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Review Article

A Vaccine-Focused Review Of Prevention And Treatment Strategies In Gynecological Cancers

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ABSTRACT

Cancer prevention through vaccination represents one of the most successful strategies developed for human cancer prevention, with HPV vaccination against cervical cancer serving as a leading example. However, the relevance of vaccine-based strategies varies substantially across five major gynecological cancers: cervical, vaginal, vulvar, endometrial, and ovarian cancer. This review examines gynecological cancers from a vaccine-centered perspective, covering prophylactic, therapeutic, personalized, and combinatorial vaccine strategies. It describes how prophylactic HPV vaccines evolved from first-generation L1 virus-like particles (VLPs) to L2- and L1/L2-based chimeric platforms and broader-spectrum vaccines, with a focus on cross-protection against non-vaccine HPV types and their potential contribution to cervical cancer eradication. Therapeutic HPV vaccines targeting E6/E7 and other early viral proteins are also reviewed. For non-HPV-associated gynecological cancers, including endometrial and ovarian cancers, the review focuses on tumor-associated antigens, cancer-testis antigens, and personalized neoantigens for vaccine development. Emerging vaccine platforms, including mRNA, DNA, peptide, viral vector, and dendritic cell vaccines, artificial intelligence-assisted antigen design, needle-free and thermostable delivery systems, and vaccine-based combination approaches with immunotherapy, are evaluated.

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Finally, the global and Indian implementation experiences are discussed, including Cervavac, an indigenous HPV vaccine. Key knowledge gaps and future directions for developing effective and accessible gynecological cancer vaccines are also identified in this review.

INTRODUCTION

Unlike other cancer control modalities, vaccines have the unique ability to protect against a cancer-causing agent prior to any malignant transformation. Vaccines can be broadly classified into three groups, with prophylactic vaccines designed to prevent infection of a carcinogen, therapeutic cancer vaccines to treat established infection, precancerous lesions, or malignancy via antigen-specific cellular immunity, and personalized, or neoantigen, vaccines made from a patient's mutations in a cancer to target unique antigens associated with his/her cancer. Common among all three classes of vaccine is the basic approach of targeting the immune response to a certain antigen, while the type of antigen varies: infectious carcinogen, tumor-associated, or tumor-specific for prophylactic vaccines and therapeutic cancer vaccines, respectively, and private neoantigen for personalized vaccines.

Cervical cancer vaccines against the human papillomavirus (HPV) are a proof of concept in the field. Genital HPV is the most prevalent STD worldwide, affecting over 80% of women by the age of 50[2]; According to WHO estimates, 5% of human malignancies, including those of the cervix, vulva, vagina, penis, anus, and oropharynx, are caused by HPV and cause over 400,000 deaths per year[3-6,11]. Preventive population vaccination has been shown to reduce high-grade cervical lesions and HPV infections by 90% in those who receive it[3,4]. The success of HPV vaccination has thus sparked great interest in developing therapeutic vaccines against cancers which do not have an infectious origin — a more difficult scientific challenge as there are no foreign, highly immunogenic targets comparable to a viral antigen.

Each of the five primary gynecological cancers, cervical, vaginal, vulvar, endometrial, and ovarian cancer, occupies a different spot on the spectrum. Cervical cancer is predominantly driven by HPV and thus constitutes the success story of vaccine-based prevention. The vaginal and vulvar cancers, though partially driven by HPV, have partial relevance of prophylactic vaccination and HPV-independent cancers. Endometrial and ovarian cancers do not have an infectious origin and do not have approved prophylactic vaccines; here, vaccine development involves only therapeutic and personalized vaccines using tumor-associated and cancer testis antigens and patients' private neoantigens. Understanding the gradation and treating gynecological cancers uniformly as HPV-driven cancer is crucial to identify the current scope of vaccines that could reduce the cancer burden.

Objective and novelty of this Review

Numerous existing reviews have summarized the efficacy and pathogenesis of the HPV vaccine or the HPV virus in isolation. Fewer studies have been conducted on organizing the field based on the vaccine development pipeline. Even fewer provide a consistent framework for the vaccine development of the five gynecological cancers, not just the HPV-driven ones. This review aims to take a vaccine-first approach, beginning with classifying the types of vaccine strategies and their relevance to cervical, vaginal, vulvar, endometrial, and ovarian cancer and introducing HPV biology only subsequently in the context necessary for understanding vaccine target selection. It discusses the evolution of prophylactic vaccines from L1 and L2 to chimeric and broad-spectrum platforms, pays special attention to the phenomenon of cross-protection with non-vaccine HPV genotypes, and

provides a consistent vaccine development discussion in the context of non-HPV gynecological cancers, which are often briefly addressed in HPV-centered reviews. Finally, it integrates novel platforms such as AI-assisted antigen design, mRNA vaccines, neoantigen vaccines, and needle-free delivery with both global and India-specific implementation approaches and identifies the knowledge gaps between the current evidence base and the goal of broad-spectrum and therapeutic vaccines of comparable efficacy to prophylactic HPV vaccines.

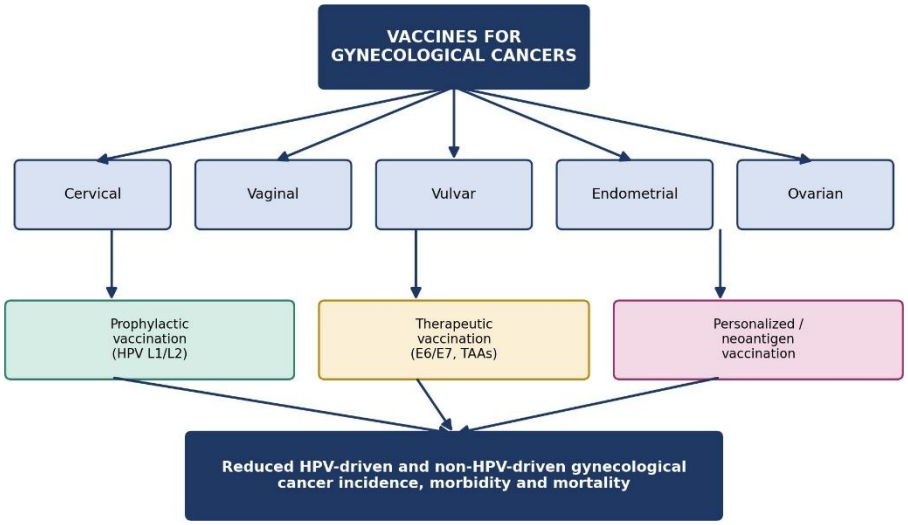

Figure 1. Overall conceptual framework: vaccine strategies mapped across the five major gynaecological cancers.

1. VACCINES IN GYNAECOLOGICAL CANCERS

Immune-based therapies, sometimes referred to as cancer vaccines, function by enlisting immune cells capable of identifying and eliminating cancer cells. They can be administered in situ, cellular, nucleic acid-based, peptide-based, or vector-based, depending on how they are formulated. The basic assumption behind cancer vaccines is that the host immune system is capable of identifying and destroying transformed cells, but tumors actively suppress its ability in the tumor's microenvironment. The microenvironment implies the delicate balance between immune surveillance and immune evasion, rather than tumor biology itself. The next classification of vaccine strategies forms the basis of the further part of this review.

A. Prophylactic vaccines: These vaccines are intended to stop illness or infection before cancer manifests. The HPV vaccine group is the most prominent illustration of this strategy in gynecological oncology. This type of vaccine blocks the initial stage of the known carcinogenic pathway by producing neutralizing antibodies against the virus's predetermined antigen. For this reason, preventive vaccinations work well against HPV-induced malignancies but are ineffective against other types.

B. Therapeutic vaccines: Therapeutic vaccines treat existing infection, intraepithelial neoplasia, or invasive cancer. They are designed to induce cytotoxic T-lymphocyte responses against

disease-associated antigens rather than to neutralise free virions.

C. **Personalized cancer vaccines:** These constructs are assembled from an individual tumour's mutations, usually as neoantigen peptide or mRNA products. They are most relevant where no universal shared target exists, notably ovarian and many endometrial cancers.

D. **Combination vaccine strategies:** Vaccine-primed T cells are necessary but often insufficient against an established, immunosuppressed tumour. Combinations with immune-checkpoint inhibitors, chemotherapy, radiotherapy or targeted agents are therefore the dominant clinical design.

2. ROLE OF VACCINES ACROSS THE FIVE MAJOR GYNAECOLOGICAL CANCERS

Before examining HPV biology or specific vaccine platforms in depth, it is useful to map where vaccination currently stands, and plausibly could stand, across each of the five major gynaecological cancers (Table 1).

Table 1. Vaccine strategies across the five major gynaecological cancers.

Cancer	HPV Association	Vaccine Type	Target	Current Status
Cervical	Strong	Prophylactic+ therapeutic	L1/L2, E6/E7	Established+ investigational
Vaginal	HPV-associated subset	Mainly prophylactic	L1/L2	Preventive evidence
Vulvar	HPV-associated + HPV-independent	Prophylactic/therapeutic	L1/L2,E6/E7, tumor antigens	Mixed
Endometrial	Not established	Therapeutic/personalized	Tumor antigens/ neoantigens	Experimental
Ovarian	Not established	Therapeutic/personalized	TAAs/ neoantigens	Experimental

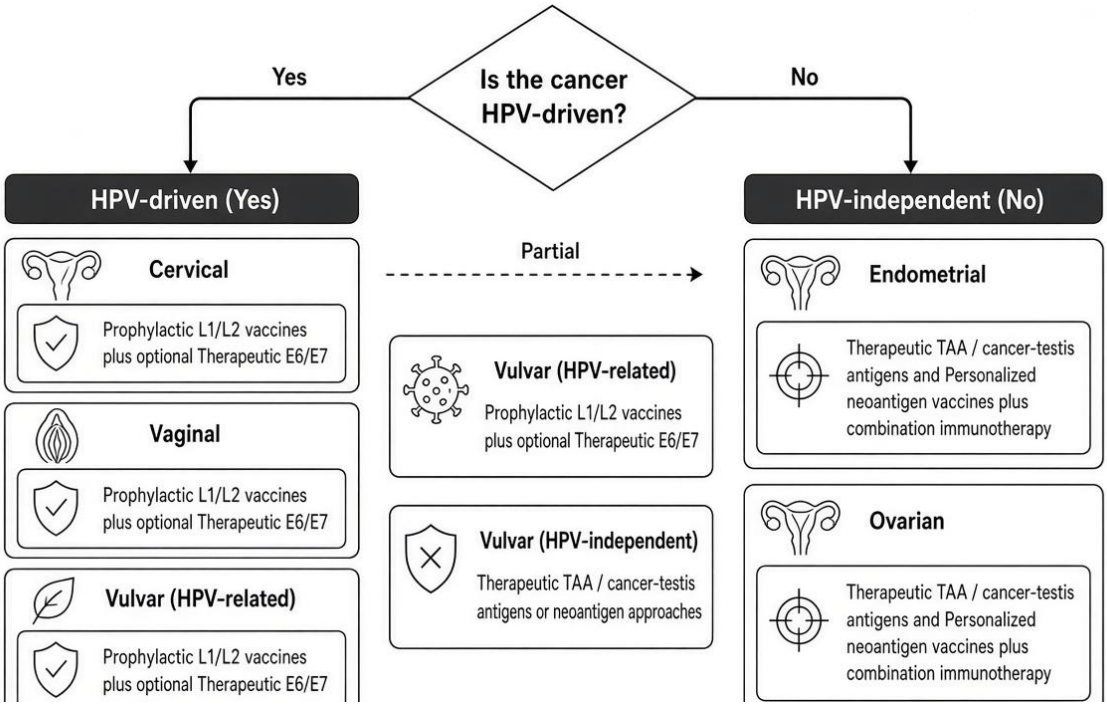

Figure 2. Decision framework for vaccine strategy according to HPV association.

Cervical Cancer — Established Vaccine-Preventable Cancer

The evidence base for the prevention of cervical cancer through vaccination is the most developed of any gynecologic malignancy. Cervical cancer is caused almost exclusively by the persistence of high-risk types of HPV, usually HPV-16 and -18, via a well-described carcinogenesis pathway [135–140]. Prophylactic HPV vaccination (Sections 5–8), as well as therapeutic HPV vaccines targeting E6/E7 (Section 9), are actively being researched and, in the case of prophylactic vaccines, are being used worldwide. Cross-protective HPV vaccines for non-vaccine HPV genotypes and next-generation L2/L1L2 vaccines (Sections 7–8) are designed to fill gaps not covered by current first-generation L1 vaccines. HPV vaccination prior to HPV infection offers the most protection because current HPV vaccines do not protect against previously acquired infections [11,13]; as there is no HPV vaccine that covers genotypes other than those in its repertoire or previously acquired infections, cervical screening is necessary in addition to HPV vaccines.

Vaginal Cancer — Preventive Relevance for HPV-Associated Disease

Vaginal cancer consists of HPV-related as well as HPV-unrelated cancers. Squamous cell carcinomas make up to 90% of vaginal cancer 212. Furthermore, HPV-DNA can be identified in 55-81% of invasive vaginal cancers and 94% of VaIN lesions if the incidence of HIV infection is high 213-220. Regarding HPV-related vaginal cancer, the preventive approach would include HPV vaccination similar to that in cervical cancer, and an E6/E7-targeted vaccine can be considered a possible future therapy for the developed lesions. Specific evidence for vaginal cancer is currently limited by the low incidence rate of the disease because most of the cases are detected as a metastatic lesion of primary vaginal carcinoma.

Vulvar Cancer — Vaccine Relevance Dependent on Tumour Etiology

The distinction between the causes of vulvar cancer is even clearer, with each having its own implications for vaccination. HPV-related vulvar squamous cell carcinoma develops through high-grade VIN and is mostly associated with HPV-16 infection, among other carcinogenic variants (HPVs [18, 33, 45,] and [52)] 215,223-228. It affects mostly younger women and has a rather favorable prognosis. On the other hand, non-HPV-related vulvar cancer is an aggressive, molecularly distinct disease that is more often found in older women and cannot be prevented by any conventional HPV vaccine. Prophylactic HPV vaccine and E6/E7-based vaccines are only applicable to HPV-related vulvar cancer, while non-HPV-related vulvar cancer will need some kind of tumor-antigen/neoantigen vaccination similar to those used in endometrial and ovarian cancers (see Section 10).

Endometrial Cancer — An Experimental Therapeutic and Personalized Vaccine Field

Prophylactic vaccinations do not play any significant part in the development of endometrial cancer, since the involvement of HPV in the etiology of endometrial cancer remains unknown or even controversial, with the overall prevalence of HPV-DNA being about 10% and varying widely (from 0 to 54.5%), depending on the study 230-233. The molecular pathogenesis of this disease is based on hormonal, metabolic, and DNA repair mechanisms that are different from the pathogenetic effects of HPV infection, and vaccines are developed exclusively for treatment purposes.

Ovarian Cancer — An Emerging Therapeutic and Personalized Vaccine Field

Also, like cervical cancer, ovarian cancer lacks an effective prophylactic vaccine, with the heterogeneity of its tumors making it unlikely that there is just one universal target for a vaccine. This is why the use of the tumor-associated antigens, cancer testis antigens, and personalized neoantigens, which are discussed in Section 10.2, is of great importance.

3. HPV AS THE MAJOR TARGET FOR PROPHYLACTIC VACCINATION IN GYNECOLOGICAL CANCERS

With the locations of interest in vaccination against gynecological cancers now defined, it may be useful to briefly consider the viral carcinogen at the center of the field's one and only prophylactic vaccine approach, HPV. HPV can be divided into high-risk (oncogenic) and low-risk types according to association with cancer; the high-risk HPV types (notably HPV-16 and 18) are the primary causes of the vast majority of cervical, vaginal and vulvar cancers attributable to HPV, while the low-risk types (notably HPV-6 and -11) cause genital warts, not cancer. The majority of HPV infections are cleared naturally by the immune system within one to two years, but the crucial element here is persistence of the high-risk type infection in the presence of continued selective pressure [41].

HPV-associated cancers of the cervix, vagina, and vulva also have the same high-risk type profile (primarily HPV-16 and -18, plus 31, 33, 45, 52, and 58), and it is this which renders HPV a perfect candidate for the development of a prophylactic vaccine: a single, defined, external antigenic source of a major share of the disease, as opposed to the internal mutation-driven processes that cause endometrial and ovarian cancers. This also explains the difference, easy to confuse, between prevention of infection by HPV (as a prophylactic vaccine must do, Sections 5–8), and treatment of established infection or lesions (as a therapeutic vaccine must do, Section 9), as quite different endeavors, each with its own specific antigenic

targets and immune mechanisms, which are the organizational framework of this paper. Molecular mechanisms of HPV transformation will not be extensively repeated here as they are well-known, and will only be addressed in the course of justifying E6/E7 protein candidacy in therapeutic vaccine strategies, Section 9.

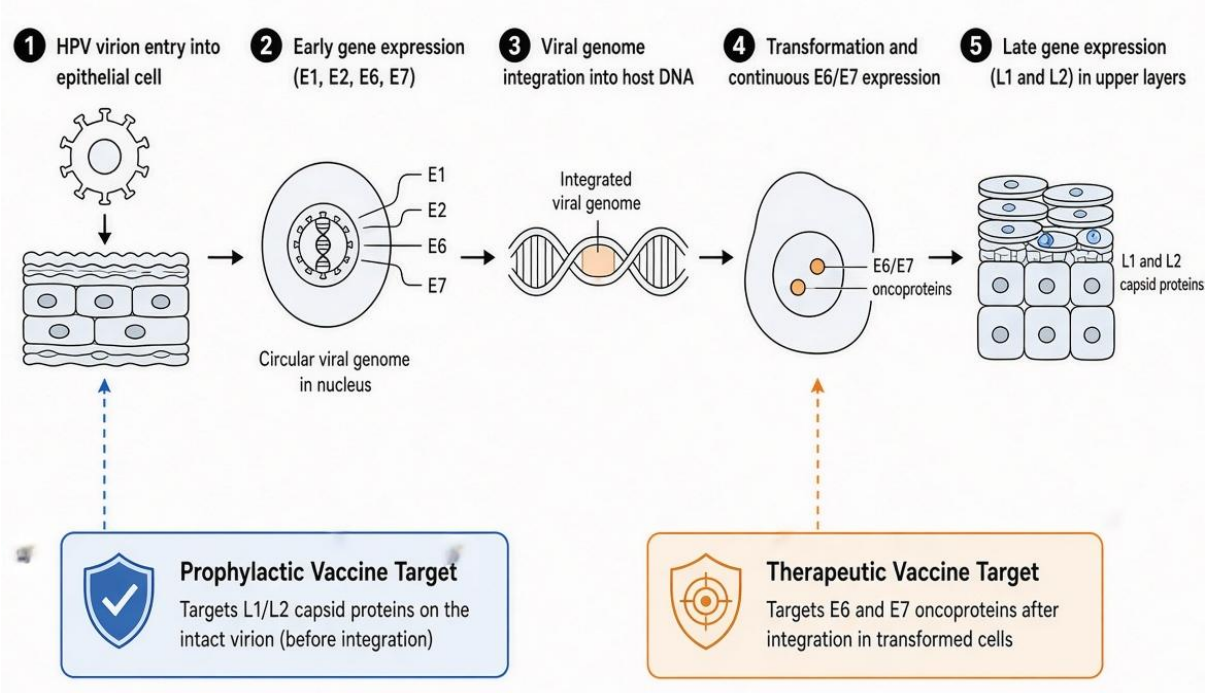

Figure 3. HPV life cycle showing distinct windows for prophylactic (L1/L2) and therapeutic (E6/E7) vaccination.

4. EVOLUTION OF PROPHYLACTIC HPV VACCINES

4.1 Development of HPV Vaccines

The history of HPV vaccine development is linked to experimental models of transgenic mice harboring HPV oncogenes. It became possible due to an important meeting of Ian Frazer with the Chinese virologist Jian Zhou at the University of Cambridge in 1989. Later, Zhou and his colleague Xiao Yi Sun joined the Frazer laboratory in Brisbane and created VLPs self-assembling from HPV major capsid protein L1 that became the core of all licensed prophylactic HPV vaccines [50,51.] The invention was filed in 1991 but officially recognized only in 2006 [50,51.] First to commercialize this innovation were Merck and GlaxoSmithKline (GSK): the quadrivalent Gardasil vaccine by Merck was licensed by the FDA in 2006, followed by the bivalent Cervarix by GSK in 2009 and nonavalent Gardasil 9 by Merck in 2014. HPV vaccines proved their efficacy in 80-90% of HPV-naïve women and 90-100% of HPV-naïve men [51.]

HPV vaccines are non-infectious recombinant vaccines constructed from purified virus-like L1 protein particles for each targeted HPV type 43. More than 98% of patients develop an antibody response one month after vaccination, and the vaccine extends B-cell immunity through the shift of the circulating antibodies balance in favor of neutralizing antibodies [43,44.] According to the CDC, the effect lasts for more than 12 months without any signs of decreasing immunity 45. A systematic review by Martinez-Gomez et al. 56 proves the immunogenicity, safety, and efficacy of

these vaccines among high-risk populations. New results about the effectiveness of dose-sparing protocols are accumulating. According to Whitworth et al. [60,] there are data supporting the same level of protection from a single dose and a multi-dose schedule. As for other aspects influencing the parents' decision to vaccinate, Sonawane et al. [61] found safety and efficacy issues to be most significant among US parents.

4.2 Licensed HPV Vaccines

Six HPV vaccines with prophylactic action have been licensed so far worldwide, which includes three bivalent vaccines, two quadrivalent vaccines, and one indigenous (non-viral) vaccine formulation (Table 2).

Bivalent (HPV16/18): The efficacious action of Cervarix against HPV-16/18 infection and grade-3 CIN has been noted, along with a good safety profile 34–38, and it also shows consistency in providing cross-protection against non-vaccine genotypes (Section 8) [112–114.]

Quadrivalent (HPV6/11/16/18): In addition to offering protection against HPV-16/18 infections, Gardasil protects against genital warts and shows efficacy against lesions in the vagina and vulva [39,40.]

Nonavalent (HPV6/11/16/18/31/33/45/52/58): This is the global standard at present and offers protection against the maximum number of directly covered genotypes, and after receiving recent FDA approval, it also covers the HPV-attributed oropharyngeal as well as other head and neck cancers [42.]

Indigenous Vaccine – Cervavac: In 2022, Cervavac, an indigenous, gender-neutral, quadrivalent vaccine (HPV6/11/16/18) was introduced by the Serum Institute of India, with particular emphasis on affordability and accessibility in LMIC countries [51–57]. This vaccine is of great significance

Table 2. Licensed Prophylactic HPV Vaccines.

Characteristic	Bivalent (Cervarix, 2007)	Quadrivalent (Gardasil, 2006)	Cervavac (2022)	Nonavalent (Gardasil 9, 2014)
Manufacturer	GlaxoSmith Kline (GSK)	Merck & Co.	Serum Institute of India Pvt. Ltd.	Merck & Co.
HPV Types	16, 18	6, 11, 16, 18	6, 11, 16	6, 11, 16, 18
			18	31, 33, 45, 52,
				58
Adjuvant	AS04	Amorphous aluminum hydroxyphosph ate e sulfate (AAHS)	AAHS	AAHS
Target Population	9–26 yrs	9–26 yrs	9–26 yrs	9–45 yrs

Indicated Cancers	Cervical cancer	Cervical, vaginal, vulvar, anal cancers and genital warts	Cervical, vaginal, vulvar, anal cancers and genital warts	Cervical, vulvar, vaginal, anal, oropharyngeal cancers and genital warts
Major Protection	Strongdirect + moderate cross-protection ([31,33,45])	Direct protection; first to add genital-wart coverage	Affordable, indigenous, gender-neutral protection	Broadest genotype coverage; >90% of cervical cancer-causing types
Limitations	Being phased out in many markets; genotype-restricted	Narrower cross-protection than bivalent; genotype-restricted	Limited long-term real-world data as yet	Higher cost/complexity; still genotype-restricted
References	59,60,112,114	52,62,112	52	62

HPV has a double-stranded DNA virus structure with early (E), late (L), and long control regions [115]. Genome integration interferes with early E2 expression, which deregulates the E6 and E7 proteins, but not exclusively via genomic methods [116]. The preventive vaccine functions through the delivery of VLPs produced from L1 (as well as future generations from L2) capsid proteins in order to trigger an immune response in the form of antibodies directed against HPV infection [120]. That is why the efficacy of such vaccines lies both in their great safety and in the major disadvantage of being preventive: they do not have any therapeutic properties since they target infections and lesions already established [121,122].

5.L1-BASED HPV VACCINES: CURRENT STANDARD

All six FDA-approved prophylactic HPV vaccines use the same principle of vaccine action – the major capsid protein L1 spontaneously assembles into virus-like particles that structurally resemble the native HPV virions but do not contain viral DNA and are thus non-infectious and unable to induce pathologies. The similarity of VLPs to the native virion surface makes it possible to produce a strong and long-lasting neutralizing antibody response, which is the key factor in the high efficacy of L1-based vaccines against the targeted genotypes [42,120].

The advantages of the above-mentioned approach include a well-tested production process, an excellent safety profile, and high efficiency (> 90%) against persistent infections and precancerous lesions caused by genotype-matched strains in HPV-naive individuals. At the same time, there are several significant limitations

related to the same biological principles that provide such an excellent efficacy for L1 vaccines. First of all, the effect is highly type-specific – due to the dominance of L1 surface loops as the target neutralizing epitopes, which differ significantly among HPV genotypes, protection is specific to the targeted genotypes only 106. Second, to extend coverage, additional L1 VLPs need to be added to the vaccine composition – just like in the case of the nonavalent vaccine in comparison with the bivalent and quadrivalent vaccines. Third, the nonavalent vaccine still leaves over a dozen additional oncogenic HPVs untargeted, and thus L1-based vaccines cannot achieve complete coverage [106,108]. It is this residual problem which has been driving the development of broad-spectrum, genotype-independent vaccines based on L2 protein.

6. L2-BASED AND L1/L2-BASED NEXT-GENERATION HPV VACCINES

6.1 L2-Based Vaccines

Whereas L1 contains highly variable surface loops, the amino-terminal region of L2 is highly conserved between HPV genotypes, containing epitopes that are cross-neutralized by antibodies against L2106,107. This conserved nature is the basis for the development of L2-based vaccines; with one conserved epitope, it is possible to protect against multiple genotypes, rather

than just a few genotypes with multivalent L1 constructs.

However, there are practical difficulties with L2-based vaccine constructs. Alone, L2 is not highly immunogenic – it is unable to self-assemble into virus-like particles like L1, and sufficient doses of epitopes needed to induce the required immune response through the native L2 are difficult to obtain [106,108]. Solutions to this problem have included concatemeric multimers of L2 epitopes, fusions to toll-like receptor ligands or T-cell epitopes, and use of heterologous nanoparticle or bacteriophage virus-like particles (VLP), where the bacteriophage PP7-based platform has induced strong cross-neutralizing and protective responses against eight different HPV types in preclinical models [110.] As L2-based epitopes do not rely on the complex capsid structure of L1, they can also be expressed in simple and low-cost prokaryotic expression systems as well, offering an alternative manufacturing solution for LMIC-relevant manufacture 106. There are several L2-based vaccine candidates at or nearing Phase I evaluation [106,111.]

6.2 L1/L2 Chimeric Vaccines

In L1/L2 chimeric vaccines, the well-characterized L1 VLP structure provides well-proven high immunogenicity and manufacturing knowledge, while the conserved L2 epitopes are incorporated into surface loops of the L1 particle, usually the DE-loop, providing the added ability for cross-protection without compromising the well-recognized immunogenicity of L1-based vaccines [108,109]. Preclinical evaluation of chimeric L1 VLP particles incorporating L2 cross-neutralization epitopes for HPV16 has demonstrated cross-neutralizing antibody responses and in vivo protection against multiple additional HPV types not present in the base L1 vaccine 108,109. The concept is appealing precisely because it does not need to compromise the proven immunogenicity of L1 with the ability for broader cross-neutralization offered by L2.

6.3 Next-Generation Broad-Spectrum Vaccines

Not limited to the individual L2 or L1/L2 constructs, there are multiple broad-spectrum or "pan-HPV" vaccine approaches that are based on combining conserved epitopes from various HPV

clades into a single antigen platform. One of these constructs is a polytopic L2 antigen called PANHPVAX, which includes cross-neutralizing epitopes from eight mucosal HPV genotypes, and its cutaneous version, CUT-PANHPVAX, from twelve cutaneous genotypes, in a heptameric nanoparticle scaffold [111]. Consistent immunogenicity across the included epitopes is a technical challenge – it was recently shown that the selection of the sequence used as inter-epitope spacers in the construct influences the resulting antibody response [111.] Thus, pan-HPV vaccine development is not just about inclusion of multiple epitopes in one vaccine, but about careful antigen presentation. Improved antigen presentation, novel adjuvants, and advanced delivery technologies (Section 13) are being evaluated to make these broad-spectrum constructs clinically relevant.

Table 3. Comparison of L1-VLP, L2-based, and L1/L2 chimeric HPV vaccine platforms.

Feature	**L1-VLP vaccines**	**L2-based vaccines**	**L1/L2 chimeric vaccines**
Antigen basis	Major capsid protein, self-assembling VLPs	Minor capsid protein, conserved N-terminal epitopes	L1 VLP scaffold displaying inserted L2 epitopes
Immunogenicity	High; strong neutralizing antibody titers	Comparatively low; requires multimerization/ car rier platforms	Retains high L1 Immunogenicity with Added L2 breadth
Protection breadth	Type-restricted; partial cross-protection to related types	Broad, cross-neutralizing across many genotypes	Broader than L1 alone; aims at pan-HPV coverage
Manufacturing	Complex; multiple VLP types needed for multivalent coverage	Simpler; can use prokaryotic expression systems	Moderate; single chimeric particle per construct
Current status	Licensed and in global use (bivalent/quadrivalent/ nonavalent/Cervavac)	Preclinical to early first-in-human candidates(e.g., RG1-VLP,	Preclinical; proof-of-concept broad protection demonstrated

		PANHPVAX)	
References	42,52–63	106,107,110,111	108,109

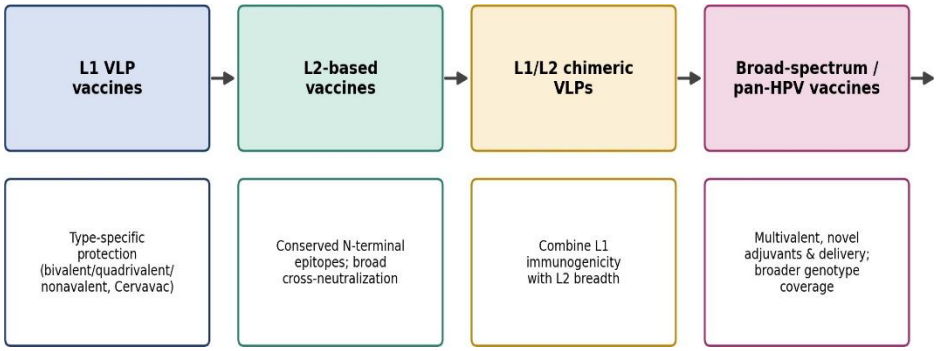

Figure 4. Evolution of HPV vaccine technology: L1 → L2 → L1/L2 chimeric → broad-spectrum/pan-HPV vaccines.

7. CROSS-PROTECTION FOLLOWING HPV VACCINATION

Cross-protection is the phenomenon of partial protection against HPV genotypes other than those included in the vaccine formulation. It stems from the fact that the non-vaccine types of HPV are phylogenetically related to certain vaccine target genotypes: HPV31, 33 and 35 are relatives of HPV16, whereas HPV45 is a relative of HPV18; this allows the generation of cross-reactive antibodies, which will partially neutralize these types of HPV. This process differs from the broad cross-protection generated by L2-based vaccines, based on conservation of epitopes in the HPV genome (section 7.1), and is a secondary effect of the phylogenetic relationship between L1 surface loops, which is why it is partial and not consistent. The landmark systematic review and meta-analysis carried out by Malagón et al., based on data from the FUTURE I/II trials of the quadrivalent vaccine and the PATRICIA, HPV007 and HPV-023 trials of the bivalent vaccine, showed that the cross-protection efficacy against persistent infection with HPV31 was significantly higher for the bivalent vaccine compared with the quadrivalent vaccine (77.1% versus 46.2%), with the same trend observed for HPV33 and HPV45, although there were great heterogeneities between different trials and decrease in cross-protection efficacy with prolongation of follow-up period in some studies[112]

The PATRICIA experiment, a largescale randomi zed study that showed the bivalent vaccine's effec tiveness, independently verified the cross-protection efficacy with the bivalent vaccination against infection and precancerous cervical cancer brought on by non-vaccine oncogenic of HPV over four years of monitoring[114.]

The Costa Rica HPV Vaccine Trial (CVT), which provided long-term data, clarified the question of how long cross-protection lasted. In women who received three doses of the bivalent vaccine, the cross-protection against the HPV31/33/45 group of genotypes was maintained for 11 years (average vaccine efficacy against this group – 64.4%, 95%

confidence interval 57.7-70.2%) and partial but statistically significant cross-protection against the HPV35 (efficacy – 23.2%) genotypes; there was no discernible decline in efficacy over this period, and even a single dose of the HPV31/33/45 genotypes was achieved with a single dose[113]. This is significant because the initial worry was t hat crossprotection would deteriorate with time; CVT findings show that this protection can be lon glasting, at least for the bivalent vaccination and t he most closely related non-vaccine genotypes.

Table 4. Cross-protection against selected non-vaccine HPV genotypes by licensed HPV vaccine.

Non-Vaccine HPV Type	Bivalent Vaccine Efficacy	Quadrivalent Vaccine Efficacy	Phylogenetic Relation	Reference
HPV31	Substantial (~77% vs persistent infection; sustained to 11 yrs)	Lower (~46%); wanes over follow-up	Related to HPV16	[112–114]
HPV33	Moderate–substantial	Lower, inconsistent	Related to HPV16	[112,113]
HPV35	Modest(~23% VEavg)	Not well established	Related to HPV16	[113]
HPV45	Substantial, combined with 31/33 (VEavg 64.4%)	Lower than bivalent	Related to HPV18	[112–114]
HPV52	Limited/inconsistent	Limited/inconsistent	Distinct clade	[112]
HPV58	Modest(~21% VEavg)	Limited/inconsistent	Distinct clade	[113]
Duration	Sustained through 11 years of trial follow-up for 31/33/45	Less durable; efficacy estimates decline with longer follow-up	—	[113]

Note: comprehensive quadrivalent-vaccine cross-protection data against HPV35 and HPV58 specifically are more limited in the literature than bivalent-vaccine data and are presented here with appropriate caution.

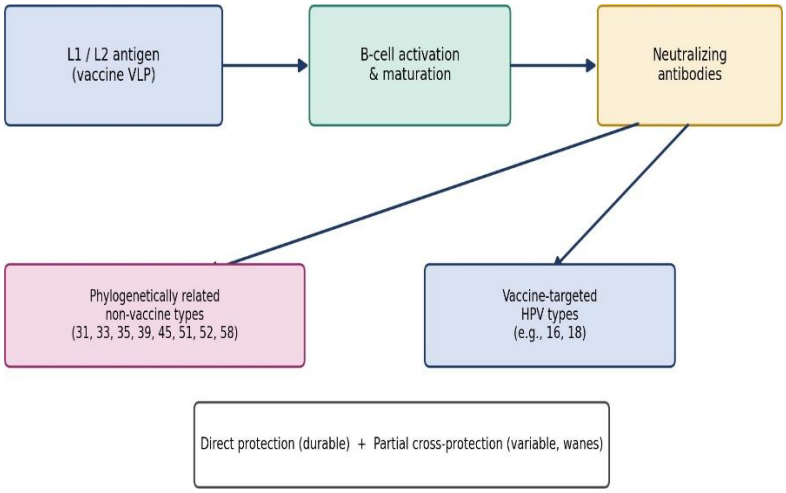

Figure 5. Cross-protection mechanism: L1/L2 antigen → B-cell response → neutralizing antibodies → protection against both vaccine-targeted and phylogenetically related non-vaccine HPV types.

This has clinical importance for the eradication of cervical cancer in two respects. The first aspect of cross protection implies that even populations vaccinated with bivalent and quadrivalent vaccines maintain protection against at least a portion of non-vaccine oncogenic strains of disease, which needs to be incorporated in population impact modeling and is one of the reasons that surveillance data have shown greater reduction in disease attributable to HPV than expected [112.] The second aspect is equally important and it implies that cross protection applies only to some HPV strains included in the nonavalent vaccine, is inconsistent among the non-vaccine HPV strains, and is less robust in the case of quadrivalent as compared to the bivalent vaccine [112,113] – that means that cross-protection can never be used as a surrogate to direct genotypic matching. It is the very lack of cross protection that drives efforts towards developing L2-based and broad-spectrum vaccines of the next generation (Section 7).

8.THERAPEUTIC HPV VACCINES

8.1 Rationale

Prophylactic vaccines target the L1/L2 capsid proteins which are responsible for the structure of the virus particle. After integration of the viral genome and transformation of cells, the presence of these capsid proteins is reduced dramatically, and there are no antigens which proved themselves to be so successful in prophylactic vaccination [145.] Therefore, therapeutic vaccines have to target other antigens – the viral oncoproteins E6 and E7 that maintain constant expression at a high level in the entire life cycle of the transformed cell and are indispensable for the maintenance of malignancy of the cell, so it is impossible for tumor cells to escape immune-escape mutation [146.]

8.2 Therapeutic Targets

The main therapeutic targets are E6 and E7 oncoproteins; the constant expression of these proteins is responsible for the degradation of p53 protein and inactivation of Rb, and they account for the most part of candidates under clinical development [146]. E2 and E1 are other potential candidate antigens, because they have high expression level before genome integration and before the dysregulation of E6/E7 proteins which occur in fully transformed cells [107,147,148.]

8.3 Vaccine Platforms

Therapeutic HPV vaccines can be peptide-, protein-, DNA-, RNA/mRNA-, viral vector-, bacterial vector- and dendritic cells-based 149. Currently none of them was approved for clinical use, but some candidates reached Phase II or Phase III [65].

8.4 Clinical Candidates

Basic proof-of-concept experiments proved the feasibility of therapeutic HPV vaccination. In a Phase I trial in women with CIN (n=31), Frazer et al. tested HPV-16-specific immunotherapy based on the E7 protein fused with ISCOMATRIX™ adjuvant; the treatment was well-tolerated and provided an immune response against HPV-16 E6/E7, including increased level of antibodies, delayed hypersensitivity, cytokine release and CD8+ T-cells response compared to the control group [49]. Also, a Phase I trial of an HPV-16 E7 peptide vaccine in women with high-grade cervical and vulvar intraepithelial neoplasia (n=18) cleared HPV in 12 patients, and three of them also cleared dysplasia [50]. In Phase I/II trial of a live recombinant vaccine with E6 and E7 expression (TA-HPV) in patients with advanced stage of cervical cancer (n=8) were found antiviral antibody responses in all patients, and HPV-specific cytotoxic T-lymphocyte response in some of them [53].

Currently, DNA vaccines are the most clinically advanced candidates. VGX-3100 – the plasmid coding HPV-16/18 E6 and E7 proteins delivered by intramuscular injection with electroporation – showed significant histological regression of CIN2/3 lesions and HPV clearance in comparison with placebo in Phase IIb, randomized, double-blind trial; this is the first therapeutic vaccine to demonstrate good efficacy in a controlled experiment [69]. Also, another DNA vaccine, which is optimized for inducing T-cells response, is GX-188E, and it proved itself to be effective against CIN3 lesions and has been successfully tested in combination with checkpoint inhibitors like pembrolizumab in advanced HPV-associated cancers [70]. Other strategies being investigated include combination with drugs reducing the immunosuppressive properties of the tumor microenvironment (like interleukin-2) and oral DNA vaccines based on HPV-16 E7 expression in Lactobacillus casei which interact with the gut-associated lymphoid tissue through Peyer's patches [66,67]. There is a large number of other candidates (including GLBL-101c, TG4001, BLS-M07, MVA-E2, chimeric VLPs, HspE7 and ZYC101a) which were effective against CIN and cervical cancer [68].

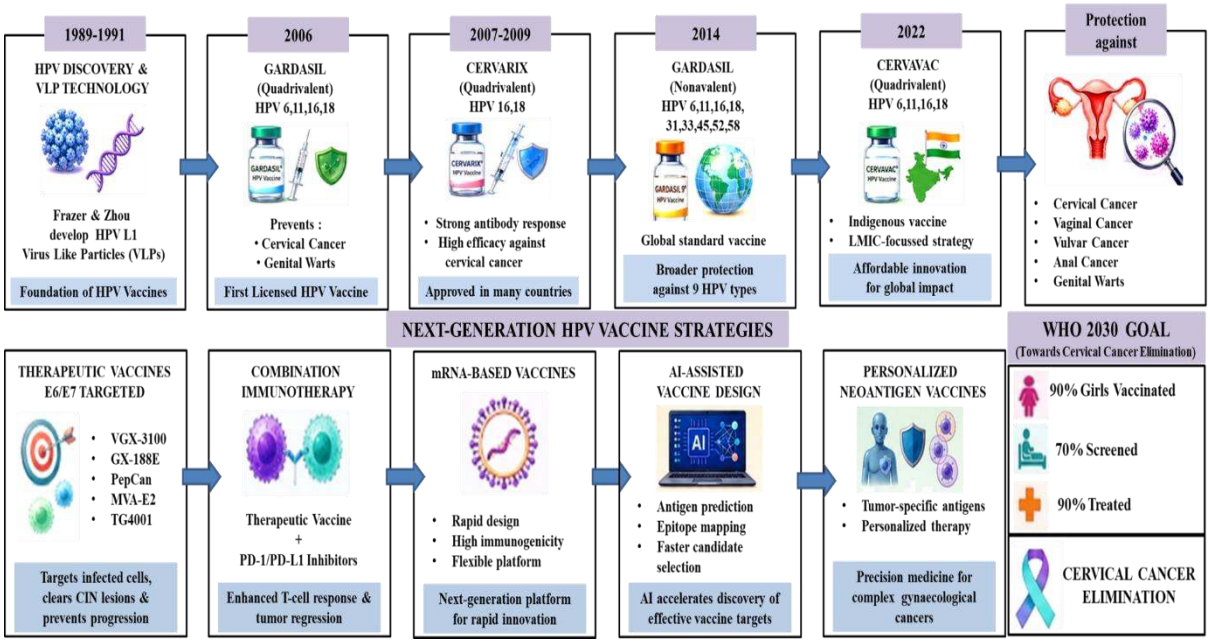

Figure 6: Evolution of HPV vaccine

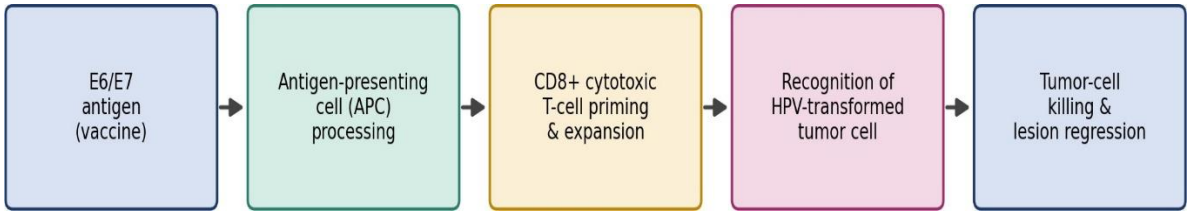

Figure 7. Therapeutic HPV vaccination mechanism: E6/E7 antigen → antigen-presenting cell → CD8+ T-cell priming → recognition of HPV-transformed tumor cells → tumor-cell killing

Table 5. Therapeutic HPV vaccine candidates targeting E6 ± E7, by antigen, platform and clinical trial phase.

Antigen Used	Nature of Vaccine	Vaccine	Clinical Trial Phase	Reference
HPV16 E6/E7 fusion protein	Live (bacterial and viral)	ADXS11-011 (bacterial)	Phase I/II	174,175
HPV-16 E6 and E7 peptide	Vector-based vaccine	TA-HPV (viral)	Early-stage clinical trials	178,179
HPV-16 E7 peptide	Peptide vaccine	ISA 101	Phase II	159-161
HPV-16 E7 fusion protein	Protein vaccine	SGN-00101	Phase II	146, 168-173
HPV 16 E6	Peptide vaccine	PepCan	Phase I	162
HPV 16/18 E6 and E7	DNA vaccine	VGX-3100	Phase III	153, 154
HPV 16 and 18 E6 and E7	DNA vaccine	GX-188E	Phase II	152

HPV 16 E6 and E7	DNA vaccine	VB10.16	Phase I/IIa	[155]
HPV 16 E6 and E7	Peptide vaccine	AMV002	Phase I	[157]
HPV 16 E6, E7, and human IL-2	Vector-based vaccine	TG4001	Phase Ib/II	[180-181]

9. VACCINES FOR NON-HPV GYNECOLOGICAL CANCERS

A gynecological – not just an HPV – perspective requires addressing the endometrial cancer, ovarian cancer, and HPV-unrelated vulvar cancer individually on a scientific level because there are no ways to reach them using conventional HPV vaccination (Sections 5-9).

9.1 Endometrial Cancer

About 25-30% of endometrial cancers are mismatch-repair deficient (dMMR) or microsatellite instability high (MSI-H) – the molecular subtypes where DNA mismatch repair defects result in high tumor mutational burden and, therefore, high neoantigen burden [26,118,119]. Such tumors exhibit increased tumor infiltrating lymphocyte and high PD-1/PD-L1 expression that makes them highly sensitive to immune checkpoint blockade therapy even in the absence of a specialized vaccine [26,27,29-31]. At the same time, this biology makes dMMR/MSI-H endometrial cancer an excellent subject for personalized neoantigen vaccination as high neoantigen load provides an abundant source of tumor specific neoepitopes for selection in next-generation sequencing-based neoantigen design pipeline (Section 12). On the contrary, pMMR endometrial cancers are usually less immunogenic with low neoantigen load, thus making combination strategies combining PARP inhibition and/or genome-wide mutagenesis the way of increasing neoantigen load for sensitization to the immune checkpoint blockade [26].

Various tumor-associated antigen (such as HER2/neu, WT1) and personalized neoantigen mRNAs, DNAs and peptide vaccines are actively researched for endometrial cancer in combination with immune checkpoint blockers, but not as monotherapies, because of the field's still preclinical and early clinical development stage [9,22,26].

9.2 Ovarian Cancer

The development of ovarian cancer vaccines has generated one of the most clinically mature personalized vaccine datasets apart from melanoma. Tumor-associated antigens such as HER-2/neu, MUC1, and folate receptor-α, cancer testis antigens such as NY-ESO-1, and personal neoantigens have been used as the target antigens delivered in the form of peptides, DNAs, mRNAs, viral vectors, and dendritic cell vaccines [22,90,115-117]. The most extensively investigated approach is the autologous dendritic cell vaccine OCDC generated by pulsed dendritic cells with oxidized whole tumor lysate. In the pilot clinical trial conducted in recurrent, platinum-treated ovarian cancer patients, OCDC generated significant prolongation of survival associated with induction of tumor antigen-specific T-cell responses either as a single agent or combined with bevacizumab and a low dose of cyclophosphamide [116]. Another trial adding aspirin and a low dose of interleukin-2 into the regimen of OCDC, bevacizumab, and cyclophosphamide resulted in positive correlations between vaccine-specific T-cell responses and prolonged time-to-progression and survival. A similar effect was observed in the murine model of the disease [117]. Dendritic cell

vaccines, in general, remain a promising direction in the development of ovarian cancer vaccines, with the whole tumor lysate approach preferable over single peptide vaccines due to its ability to induce responses to multiple neoantigens and, thereby, decrease chances of tumor antigen loss-mediated immune escape [115].

9.3 HPV-independent Vulvar Cancer

HPV-independent vulvar cancer is molecularly distinct from its HPV-related subtype and, as explained in Section 3.3, does not benefit from any conventional HPV vaccination. Thus, as it is similar to other non-infectious epithelial malignancies in terms of mutational landscape, tumor antigen and personalized neoantigen vaccines (the same approach that is currently pursued in the development of endometrial and ovarian cancer vaccines) represent the most likely approach for the disease's vaccination in the future, although there are almost no dedicated vaccine trials in HPV-independent vulvar cancer, thus constituting one of the clearest knowledge gaps identified in Section 16.

Table 6. Therapeutic and personalized vaccine strategies for endometrial and ovarian cancer, by antigen class and platform.

Cancer	Antigen Class / Target	Platform	Approach / Candidate Example	Reference
Endometrial	Neoantigens (dMMR/MSI-H tumors)	mRNA / peptide / personalized	High tumor mutational burden exploited for neoantigen vaccination; combined with checkpoint blockade	[26,27,29–31,118,119]
Endometrial	Tumor-associated antigens (e.g., HER2/neu, WT1)	Peptide/protein	TAA-directed vaccination as adjunct to standard therapy	[9,22]
Ovarian	Tumor-associated antigens (HER-2/neu, MUC1,	Whole tumor-lysate dendritic cell (OCDC)	Autologous DC vaccine + bevacizumab ± cyclophosphamide	[115–117]

	folate receptor)			
Ovarian	Cancer-testis antigens (e.g., NY-ESO-1)	Peptide / DNA	Antigen-specific vaccination, often with adjuvant	[22,90]
Ovarian	Personal neoantigens	DC / mRNA / peptide, NGS-guided	Personalized neoantigen-pulsed DC vaccines; combination immunotherapy	[86,87,90,115–117]

10. EMERGING VACCINE PLATFORMS

Both in the case of HPV-related and non-HPV gynecological cancers, the list of platforms involved is always the same: mRNA-based, DNA-based, viral/bacterial vector vaccines, peptides/protein subunit-based, dendritic cell vaccines, nanoparticle vaccines, chimeric VLPs, and neoantigen-based personalized vaccines. The technology of mRNA, which has proven its potential in manufacturing and adaptability due to lessons learned from combating COVID-19, is gaining popularity in the context of expanding coverage by genotypes of prophylactic vaccines and therapeutic vaccines targeting E6/E7 and neoantigens [23]. DNA-based vaccines, for example, VGX-3100 and GX-188E (Section 9.4), have reached the highest development level among therapeutic vaccines used in HPV diseases. Viral and bacterial vector-based vaccines, e.g., TA-HPV, ADXS11-011, TG4001, benefit from the intrinsic vector's immunogenic potential and enhance antigen presentation. Personalized and very potent dendritic cell vaccines (especially developed for ovarian cancer treatment; Section 10.2) are quite resource-intensive. Nanoparticle platforms and chimeric VLPs (Section 7) are often applied for delivery of difficult-to-present antigens like the L2 epitope. These platforms and their main applications and strengths are summarized in Table 7.

Table 7. Emerging vaccine technologies relevant to gynecological cancer prevention and treatment.

Technology	Application	Advantage	Reference
mRNA vaccines	Prophylactic genotype expansion; therapeutic E6/E7 and neoantigen delivery	Rapid design/adaptation; scalable manufacturing	23
AI-assisted antigen design	Epitope prediction (MHC binding, processing, immunogenicity); neoantigen prioritization	Speeds candidate selection; enables personalization	39, 84–87

Personalized neoantigen vaccines	Patient-specific mutation-derived antigens	High tumor specificity; reduced off-target risk	22, 86, 87
Dendritic-cell vaccines	Ex vivo antigen loading and reinfusion	Potent antigen presentation; used in ovarian cancer trials	89, 90, 115–117
Needle-free injection/microneedles	Prophylactic and therapeutic vaccine delivery	Reduced anxiety/cold-chain burden; self-administration potential	91–95
Thermostable formulations	Vaccine storage and transport in LMICs	Removes strict cold-chain dependency	52, 63
Chimeric VLPs / L2 platforms	Broad-spectrum prophylaxis	Cross-genotype protection from a single construct	106–111

11. ARTIFICIAL INTELLIGENCE AND PRECISION VACCINE DEVELOPMENT

AI revolutionizes vaccine development by enabling accelerated identification of antigen targets, immunogen design, manufacturing, and surveillance. AI techniques allow for comprehensive analysis of genomic, proteomic, and immunological data to accelerate discovery of vaccine targets and to predict peptide immunogenicity based on such characteristics as HLA/MHC binding, antigen processing, epitope presentation, and similarity to host proteins [39,84–87]. In the course of the COVID-19 pandemic, AI allowed for accelerated antigen target identification, while generative adversarial networks were used to design new influenza immunogens with improved antigenicity and cross-reactivity [84,85]; currently, deep learning-based pipelines are being utilized to improve neoantigen selection and personalize cancer vaccines, including those targeting gynecological cancers [86,87].

In the context of personalized vaccine design specifically, which is most applicable to endometrial and ovarian cancer (Section 10), the typical AI-assisted pipeline involves sequencing of tumor and normal tissue samples, mutational analysis, identification of candidate neoantigens, computational prediction of MHC binding, antigen processing, transcript expression, clonality, followed by vaccine construct synthesis as a peptide or mRNA vaccine. Structural modeling and AI-based optimization of vaccine constructs are included in the pipeline, and there are growing attempts to use a combination of AI-based antigen selection and a multi-omics approach, which includes genomic, transcriptomic, and microbiome (as mentioned below) data, for further refinement of candidate selection and immunogenicity prediction before vaccine manufacture.

12. NOVEL VACCINE DELIVERY TECHNOLOGIES

Delivery technology increasingly defines the ability to deliver an immunologically promising vaccine construct to its target population. Novel adjuvants, thermostable formulations, and needle-free injection (NFI) systems allow to achieve both immunological improvement and improved acceptance. With delivery of vaccine through

liquid jet technology, NFI systems eliminate the anxiety associated with needle injections, increase comfort and privacy of patients, and enable self-injection and lower resource utilization — features especially important for school- and community-based vaccination in LMICs [91–95]. Dissolving microneedle system is known to preserve the structural stability of HPV VLPs while providing for long-lasting protection via mucosal route of vaccination [93].

Thermostable formulations provide an answer to one of the most persistent issues related to LMIC vaccine introduction: the currently licensed quadrivalent vaccine is stable at temperatures up to 25°C for up to 72 hours, and the nonavalent vaccine — at 8–25°C within the same period of time, thus partially reducing the dependence on cold chain 52,63. Nanoparticle delivery systems, several of which have been previously mentioned as antigen display platform for L2-based vaccines (Section 7.1), are also used as a delivery technology to protect the unstable

antigen and provide for a mucosal route of vaccination, which could potentially be closer to the route of natural HPV infection. Altogether, these technologies are crucial to closing the gap in global coverage as well as improving vaccine efficacy in developed countries, and are further discussed in the LMIC context (Section 15).

13. COMBINATION STRATEGIES

Therapeutic and personalized vaccines in HPV-positive and non-HPV-driven gynecological cancers are increasingly used not as monotherapies, but as components of combination immunotherapy. The logic behind each combination strategy is always the same: a vaccine primes and expands antigen-specific T cells, but an established, immunosuppressed tumor restricts the function of these T cells via such checkpoint pathways as PD-1/PD-L1 and CTLA-4; thus, vaccine priming is usually necessary, but insufficient for clinical benefit.

Vaccine + immune checkpoint inhibitors. GX-188E in combination with pembrolizumab showed activity in HPV-associated cervical cancer 70; in case of dMMR/MSI-H endometrial cancer, PD-1/PD-L1 blockade already produces durable clinical response independently of vaccination, which makes a combination with vaccine highly promising when neoantigen vaccines will mature [26,29–31]; and PARP inhibitor combinations are being investigated specifically for sensitization of pMMR endometrial tumors to checkpoint blockade through increased genomic instability and neoantigen generation [26].

Vaccine + chemotherapy. Low-dose cyclophosphamide was used alongside dendritic cell vaccine in case of ovarian cancer in order to inhibit the regulatory T-cell activity that could otherwise suppress vaccine-induced response [116,117].

Vaccine + targeted therapy. Bevacizumab, a monoclonal antibody against VEGF, was used in combination with OCDC dendritic cell vaccine in ovarian cancer for tumor vessel normalization and T-cell infiltration into the tumor microenvironment, which is one of the key reasons for inefficacy of checkpoint inhibitors in ovarian cancer [116,117].

Vaccine + radiotherapy. Tumor-antigen release and local inflammation induced by radiotherapy are becoming recognized as a complementary tool to vaccine priming, although the trials of vaccine-radiotherapy combinations are still quite limited compared to those for checkpoint inhibitors.

In all these combinations, the sequence is the same: vaccine-primed antigen-specific T-cell activation and subsequent removal of a particular

barrier for T-cell function (either checkpoint pathway or a regulatory T cell activity), resulting in improved tumor cell killing.

14. GLOBAL AND INDIAN PERSPECTIVE

14.1 Global Perspective

HPV vaccination is universally acknowledged as the key cornerstone for achieving cervical cancer elimination. In 2020, the WHO launched the Global Strategy to Accelerate the Elimination of Cervical Cancer, adopted by 194 countries, with the 2030 target for 90% vaccination coverage for all girls at age 15 years, along with 70% screening and 90% treatment

— the WHO's 90-70-90 strategy. However, the issue is particularly pressing for the Commonwealth, whose contribution to the burden of global cervical cancer is estimated at 40% as compared to many developed countries, with India contributing substantially; the Commonwealth Secretariat and Union for International Cancer Control created a joint taskforce on cervical cancer elimination in 2021. In 2022, SAGE recommended single-dose HPV vaccination as equally effective to two or three doses — a breakthrough for access in resource-poor settings [62]. On the foundation of this recommendation, UNICEF launched Big Catch-Up initiative in 2023 to compensate for the loss of vaccination coverage due to COVID-19 pandemic [72]. School-based administration of vaccination, employed in Delhi, Punjab and Sikkim, among others (Section 15.2), is the preferred worldwide strategy for mass vaccination of adolescent girls. A time trend analysis conducted in 2025 showed a decreasing trend in incidence rate of cervical cancer in most assessed countries; now, 148 WHO member states include HPV vaccination in their national immunization programs, and upper-middle income countries report the highest percentage of first-dose coverage of 71.7% (95% CI 59.1-78.6%) [73]. These persistent barriers to LMICs HPV vaccination are described in detail in Section 16.

14.2 Indian Perspective

India exemplifies both the potential of vaccine science and its difficulties in translating into impact on the population. Cervical cancer is the second leading cause of mortality from cancers in India, with incidence ranging from 6-29% and mortality at 9.1%; initiatives of Ayushman Bharat (Health and Wellness Centers and PM-JAY), along with the National Cancer Grid, aim to improve access to cancer care 74. Disparities between regions are significant — Papumpare district of Arunachal Pradesh reports one of the highest incidences in Asia — and have historically contributed to the distrust and delayed adoption of vaccination 72. Although HPV vaccines Gardasil and Cervarix became available in India in 2008, the initial demonstration project conducted jointly by PATH and ICMR was discontinued due to concerns about deaths that turned out to be unrelated to vaccination 75, leaving behind the legacy of public distrust, still impacting vaccine hesitancy in the region (Section 16). Nonetheless, momentum was achieved at the state level: a vaccination program based in schools began in 2016 in Delhi and in 2017 in Punjab districts, while the program for girls aged 9-14 covered the entire state of Sikkim.

The pivotal event occurred in 2022 with the creation of Cervavac, the first domestic HPV vaccine in India, developed by the Serum Institute of India in cooperation with the Department of Biotechnology specifically to be affordable, accessible, and suitable for addressing the rural-urban gap [51]. Upon DCGI approval, Cervavac was gradually integrated into India's immunization program starting from 2023 under the recommendations of the National Technical

Advisory Group on Immunization (NTAGI) 76. Apart from affordability, the domestic production of Cervavac ensures India's vaccination program is secure from issues related to international supply and high prices that have historically restricted access to imported vaccines in other LMICs, while the public health importance of Cervavac extends to serving as an example for other LMICs to develop indigenous vaccines for their needs. The inclusion of HPV vaccination into a comprehensive program involving awareness campaigns and training of healthcare providers, along with integration of HPV vaccination into India's cervical cancer screening infrastructure, is essential for reducing cervical cancer incidence in India.

15. CHALLENGES AND KNOWLEDGE GAPS

15.1 Prophylactic Vaccines

- Limited genotype coverage: the nonavalent vaccine itself still results in high-risk genotype remnants outside its coverage, imperfectly compensated by cross-protection (Chapter 8) [106,112,113].
- Inequities in vaccine uptake and access across the world, with LMICs disproportionately impacted due to cost, cold chain requirements, and multidose nature [2,75,77].
- HPV-related vaccine hesitancy, misinformation, and stigma in some settings, e.g., in India [75,80].
- Lack of information about duration of protection in next-generation vaccines (single-dose regimens, L2/L1L2 constructs) based on long-term follow-up data.

15.2 Therapeutic vaccines

- Tumor heterogeneity, especially that seen in ovarian cancer, constrains efficacy of the single-antigen vaccines [13,22].
- Immunosuppressive nature of tumor microenvironment prevents T cell activation even when antigen-specific priming is achieved [13,22].
- Risk of antigen loss and immunoevasion exists for single-target vaccines; multi-antigen and whole-lysate vaccines are therefore preferred (Chapter 10.2).
- T-cell exhaustion in chronically antigen-exposed tumors does not allow for the durable control of tumors by vaccines alone without checkpoint inhibitors.
- Limited infiltration of vaccine-primed T cells into tumors, especially in ovarian cancer, necessitates combination therapy with anti-angiogenic drugs, e.g., bevacizumab (Chapter 14).

15.3 Personalized vaccines

- Cost of personalized manufacturing is still significantly higher than that of off-the-shelf vaccines.
- Manufacturing time from tumor biopsy to vaccine administration should be quick enough to become clinically relevant, especially in the case of aggressive tumors.
- Sequencing needs (tumor + matched normal tissue) impose an additional logistical burden not present for the prophylactic or standard therapeutic vaccines.
- Neoantigen prediction accuracy is not ideal; not all computationally predicted neoantigens are immunogenic.
- The manufacturing and regulatory framework is not yet fully developed for individualized patient-specific biologicals compared to vaccines' approval process.

16. FUTURE DIRECTIONS

The trajectory of vaccine science in gynecological cancer follows a coherent progression, from first-generation prophylaxis toward increasingly precise, personalized, and combined immunotherapy:

L1-VLP → L2 conserved epitopes → L1/L2 chimeric vaccines → broad-spectrum/pan-HPV vaccines → therapeutic E6/E7 vaccines → mRNA vaccines → AI-assisted neoantigen vaccines

→ personalized gynecological cancer vaccines → combination immunotherapy.

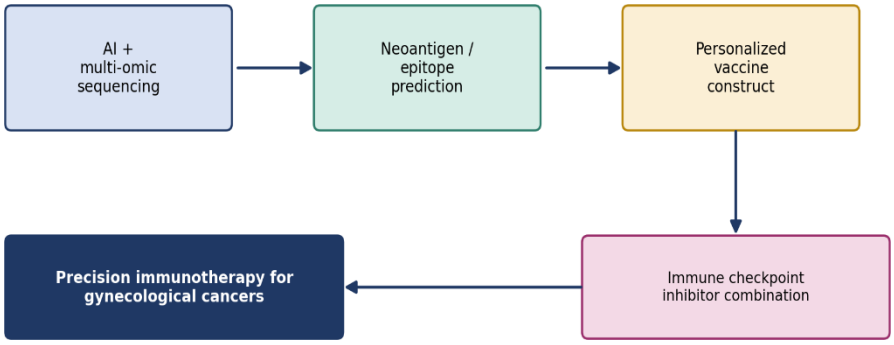

Figure 8. Future of gynecological cancer vaccines: AI + sequencing → neoantigen prediction → personalized vaccine → checkpoint-inhibitor combination → precision immunotherapy.

Indeed, all developments in L2/L1L2, mRNA and neoantigen technology, AI-supported vaccine designs, and combination immunotherapy are, in a sense, efforts to make up for the shortcomings of the first-generation L1-VLP vaccines. In terms of delivery, HPV vaccination programs in national healthcare systems and in LMICs in general, supported by digital platforms such as U-WIN and CoWIN, can help track and monitor progress; moreover, the experience of Gavi, UNICEF and WHO shows that the integration of routine immunization campaigns with public-awareness campaigns targeted at adolescent girls could be highly effective 83. Scientifically, WHO's 90-70-90 elimination strategy, including the recommendations made by SAGE on the use of single dose vaccines, combined with scale-up of the indigenous product Cervavac is the next step towards affordable and accessible prophylactic vaccines [51,62,76]; moreover, the future prophylactic vaccines can expand the spectrum of the genotypes covered by the L2/L1L2 and mRNA vaccines 23,106–111; finally, the late-phase therapeutic vaccines targeted at E6/E7 keep developing [104,105]. Finally, endometrial and ovarian cancers would benefit from the personalized neoantigen and combination immuno-therapy approach discussed in Sections 10-14, which would require continued investments in sequencing capacity, fast and efficient algorithms for predicting the neoantigens, as well as regulatory frameworks for individualized biologics – all problems mentioned in Section 16.3.

17. CONCLUSION

Vaccination of gynecological cancers covers the full spectrum – from the proven high success rate of HPV prophylactic vaccine in cervical cancer to the cutting edge of personalized treatment vaccine for endometrial and ovarian cancer. Considering vaccination development based on this spectrum allows understanding what was achieved and what

is really possible at the moment. Development of bivalent, quadrivalent, and nonavalent L1-VLP vaccines and affordable indigenous vaccines like Cervavac made an important contribution to prevention of cervical

cancer [62,75,76], and further achievements of the field, including the use of L2-based and L1/L2 chimeric platforms providing broad cross-genotype protection, are being moved from preclinical proof-of-concept to first-in-human study 106-111. Therapeutic vaccines like VGX-3100 and GX-188E showed that vaccination can also be applied to established lesions, not only for infections 69,70,104,105, and the same methodology – tumor-associated antigens, cancer-testis antigens, and personalized neoantigens identified using AI-assisted sequencing methods – is being used in cases of endometrial and ovarian cancer, which do not have any infection cause to target 22,86,87,115-119. Achievements in the field are still unbalanced: cross-protection remains partial and inconsistent, not comprehensive (Section 8); non-HPV gynecological cancers have no universal targets and face an immunosuppressive tumor microenvironment (Section 16.2), and problems in access to vaccines, cultural barriers, and logistical constraints continue to restrict the usage of even the most established vaccine in the field [77.] Further advances in the field will require closing the gap in genotype coverage using next-generation vaccines, further development of therapeutic and personalized vaccines overcoming the barriers discussed in Section 16, and integration of all this knowledge in combination with screening, treatment and immune-therapy approaches – the combination, which will finally decide the fate of cervical cancer elimination and development of vaccine for other gynecological cancers [21,77].

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REFERENCES

1. Ferlay, J., et al., Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer, 2015. 136(5): p. E359-E386.
2. Bosch, F.X., et al., HPV-FASTER: broadening the scope for prevention of HPV-related cancer. Nature reviews Clinical oncology, 2016. 13(2): p. 119-132.
3. Sullivan, R., et al., Global cancer surgery: delivering safe, affordable, and timely cancer surgery. The Lancet Oncology, 2015. 16(11): p. 1193-1224.
4. Atun, R. et al., Expanding global access to radiotherapy. The Lancet Oncology, 2015. 16(10): p. 1153-1186.
5. Alliance, W.P.C. and W.H. Organization, Global atlas of palliative care at the end of life. London: Worldwide Palliative Care Alliance, 2014. 111.
6. Ginsburg, O., et al., The global burden of women's cancers: a grand challenge in global health. The Lancet, 2017. 389(10071): p. 847-860.
7. Tyagi, S., Maternity Health and Safety.
8. Reid, B.M., J.B. Permuth, and T.A. Sellers, Epidemiology of ovarian cancer: a review. Cancer biology & medicine, 2017. 14(1): p. 9-32.
9. Urick, M.E. and D.W. Bell, Clinical actionability of molecular targets in

endometrial cancer. Nature Reviews Cancer, 2019. 19(9): p. 510-521.
10. Bosch, F.X., et al., Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. Obstetrical & Gynecological Survey, 1995. 50(10): p. 725-727.
11. Walboomers, J.M. et al., Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. The Journal of Pathology, 1999. 189(1): p. 12-19.
12. Funston, G., et al., Recognizing gynecological cancer in primary care: risk factors, red flags, and referrals. Advances in Therapy, 2018. 35(4): p. 577-589.
13. Jelovac, D. and D.K. Armstrong, Recent progress in the diagnosis and treatment of ovarian cancer. CA: a cancer journal for clinicians, 2011. 61(3): p. 183-203.
14. Hennessy, B.T., R.L. Coleman, and M. Markman, Ovarian cancer. The Lancet, 2009. 374(9698): p. 1371-1382.
15. Beaulieu, N., et al., Breakaway: The global burden of cancer-challenges and opportunities. The Economist Intelligence Unit, 2009. 2: p. 35-55.
16. Parkin, D.M., et al., Global cancer statistics, 2002. CA: a cancer journal for clinicians, 2005. 55(2): p. 74-108.
17. Fader, A.N., et al., Endometrial cancer and obesity: epidemiology, biomarkers, prevention and survivorship. Gynecologic Oncology, 2009. 114(1): p. 121-127.
18. Iyoke, C.A. and G.O. Ugwu, Burden of gynaecological cancers in developing countries. World Journal of Obstetrics and Gynecology, 2013. 2(1): p. 1-7.
19. Lee, J.T., et al., Diversity of sexual activity and correlates among women with gynecological cancer. Gynecologic Oncology, 2020. 159(2): p. 503-508.
20. Kulkarni, A., et al., Sexual health and function among patients receiving systemic therapy for primary gynecologic cancers. Gynecologic Oncology, 2022. 165(2): p. 323-329.
21. Sung, H., et al., Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 2021. 71(3): p. 209-249.
22. Poland, G.A., I.G. Ovsyannikova, and R.M. Jacobson, Personalized vaccines: the emerging field of vaccinomics. Expert opinion on biological therapy, 2008. 8(11): p. 1659-1667.
23. Tian, Y., et al., Development of therapeutic vaccines for the treatment of diseases. Molecular Biomedicine, 2022. 3(1): p. 40.
24. Senkomago, V., Human papillomavirus--attributable cancers---United States, 2012--2016. MMWR. Morbidity and mortality weekly report, 2019. 68.
25. Houlihan, C.F., et al., Human papillomavirus DNA detected in fingertip, oral and bathroom samples from unvaccinated adolescent girls in Tanzania. Sexually Transmitted Infections, 2019. 95(5): p. 374-379.
26. Das, B.C., et al., Prospects and prejudices of human papillomavirus vaccines in India. Vaccine, 2008. 26(22): p. 2669-2679.
27. Longworth, M.S. and L.A. Laimins, Pathogenesis of human papillomaviruses in differentiating epithelia. Microbiology and Molecular Biology Reviews, 2004. 68(2): p. 362-372.
28. McBride, A.A., Human papillomaviruses: diversity, infection and host interactions. Nature Reviews Microbiology, 2022. 20(2): p. 95-108.
29. Aranda-Rivera, A.K., et al., Regulation of autophagy by high-and low-risk human papillomaviruses. Reviews in Medical Virology, 2021. 31(2): p. e2169.
30. Seyoum, A. et al., High rate of non-vaccine targeted high-risk HPV genotypes circulate

among women in Eastern Ethiopia. Scientific Reports, 2024. 14(1): p. 958.
31. Burd, E.M., Human papillomavirus and cervical cancer. Clinical Microbiology Reviews, 2003. 16(1): p. 1-17.
32. Lu, Y., et al., Global burden of oropharyngeal cancer attributable to human papillomavirus by anatomical subsite and geographic region. Cancer Epidemiology, 2022. 78: p. 102140.
33. Moscicki, A.-B., et al., Updating the natural history of human papillomavirus and anogenital cancers. Vaccine, 2012. 30: p. F24-F33.
34. Serrano, B., et al., Human papillomavirus genotype attribution for HPVs 6, 11, 16, 18, 31,33, 45, 52 and 58 in female anogenital lesions. European Journal of Cancer, 2015. 51(13): p.1732-1741.
35. Gillison, M.L., et al., Human papillomavirus and diseases of the upper airway: head and neck cancer and respiratory papillomatosis. Vaccine, 2012. 30: p. F34-F54.
36. Bonanni, P., S. Boccalini, and A. Bechini, Efficacy, duration of immunity and cross protection after HPV vaccination: a review of the evidence. Vaccine, 2009. 27: p. A46-A53.
37. Szymonowicz, K.A. and J. Chen, Biological and clinical aspects of HPV-related cancers. Cancer biology & medicine, 2020. 17(4): p. 864-878.
38. McLaughlin-Drubin, M.E. and K. Münger, Oncogenic activities of human papillomaviruses. Virus Research, 2009. 143(2): p. 195-208.
39. Yu, L., V. Majerciak, and Z.-M. Zheng, HPV16 and HPV18 genome structure, expression, and post-transcriptional regulation. International journal of molecular sciences, 2022. 23(9): p. 4943.
40. Graham, S.V., Human papillomavirus: gene expression, regulation and prospects for novel diagnostic methods and antiviral therapies. Future Microbiology, 2010. 5(10): p. 1493-1506.
41. Stanley, M., Pathology and epidemiology of HPV infection in females. Gynecologic Oncology, 2010. 117(2): p. S5-S10.
42. Moody, C.A. and L.A. Laimins, Human papillomavirus oncoproteins: pathways to transformation. Nature Reviews Cancer, 2010. 10(8): p. 550-560.
43. Chow, L.T. and T.R. Broker, Human papillomavirus infections: warts or cancer? Cold Spring Harbor perspectives in biology, 2013. 5(7): p. a012997.
44. Letafati, A., et al., Emerging paradigms: unmasking the role of oxidative stress in HPV-induced carcinogenesis. Infectious Agents and Cancer, 2024. 19(1): p. 30.
45. Yu, L. et al., HPV oncogenes expressed from only one of multiple integrated HPV DNA copies drive clonal cell expansion in cervical cancer. MBio, 2024. 15(5): p. e00729-24.
46. Graham, S.V., The human papillomavirus replication cycle, and its links to cancer progression: a comprehensive review. Clinical Science, 2017. 131(17): p. 2201-2221.
47. Boulet, G., et al., Human papillomavirus: E6 and E7 oncogenes. The international journal of biochemistry & cell biology, 2007. 39(11): p. 2006-2011.
48. Choo, K.-B., C.-C. Pan, and S.-H. Han, Integration of human papillomavirus type 16 into cellular DNA of cervical carcinoma: preferential deletion of the E2 gene and invariable retention of the long control region and the E6/E7 open reading frames. Virology, 1987. 161(1): p. 259-261.
49. Khan, A., et al. Insights into the role of complement regulatory proteins in HPV mediated cervical carcinogenesis. in Seminars in cancer biology. 2022. Elsevier.
50. Frazer, I.H., The HPV vaccine story. 2019, ACS Publications. p. 210-212.

51. Khanam, Z. and N. Gupta, Evolving Trends In Hpv Vaccination In India And The World. 2024.
52. Crum, C., C. Jones, and P. Kirkpatrick, Quadrivalent human papillomavirus recombinant vaccine. Nature Reviews Drug Discovery, 2006. 5(8): p. 629-630.
53. Villa, L.L., et al., Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. The Lancet Oncology, 2005. 6(5): p. 271-278.
54. Villa, L.L., et al., Immunologic responses following administration of a vaccine targeting human papillomavirus Types 6, 11, 16, and 18. Vaccine, 2006. 24(27-28): p. 5571-5583.
55. Harper, D.M., et al., Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. The Lancet, 2004. 364(9447): p. 1757-1765.
56. Harper, D.M., et al., Sustained efficacy up to 4· 5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised controlled trial. The Lancet, 2006. 367(9518): p. 1247-1255.
57. Villa, L., et al., High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. British journal of cancer, 2006. 95(11): p. 1459-1466.
58. Suzich, J.A. et al., Systemic immunization with papillomavirus L1 protein completely prevents the development of viral mucosal papillomas. Proceedings of the National Academy of Sciences, 1995. 92(25): p. 11553-11557.
59. Keam, S.J. and D.M. Harper, Human papillomavirus types 16 and 18 vaccine (recombinant, AS04 adjuvanted adsorbed) \Cervarix™\. Drugs, 2008. 68(3): p. 359-372.
60. Chauhan, S. and Y.P. Khasa, Challenges and Opportunities in the Process Development of Chimeric Vaccines. Vaccines, 2023. 11(12): p. 1828.
61. Stanley, M., Immune responses to human papillomavirus. Vaccine, 2006. 24: p. S16-S22.
62. Cervavac \Quadrivalent Human Papillomavirus (HPV Types 6, 11, 16, & 18) Vaccine (Recombinant)\ \Product Information\. \cited 2025 07/10\; Available from: https://www.merckvaccines.com/gardasil9/{.underline} (https://www.merckvaccines.com/gardasil9/).
63. Bagarazzi, M.L. et al., Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. Science Translational Medicine, 2012. 4(155): p. 155ra138-155ra138.
64. Smalley Rumfield, C., et al., Therapeutic vaccines for HPV-associated malignancies. ImmunoTargets and Therapy, 2020: p. 167-200.
65. Park, Y.-C., et al., A phase 1/2a, dose-escalation, safety and preliminary efficacy study of oral therapeutic vaccine in subjects with cervical intraepithelial neoplasia 3. Journal of Gynecologic Oncology, 2019. 30(6).
66. Garbuglia, A.R., et al., The use of both therapeutic and prophylactic vaccines in the therapy of papillomavirus disease. Frontiers in Immunology, 2020. 11: p. 188.
67. Khalil, A.I., et al., Efficacy and safety of therapeutic HPV vaccines to treat CIN 2/CIN 3 lesions: a systematic review and meta-

analysis of phase II/III clinical trials. BMJ Open, 2023. 13(10): p. e069616.
68. Bhuyan, P.K., et al., Durability of response to VGX-3100 treatment of HPV16/18 positive cervical HSIL. Human vaccines & immunotherapeutics, 2021. 17(5): p. 1288-1293.
69. Lim, M.C., et al., GX-188E DNA vaccine plus pembrolizumab in HPV 16-and/or 18-positive recurrent or advanced cervical cancer: a phase 2 trial. EClinicalMedicine, 2024. 74.
70. Saslow, D., et al., Human papillomavirus vaccination 2020 guideline update: American Cancer Society guideline adaptation. CA: a cancer journal for clinicians, 2020. 70(4): p. 274-280.
71. Geneva: WHO, World Health Organization. Global partners announce a new effort -- "The Big Catch-up" -- to vaccinate millions of children and restore immunization progress lost during the pandemic. 2023 April 23
72. Han, J., et al., Global HPV vaccination programs and coverage rates: a systematic review. EClinicalMedicine, 2025. 84.
73. Gupta, K., R. Mandal, and P. Chatterjee, Navigating the landscape of cervical cancer in India: Epidemiology, prevention, current status, and emerging solutions. Journal of Obstetrics and Gynaecology Research, 2024. 50: p. 55-64.
74. Burki, T.K., India rolls out HPV vaccination. The Lancet Oncology, 2023. 24(4): p. e147.
75. ICO / IARC HPV and Cancer Information Centre (HPV Information Centre).Human Papillomavirus and Related Diseases in India. 10 March 2023.
76. Bruni, L., et al., HPV vaccination introduction worldwide and WHO and UNICEF estimates of national HPV immunization coverage 2010--2019. Preventive Medicine, 2021. 144: p. 106399.
77. Mahajan, I., et al., Early adoption of innovation in HPV prevention strategies: closing the gap in cervical cancer. ecancermedicalscience, 2024. 18: p. 1762.
78. Jim, C.C., et al., Human papillomavirus vaccination practices among providers in Indian health service, tribal and urban Indian healthcare facilities. Journal of Women\'s Health, 2012. 21(4): p. 372-378.
79. Canon, C., et al., Knowledge and attitudes towards human papillomavirus (HPV) among academic and community physicians in Mangalore, India. Journal of Cancer Education, 2017. 32(2): p. 382-391.
80. Shetty, S., et al., An exploratory study of undergraduate healthcare student perspectives regarding human papillomavirus and vaccine intent in India. Women\'s Health, 2021. 17: p. 17455065211055304.
81. Christen, P., et al., Health and economic impact of the human papillomavirus (HPV) vaccine in Mozambique. medRxiv, 2025: p. 2025.06. 17.25329752.
82. Poddar, A. and S. Rao, Overcoming barriers of cervical cancer elimination in India: A practice-to-policy-level advocacy. Journal of Cancer Policy, 2025. 43: p. 100521.
83. Olawade, D.B., et al., Leveraging artificial intelligence in vaccine development: A narrative review. Journal of Microbiological Methods, 2024. 224: p. 106998.
84. Aswathy, R., et al., Advancing miRNA cancer research through artificial intelligence: from biomarker discovery to therapeutic targeting. Medical Oncology, 2024. 42(1): p. 30.
85. Kong, H., Advances in personalized Cancer vaccine development: AI applications from neoantigen discovery to mRNA formulation. BioChem, 2025. 5(2): p. 5.
86. Cai, Y. et al., Artificial intelligence applied in neoantigen identification facilitates

personalized cancer immunotherapy. Frontiers in Oncology, 2023. 12: p. 1054231.
87. Du, J., et al., Using machine learning-based approaches for the detection and classification of human papillomavirus vaccine misinformation: Infodemiology study of Reddit discussions. Journal of Medical Internet Research, 2021. 23(8): p. e26478.
88. Santin, A.D., et al., Human papillomavirus type 16 and 18 E7-pulsed dendritic cell vaccination of stage IB or IIA cervical cancer patients: a phase I escalating-dose trial. Journal of Virology, 2008. 82(4): p. 1968-1979.
89. Lei, W., et al., Cancer vaccines: platforms and current progress. Molecular Biomedicine, 2025. 6(1): p. 3.
90. Mao, S., et al., A highly efficient needle-free-injection delivery system for mRNA-LNP vaccination against SARS-CoV-2. Nano Today, 2023. 48: p. 101730.
91. Peng, S., et al., Immune responses, therapeutic anti-tumor effects, and tolerability upon therapeutic HPV16/18 E6/E7 DNA vaccination via needle-free biojector. MBio, 2023. 14(5): p. e02121-23.
92. Kim, H., et al., Dissolving Microneedle for Maintaining the Integrity of HPV Virus-Like Particles Enabling Durable Sterile Protection Across Various Mucosal Tissues. Advanced Healthcare Materials, 2025: p. 2500963.
93. Elvidge, S., Merck tests needle-free vaccines. Nature Biotechnology, 2012. 30(12): p. 1155-1156.
94. Peng, S., et al., Improved efficacy of therapeutic HPV DNA vaccine using intramuscular injection with electroporation compared to conventional needle and needle-free jet injector methods. Cell & Bioscience, 2024. 14(1): p. 154.
95. Paul, P., et al., Acceptability of HPV vaccine implementation among parents in India. Health care for women international, 2014. 35(10): p. 1148-1161.
96. Madhivanan, P., et al., Human papillomavirus vaccine acceptability among parents of adolescent girls: obstacles and challenges in Mysore, India. Preventive Medicine, 2014. 64: p. 69-74.
97. Mukherjee, S., et al., Correlates of completing routine vaccination among children in Mysore, India. Journal of infection and public health, 2015. 8(1): p. 62-71.
98. Roy, S., A. Shankar, and G.K. Rath, HPV vaccination of girl child in India: Intervention for primary prevention of cervical cancer. Asian Pacific journal of cancer prevention: APJCP, 2018. 19(9): p. 2357.
99. Nassuuna, J., et al., Helminth-driven gut inflammation and microbial translocation associate with altered vaccine responses in rural Uganda. npj Vaccines, 2025. 10(1): p. 56.
100. Kulal, S., et al., The Sociocultural Determinants of Cervical Cancer Outcomes in India: A Critical Review of Diagnostic Delays and Treatment Disparities. Cureus, 2025. 17(7).
101. Ruzindana, K. and R.I. Anorlu, Global disparities in gynecologic cancer outcomes: a call for action. International Journal of Gynecology & Obstetrics, 2025. 171: p. 210-220.
102. Wood, D., et al., Assuring the quality, safety and efficacy of HPV vaccines: The scientific basis of regulatory expectations pre- and post-licensure. Vaccine, 2006. 24: p. S187-S192.
103. Trimble, C.L., et al., Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-

controlled phase 2b trial. The Lancet, 2015. 386(10008): p. 2078-2088.
104. Choi, Y.J., et al., A phase II, prospective, randomized, multicenter, open-label study of GX-188E, an HPV DNA vaccine, in patients with cervical intraepithelial neoplasia 3. Clinical Cancer Research, 2020. 26(7): p. 1616-1623.
105. Schellenbacher, C., R.B. Roden, and R. Kirnbauer, Developments in L2-based human papillomavirus (HPV) vaccines. Virus Research, 2017. 231: p. 166-175.
106. Jiang, R.T., et al., Progress and prospects for L2-based human papillomavirus vaccines. Expert review of vaccines, 2016. 15(7): p. 853-862.
107. Pouyanfard, S. and M. Muller, Human papillomavirus first and second generation vaccines —current status and future directions. Biological Chemistry, 2017. 398(8): p. 871-889.
108. Schellenbacher, C., R. Roden, and R. Kirnbauer, Chimeric L1-L2 virus-like particles as potential broad-spectrum human papillomavirus vaccines. Journal of Virology, 2009. 83(19): p. 10085-10095.
109. Tumban, E., et al., A pan-HPV vaccine based on bacteriophage PP7 VLPs displaying broadly cross-neutralizing epitopes from the HPV minor capsid protein, L2. PLoS ONE, 2011. 6(8): p. e23310.
110. Ahmels, M. et al., Next generation L2-based HPV vaccines cross-protect against cutaneous papillomavirus infection and tumor development. Frontiers in Immunology, 2022. 13: p. 1010790.
111. Malagon, T., et al., Cross-protective efficacy of two human papillomavirus vaccines: a systematic review and meta-analysis. The Lancet Infectious Diseases, 2012. 12(10): p. 781-789.
112. Tsang, S.H., et al., Durability of cross-protection by different schedules of the bivalent HPV vaccine: the CVT trial. Journal of the National Cancer Institute, 2020. 112(10): p. 1030-1037.
113. Wheeler, C.M., et al., Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. The Lancet Oncology, 2012. 13(1): p. 100-110.
114. Wu, Y., et al., Dendritic cell vaccines in ovarian cancer. Frontiers in Immunology, 2021. 11: p. 613773.
115. Tanyi, J.L. et al., Personalized cancer vaccine effectively mobilizes antitumor T cell immunity in ovarian cancer. Science Translational Medicine, 2018. 10(436): p. eaao5931.
116. Tanyi, J.L. et al., Personalized cancer vaccine strategy elicits polyfunctional T cells and demonstrates clinical benefits in ovarian cancer. NPJ Vaccines, 2021. 6(1): p. 36.
117. Yamashita, H. et al., Microsatellite instability is a biomarker for immune checkpoint inhibitors in endometrial cancer. Oncotarget, 2018. 9(5): p. 5652-5664.
118. Liu, Y. and B. Weigelt, A tale of two pathways: review of immune checkpoint inhibitors in DNA mismatch repair-deficient and microsatellite instability-high endometrial cancers. Cancer, 2024. 130(10): p. 1733-1746.

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