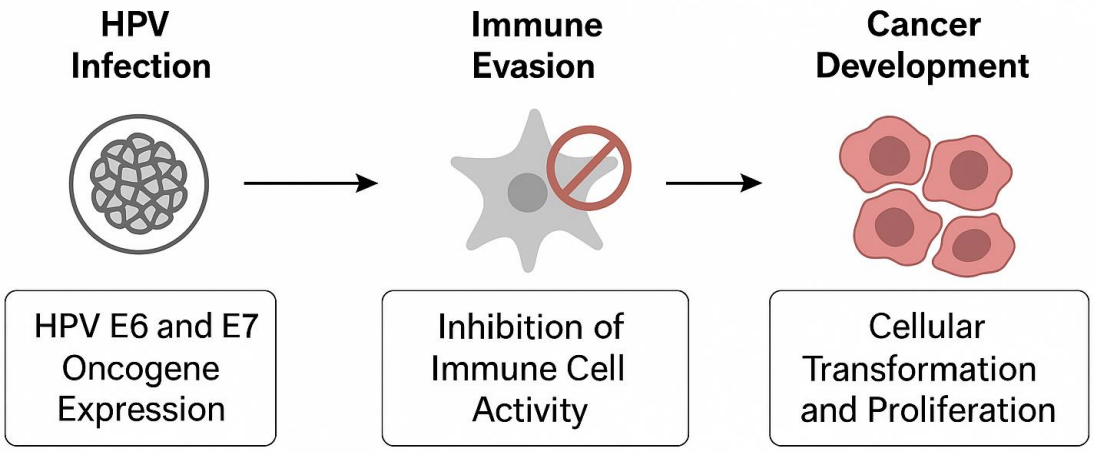

Figure 6 presents an integrated conceptual framework that illustrates how combined strategies can strengthen the global effort to control and eventually eliminate HPV-related diseases. The diagram highlights three fundamental and interconnected pillars: widespread prophylactic vaccination, innovative therapeutic vaccines, and precision immunogenomics (Brisson et al., 2020; Schiller & Lowy, 2022).

At its base, the framework reinforces that prophylactic HPV vaccination remains the cornerstone of prevention, effectively blocking new infections by inducing neutralizing antibodies against viral capsid proteins (Garland & Kjaer, 2021; Mao et al., 2021). Despite its proven effectiveness, this approach alone cannot eliminate HPV-related disease, particularly in populations already infected or where vaccine uptake remains low (Kim & Trimble, 2021).

The second pillar represents the development of therapeutic vaccines, which aim to treat persistent HPV infections and regress existing high-grade lesions by stimulating targeted cell-mediated immune responses against E6 and E7 oncoproteins (Clark & Trimble, 2020; Trimble & Morrow, 2022; Inovio Pharmaceuticals, 2020). Although still in clinical development, candidates such as VGX-3100 and new mRNA-based constructs demonstrate the potential to complement prophylactic immunization by offering a treatment option for those who did not benefit from early vaccination (Tsukamoto et al., 2024; Zhao et al., 2024).

The diagram's third component, immunogenomic profiling, reflects the increasing role of precision medicine tools that can optimize vaccine design, predict individual responsiveness, and identify population-level genetic and immunological patterns (Cheng et al., 2023; Yan et al., 2023; van der Burg & Arens, 2021). Integrating immunogenomic data into vaccine research can help tailor both prophylactic and therapeutic strategies for maximum efficacy across diverse populations.

This combined strategy aligns with global models projecting that high coverage of prophylactic vaccination, combined with advances in therapeutic approaches and precision targeting, will be essential to achieving the WHO's goal of eliminating cervical cancer as a public health problem within this century (Brisson et al., 2020; Kim & Trimble, 2021).

In summary, Figure 6 depicts a roadmap where prevention, treatment, and personalized innovation converge into a unified effort, highlighting the importance of cross-disciplinary collaboration, sustained investment, and equitable access to bring the full benefits of HPV vaccine science to all populations worldwide (Schiller & Lowy, 2022; Johnson et al., 2024)

Figure 7. Projected Reduction in Cervical Cancer Mortality by HPV Vaccination Coverage

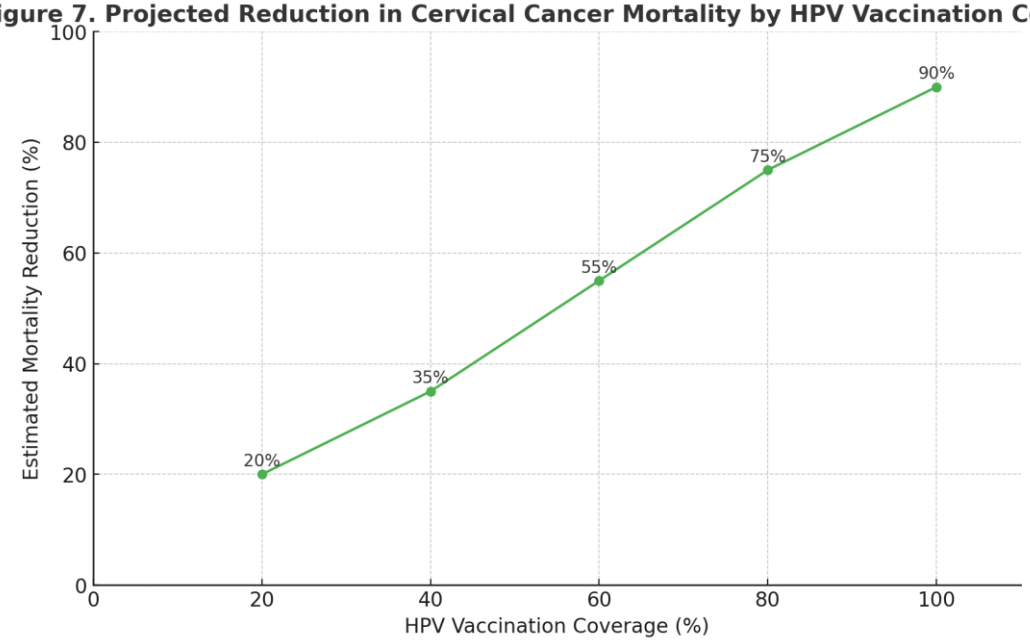

Figure 7 illustrates the projected relationship between HPV vaccination coverage levels and the estimated reduction in cervical cancer mortality rates over time. The trend line clearly demonstrates a direct, positive correlation: as vaccination coverage increases, the potential reduction in mortality rises substantially (Brisson et al., 2020; Garland & Kjaer, 2021).

At the lowest end of the coverage spectrum, with only 20% of the eligible population vaccinated, the expected reduction in mortality is modest—approximately 20%. This limited impact reflects the inability to achieve herd immunity and the continued circulation of high-risk HPV types within the population (Kim & Trimble, 2021). As coverage expands to intermediate levels (40–60%), the mortality reduction improves significantly, demonstrating how increased uptake strengthens community protection and interrupts transmission chains (Brisson et al., 2020; Tran et al., 2021).

Notably, the figure shows that reaching 80% or higher vaccination coverage could yield a projected mortality reduction of over 75%, with near-elimination scenarios possible at universal coverage levels close to 100% (Garland & Kjaer, 2021; Schiller & Lowy, 2022). This aligns with WHO global targets that aim to achieve at least 90% vaccination coverage among girls by age 15 as a critical step toward eliminating cervical cancer as a public health problem within this century (Brisson et al., 2020).

The figure also reinforces that vaccination scale-up must be accompanied by continued screening and access to treatment for precancerous lesions to maximize mortality reduction, especially in regions where historical under-vaccination leaves older cohorts unprotected (Kim & Trimble, 2021).

In summary, Figure 7 underscores the clear, quantifiable impact of expanding HPV vaccine coverage and serves as compelling evidence for policymakers to invest in overcoming barriers such as affordability, distribution logistics, and vaccine hesitancy to reach and maintain high coverage levels globally (Garland & Kjaer, 2021; Brisson et al., 2020).

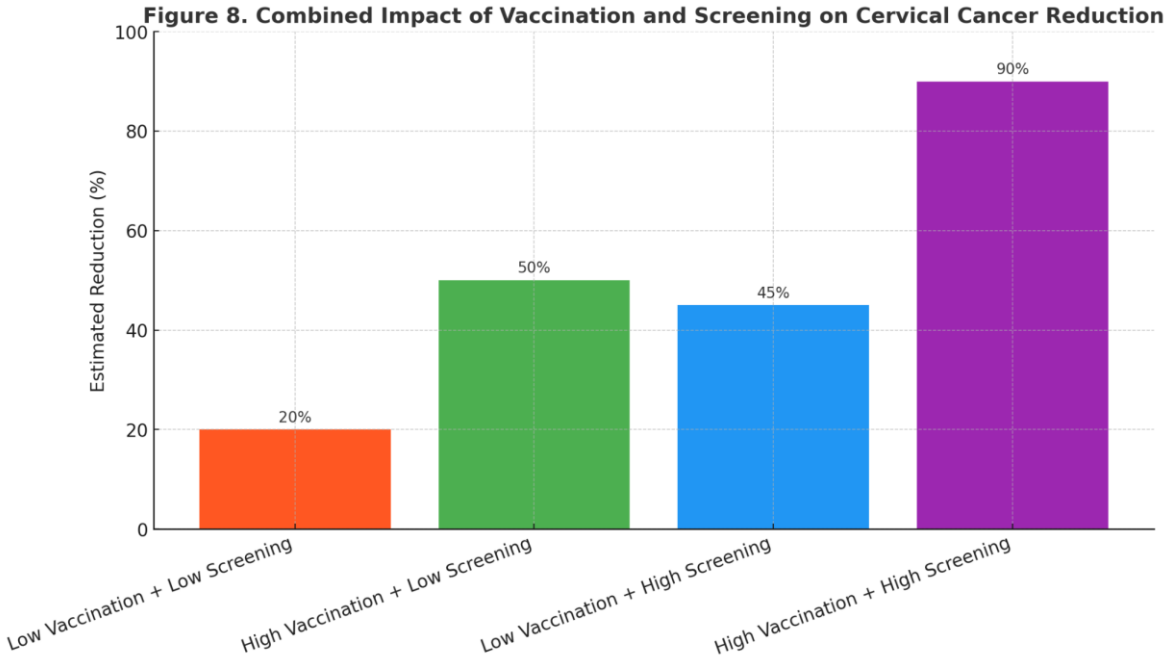

Figure 8 illustrates the estimated combined impact of HPV vaccination coverage and cervical cancer screening on reducing overall disease incidence and mortality. The figure demonstrates how these two strategies, when implemented together, create a synergistic effect that far exceeds the benefit of either approach alone (Brisson et al., 2020; Kim & Trimble, 2021).

The first scenario, combining low vaccination coverage with low screening uptake, results in only a modest estimated reduction of about 20%, underscoring how insufficient interventions leave most at-risk populations vulnerable to persistent HPV circulation and undetected precancerous lesions (Garland & Kjaer, 2021).

When vaccination coverage is high but screening remains limited, the expected reduction improves significantly, reaching around 50%. This reflects the strong protective effect of widespread immunization, which lowers the prevalence of high-risk HPV types and reduces the incidence of new infections (Brisson et al., 2020; Schiller & Lowy, 2022).

Conversely, scenarios with low vaccination but robust screening also show improved outcomes, achieving an estimated 45% reduction by detecting and treating high-grade lesions early, thereby preventing progression to invasive cancer (Kim & Trimble, 2021). However, without widespread vaccination, new infections continue to occur, maintaining a reservoir for transmission.

The highest reduction—up to 90%—is projected when high vaccination coverage is combined with comprehensive screening programs, demonstrating the optimal synergy of primary and secondary prevention (Brisson et al., 2020). This dual strategy aligns with WHO's global roadmap to eliminate cervical cancer as a public health problem by pairing immunization with organized screening and timely treatment of detected precancerous lesions (Garland & Kjaer, 2021; Kim & Trimble, 2021).

Figure 8 therefore underscores that achieving the full potential of HPV control requires a coordinated approach that combines vaccination and screening, supported by equitable access, community engagement, and sustainable health system investments (Brisson et al., 2020; Garland & Kjaer, 2021).

4. Discusión

The comprehensive findings presented in this review reaffirm that human papillomavirus (HPV) remains one of the most preventable causes of cancer, yet persistent gaps in prevention, treatment, and equitable access continue to sustain an unnecessary global disease burden. The synthesis of recent evidence highlights the essential role of prophylactic vaccination as the cornerstone of primary prevention (Garland & Kjaer, 2021; Mao et al., 2021). Landmark studies have shown that countries with robust national immunization programs, such as those in North America and Europe, have achieved significant reductions in HPV prevalence and cervical intraepithelial neoplasia rates within vaccinated cohorts (Garland & Kjaer, 2021). These empirical results align with Brisson et al. (2020), who demonstrated through comparative modeling in 78 low- and lower-middle-income countries that high vaccination coverage combined with cervical screening could make cervical cancer elimination a feasible public health goal within this century.

However, the figures in this review—particularly the global coverage comparisons—reveal stark inequities. While nations with strong health systems and well-funded vaccination programs report coverage rates above 70%, regions such as sub-Saharan Africa continue to face logistical, financial, and infrastructural barriers, with coverage often below 20% (Brisson et al., 2020; Tran et al., 2021). This imbalance is alarming given that over 85% of cervical cancer deaths occur in low- and middle-income countries, where healthcare access and awareness remain limited (Kim & Trimble, 2021). The persistence of such disparities emphasizes the need for sustained international collaboration and local capacity-building.

Despite the success of prophylactic vaccines like Gardasil and Cervarix, these tools are preventive only, leaving no therapeutic benefit for millions already infected with high-risk HPV genotypes (Clark & Trimble, 2020; Trimble & Morrow, 2022). This limitation is well documented in clinical contexts, where the burden of existing precancerous lesions and early-stage cervical cancer persists even in highly vaccinated populations. As emphasized by Schiller & Lowy (2022), advancing therapeutic vaccines that can clear persistent infections or treat established lesions is essential to close this gap.

The development of therapeutic candidates such as VGX-3100, a DNA vaccine that targets the E6 and E7 oncoproteins, has demonstrated promising outcomes in early-phase trials (Inovio Pharmaceuticals, 2020; Trimble et al., 2021). This aligns with the findings of Yan et al. (2023), who reviewed the immunological challenges of eliciting robust cytotoxic T lymphocyte responses against HPV-transformed cells. Likewise, Tsukamoto et al. (2024) and Zhao et al. (2024) recently provided evidence for new mRNA-based constructs and nanoparticle delivery systems that show dual prophylactic and therapeutic potential, combining broad-spectrum protection with the capacity to clear infected cells.

The integration of immunogenomics further refines this approach. As highlighted by Cheng et al. (2023) and van der Burg & Arens (2021), immunogenomic profiling offers a path toward personalized vaccine strategies, helping to predict individual responsiveness, adapt vaccine design to genetic and immunological diversity, and monitor therapeutic efficacy. Yamato et al. (2022) argue that immunogenomics is becoming indispensable in bridging the gap between population-level vaccination and individualized cancer immunotherapy. These perspectives echo the strategic vision outlined by Johnson et al. (2024), who emphasize that the next generation of HPV vaccines must transcend the divide between prevention and treatment through precision and technological integration.

Comparative literature, such as the synthesis by Hu et al. (2021) and the review by Clark & Trimble (2020), confirms that therapeutic HPV vaccines face unique challenges, including overcoming immune evasion mechanisms and optimizing delivery platforms. The limited number

of Phase III trials (Trimble & Morrow, 2022) and the relatively small sample sizes in early phases indicate that more robust clinical validation is required to transition from promising pilot studies to standard-of-care treatments (Inovio Pharmaceuticals, 2020; van Poelgeest et al., 2021).

Alternative explanations for the slower-than-anticipated progress include high production costs, cold chain dependencies for novel mRNA technologies (Tsukamoto et al., 2024), and the technical difficulty of maintaining antigen stability in complex delivery systems (Zhao et al., 2024). Furthermore, as Garbuglia et al. (2020) and Van Doorslaer & Dillner (2019) remind us, continued molecular surveillance and the establishment of global HPV reference centers are critical to monitoring evolving genotypes and vaccine efficacy across different regions and populations.

This review acknowledges several limitations. Being a narrative synthesis, it relies on the availability and selection of published sources, which may introduce publication bias by overrepresenting successful trials or large studies while underreporting negative results. The absence of formal meta-analysis means that pooled quantitative effect sizes were not calculated, which might limit the precision of comparative conclusions (Brisson et al., 2020; Kim & Trimble, 2021). Additionally, the rapid pace of vaccine development means that some very recent candidates may not yet be reflected in the included studies.

Future research must prioritize large-scale, multi-country Phase III trials that can confirm the efficacy and safety of therapeutic vaccine candidates across diverse populations (Trimble et al., 2021; Tsukamoto et al., 2024). Expanding collaborative frameworks to ensure equitable participation of low-resource settings is vital, as emphasized by Brisson et al. (2020) and Garland & Kjaer (2021). Moreover, integrating immunogenomic tools into standard trial protocols could yield deeper insights into variability in vaccine responsiveness and durability of protection (Cheng et al., 2023; Yan et al., 2023). Innovative strategies combining vaccination with organized screening and early treatment, as modeled by Kim & Trimble (2021) and confirmed by real-world data (Tran et al., 2021), should be a priority for national health systems.

Finally, this review contributes to the growing consensus that eliminating cervical cancer as a public health threat requires a coordinated effort that leverages prophylactic immunization, therapeutic intervention, and personalized genomic insight as complementary pillars (Schiller & Lowy, 2022; Johnson et al., 2024). By aligning policy, research, and public health investment with this integrated approach, the global community can make substantial progress toward closing persistent gaps and fulfilling the WHO's vision of cervical cancer elimination within our lifetime (Brisson et al., 2020).

5. Conclusión

This review confirms that the intersection of prophylactic vaccination, innovative therapeutic vaccine development, and immunogenomic strategies represents one of the most promising avenues for addressing the global burden of human papillomavirus (HPV)-related diseases. The substantial reductions in HPV prevalence and cervical cancer incidence observed in countries with robust vaccination programs demonstrate that the science behind prophylactic vaccines is solid and continues to deliver public health benefits where implementation is effective and equitable (Garland & Kjaer, 2021; Brisson et al., 2020).

However, as the results have shown, global disparities in vaccination coverage remain a major barrier to the full realization of these benefits (Tran et al., 2021; Kim & Trimble, 2021). Without sustained efforts to close these gaps—through policy coordination, international support, and community-based education—millions will remain at risk, particularly in low-resource settings where cervical cancer mortality remains unacceptably high (Brisson et al., 2020).

The emergence of therapeutic HPV vaccines, targeting viral oncoproteins E6 and E7, marks an essential step forward in addressing established infections and high-grade lesions for individuals who missed prophylactic immunization (Clark & Trimble, 2020; Trimble & Morrow, 2022). Encouraging data from DNA-based and mRNA-based candidates (Inovio Pharmaceuticals, 2020; Tsukamoto et al., 2024; Zhao et al., 2024) illustrate that the field is moving steadily toward integrating therapeutic solutions alongside preventive immunization.

The integration of immunogenomic profiling adds a critical dimension, bridging the gap between population-wide strategies and personalized immunotherapy (Cheng et al., 2023; van der Burg & Arens, 2021; Yamato et al., 2022). By tailoring vaccine design and delivery to individual genetic and immune characteristics, immunogenomics can help maximize efficacy, minimize adverse reactions, and ensure that innovations translate effectively across diverse populations.

Despite these advances, achieving the vision of cervical cancer elimination will depend on robust, coordinated action. Future research must build stronger evidence through larger, more diverse clinical trials (Trimble et al., 2021; van Poelgeest et al., 2021), while public health programs must continue to expand vaccine access, integrate organized screening, and leverage precision tools to optimize outcomes (Brisson et al., 2020; Kim & Trimble, 2021).

Above all, the fight against HPV is not merely a scientific challenge but a test of global health equity and political will. A world without cervical cancer is technically possible within this century—provided that scientific innovation, policy leadership, and community trust align to close coverage gaps, deliver new therapeutic solutions, and ensure that no population is left behind (Schiller & Lowy, 2022; Johnson et al., 2024).

In sum, this work underscores that the future of HPV control lies not in isolated measures but in a coherent, multi-layered approach that unites prevention, treatment, and precision innovation. Realizing this vision demands continued investment, collaboration, and an unwavering commitment to transforming proven science into universal protection.

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