# Human papillomavirus in cancer: Pathogenesis and vaccination approaches

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## Abstract

Human papillomavirus (HPV) is a small, non-enveloped virus that infects cutaneous and mucosal epithelium. It is sexually transmitted, and persistent infections with high-risk strains, such as HPV-16 and HPV-18, have been identified as contributing factors to 70% of global cervical cancer cases. Cervical cancer is a serious problem in developing countries such as South Africa, where early detection of precancerous lesions and comorbidities remains a challenge. The oncogenic activity of high-risk HPV strains is driven by the overexpression of E6 and E7 oncoproteins that bind to and inactivate key cell cycle regulators in host cells, such as tumour suppressor protein p53 and retinoblastoma protein (pRb), resulting in the transformation of normal cells into cancerous cells. Since cervical cancer is a global health problem, vaccines that prevent and target HPV infections have been developed to eliminate HPV-related cancers. Prophylactic vaccines are based on virus-like particles derived from genotype-specific L1 proteins and are essential for preventing HPV infections by inducing neutralising antibodies. School-based vaccination programmes in South Africa provide a single-dose of a L1-based bivalent vaccine, Cervarix, to girls over 9 years of age. While prophylactic vaccines prevent HPV infections, they have no therapeutic effect in patients with established infections. Therefore, therapeutic vaccines, such as ADXS11-001 and MVA-E2, which induce cell-mediated immune responses against viral oncoproteins E6 and E7 in HPV-related cancer, are currently under clinical investigation worldwide. The types of therapeutic vaccines that have been developed and evaluated in clinical trials include vector-, peptide- and protein-, whole-cell-, and nucleic acid-based vaccines; however, none have been approved for clinical use. Improving the efficacy of prophylactic and therapeutic vaccines remains critical for targeting HPV-related cancers.

**Keywords:** cancer, human papillomavirus, infection, vaccines



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## Introduction

The human papillomavirus (HPV) infection is the most common sexually transmitted infection worldwide. In 2022, an estimated 1 505 394 HPV-related cancer cases and 755 303 deaths were reported globally.[1] Although HPV infection is more common in women, with an estimated 80% of women contracting HPV by the age of 50, it can be contracted by sexually active men and women.[2] Geographically, there are significant differences in HPV infection rates, with developing nations exhibiting a higher prevalence of new infections and mortality than developed nations.[1] The region with the highest incidence of HPV-related cancer is sub-Saharan Africa (SSA) with 120 000 cases reported in 2018, and a disproportionate number of young South African women (< 25 years) being affected.[3,4] The high burden of HPV-related cancer in SSA is likely due to the high cost of co-financing vaccines subsidies, inadequate infrastructure for vaccine cold-storage, logistical issues when transporting large quantities of vaccines, vaccine hesitancy due to misinformation and a lack of education and limited access to screening programmes.[3,5,6] Despite companies such as Gavi (the Vaccine Alliance) subsidising HPV vaccines in 57 low-income countries, national HPV vaccination programmes are not yet universally available in countries such as Angola, Ghana, Namibia and Madagascar.[6,7]

## Epidemiology and oncogenic classification of human papillomavirus

HPV is a non-enveloped deoxyribonucleic acid (DNA) virus that infects the skin and mucous membranes, with more than 200 different strains identified.[8] Currently, high-risk HPV strains responsible for the majority of HPV-related cancers include HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, and -68. Furthermore, HPV-16, -18, -31, -33, and -58 are commonly identified in cervical cancer, with HPV-16 and -18 responsible for more than 70% of all cervical cancer cases.[9] In contrast, low-risk HPV strains, such as HPV-6 and -11, induce genital warts and papillomatosis of the larynx.[10] Most HPV infections are asymptomatic and transient; however, if spontaneous clearance of the virus does not occur, persistent infection (lasting more than 24 months) with high-risk HPV can result in precancerous lesions and ultimately lead to the development of various cancers over 15–20 years.[6,10] In immunocompromised individuals, such as human immunodeficiency virus (HIV)-positive women, the development of cervical cancer from an HPV infection is faster (5–10 years) and 6 times more likely compared to HIV-negative women.[6,11,12] If cancer is diagnosed early, it can be treated with surgery, chemotherapy or radiation, therefore, the prevention and early detection of HPV infections are essential to detect pre-cancerous lesions and reduce the risk of oncogenesis.[5,13]

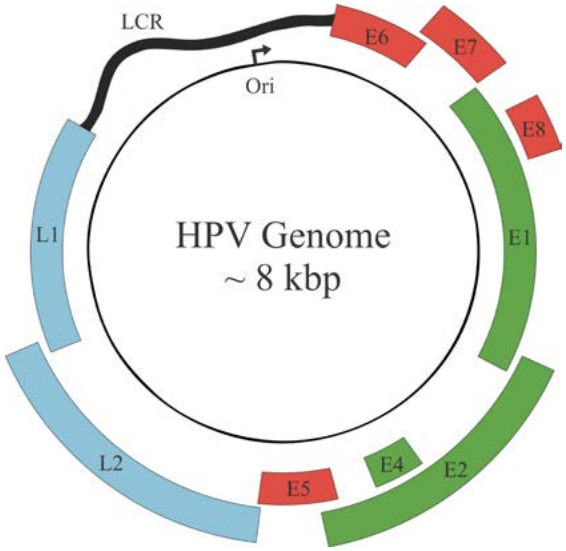


**Figure 1:** Human papillomavirus genome. HPV is a double-stranded DNA virus of approximately 8 kbp, consisting of early (E1-E8), late (L1 and L2), and long control regions (LCR). The early region includes genes essential for viral replication (green) and oncogenesis (red), whereas the late proteins are capsid proteins necessary for the formation of new virions.

Ori – Origin of replication, kbp – Kilobase pairs

## Transmission and oncogenesis of human papillomavirus

HPV has a double-stranded circular DNA genome of approximately 8 kilobase pairs (kbp) encoding early (E) region proteins, late (L) region proteins, and an upstream regulatory region (URR) (Figure 1).[2,14] The early region encodes seven non-structural proteins linked to viral replication, namely E1, E2, E1^E4, E5, E6, E7, and E8^E2. The viral proteins E6 and E7 target several host oncogenic and tumour suppressor proteins such as p53 and pRB in the host cell.[14] Viral capsid proteins consist of L1 and L2 proteins and the URR, responsible for regulating DNA replication and is used for HPV classification.[2,14]

HPV transmission primarily occurs during sexual contact through skin-to-skin or skin-to-mucosa contact; however, non-sexual transmission, including indirect transmission via hands, perinatal transmission from mother-to-child and transmission via blood are also possible.[2,15] The HPV virus enters the basal layer of the epithelium through micro-wounds or micro-abrasions, and attaches to cellular receptors on the basal cells (Figure 2).[16] Entry of the HPV into host cells is facilitated through endocytosis when the L1 viral capsid protein attaches to heparan sulphate

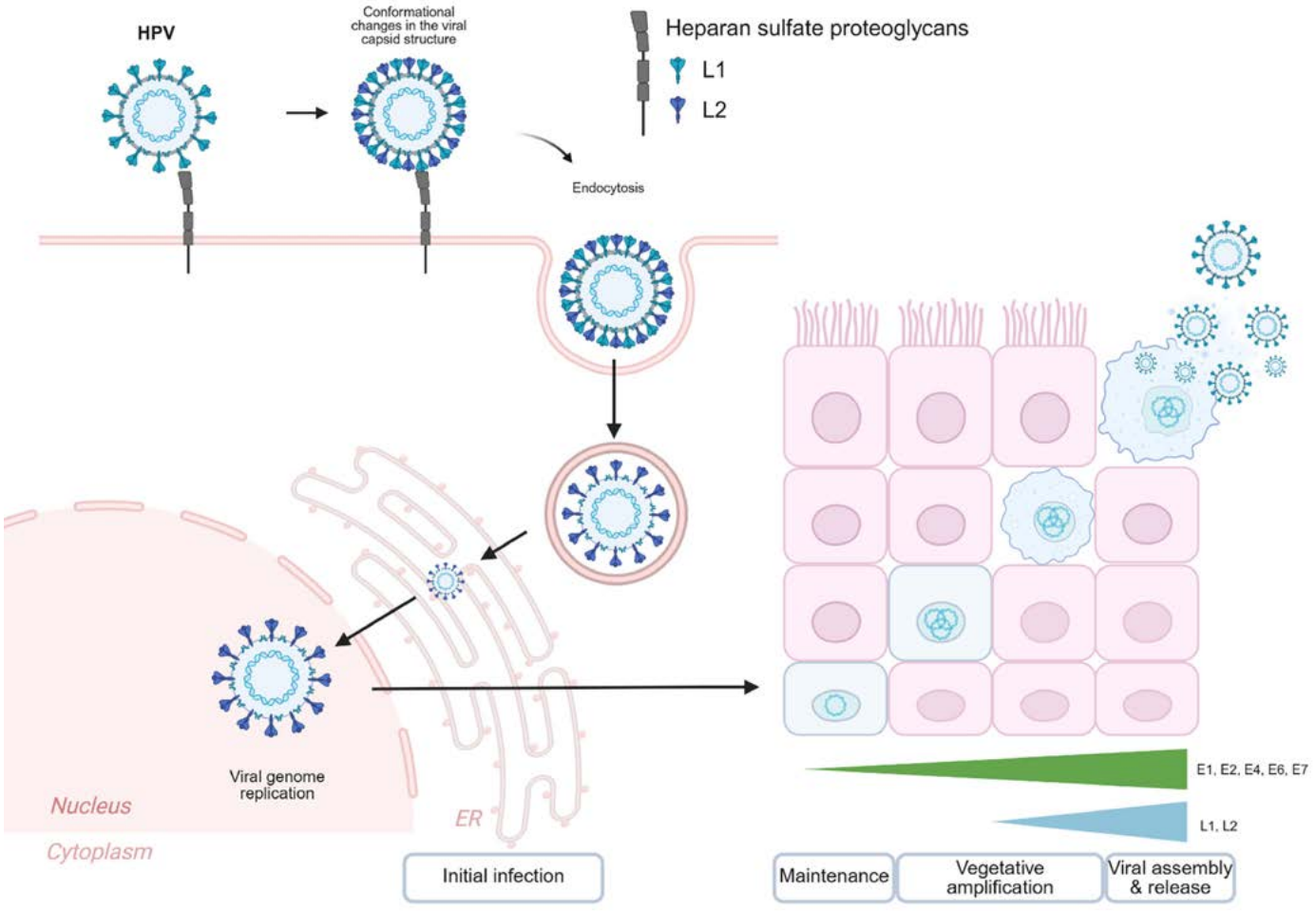


***Figure 2:*** Lifecycle of high-risk HPV. HPV enters basal epithelial cells upon trauma and undergoes various stages: infection, maintenance, vegetative replication, viral assembly, and release. The virus binds to heparan sulphate proteoglycans through L1 capsid proteins. Subsequently, conformational changes expose L2 capsid proteins, and the viral particle is internalised into the host cell. The L2-DNA complex is delivered to the Golgi network, from where it enters the nucleus during mitosis. Early genes E1, E2, E4, E6, and E7 and late genes including L1 and L2 are expressed in stratified epithelial cells during infection, viral genome replication, and virion release. (Biorender, 2026)

proteoglycans.[16] This leads to conformational changes in the viral capsid structure, which expose the L2 capsid protein on the surface of the viral particle.[17] Next, the N-terminal of L2 is cleaved by proprotein convertase furin, which facilitates the transfer of the viral particle to a secondary receptor and results in subsequent internalisation.[18]

HPV infection undergoes four stages in its life cycle: initial, maintenance, vegetative amplification, and viral assembly and release.[5] Inside the host basal cell, the viral particle travels within endosomes, where the viral capsid is disassembled in a low pH environment. From there, the L2-related viral genome is transported to the trans-Golgi network and ultimately released in proximity to the host nuclear membrane.[19] Entry of the L2-viral genome complex into the nucleus occurs during early mitosis when the nuclear envelope is disrupted.[20] Once inside the nucleus, viral genome replication depends on host DNA replication machinery, and E1 helicase and E2 proteins which initiate viral genome replication are expressed.[21] In high-risk HPV strains, the expression of E6 and E7 promotes cell cycle progression and prevents apoptosis, as these oncoproteins bind to the host p53 tumour suppressor protein and the cell cycle regulator protein pRb, respectively.[22] During the initial infection phase, a low copy number (50–100 per cell) of the viral genome is generated as genome amplification is inhibited by the interaction of host nuclear receptor corepressor and silencing mediator for retinoid and thyroid hormone receptors (NCOR/SMRT) complexes with E8^E2C proteins.[8] Thereafter, the maintenance phase is initiated, and a constant number of viral genomes exist as extrachromosomal plasmids in the undifferentiated basal cells to create a persistent infection.[23] Normally, when daughter cells detach from basal cells, there is a loss of nuclei as cell proliferation is inhibited; however, HPV-infected cells remain active in the cell cycle due to the E7 protein.[22] Therefore, vegetative amplification of the viral genomes occurs in differentiated keratinocytes of the stratified epithelium and produces thousands of viral genomes. Additionally, capsid proteins L1 and L2 are expressed, which results in the assembly and release of newly formed virions during desquamation of the outer layers.[22] The time taken from initial infection to the production of new virions is at least 3 weeks, since this is the time taken for basal cells to differentiate, migrate to the epithelium surface and desquamate.[24]

Most HPV infections are resolved on their own through the cell-mediated immune system; however, persistent infection with high-risk HPV can lead to the integration of part of the viral genome within the host genome, facilitating the development of cancer. Integration of the viral genome typically results in the overexpression of oncoproteins E6 and E7.[25] Unregulated expression of E6 and E7 interferes with the functions of tumour suppressor genes, such as p53 and pRB, respectively. In normal cells, p53 detects DNA damage and inhibits cell proliferation to allow for DNA repair or cell apoptosis; however, E6 interaction results in p53 degradation and ultimately genome instability.[26] The retinoblastoma protein and structurally related p107 and p130 proteins regulate cell cycle progression by binding and inhibiting E2F transcriptional factors that regulate the expression of genes necessary for DNA synthesis and cell division. However, high-risk HPV E7 proteins target pRB and related proteins for protein degradation, which releases E2F transcription factors and results in the expression of genes necessary for cell cycle progression.[27] Ultimately, this results in the uncontrolled growth of infected cells.

Therefore, long-term persistent infection with high-risk HPV results in cellular alterations and precancerous lesions that, if left untreated, could develop into cancer. Viral genome integration and subsequent E6 and E7-mediated mutations are seen in 74% of HPV-16 and 100% of HPV-18 infected cervical carcinomas.[28] It is estimated that persistent high-risk HPV infections result in 6 types of cancers and cause 90% of cervical and anal cancers, 70% of vaginal, vulvar and oropharyngeal cancers and 60% of penile cancers.[5,29] These organs have interior surfaces lined with squamous cells that become infected with HPV.[2]

HPV infection and HIV co-infections contribute to cervical cancer oncogenesis due to the pronounced proliferative effects of viral oncoproteins E5, E6, and E7 in immunocompromised HIV-positive patients. Furthermore, immune response in patients co-infected with HPV and HIV, which consist of impaired T-cells and immature dendritic cells, is insufficient to clear persistent HPV infections.[30] HIV-infections also accelerate the progression of precancerous lesions to cervical cancer by inducing epithelial-mesenchymal transition, which facilitates cell growth and metastasis, through the activation of the canonical Wnt signalling pathway.[30] One of the main strategies to reduce the incidence of cervical cancer is routine screening for precancerous lesions that can be treated before progressing to cervical cancer.[12]

## Screening and diagnosis of HPV-induced lesions

A persistent high-risk HPV infection can result in precancerous lesions; therefore, early diagnosis and regular screening are essential to stop the development of cancer.[2,5] Various methods are available to detect precancerous changes in the form of lesions in cervical cells.

Cytological strategies have been implemented to identify precancerous lesions formed due to HPV infections, such as the Papanicolaou (Pap) smear, colposcopy, visual inspection test with acetic acid (VIA), and thin prep cytologic test (TCT). For cervical cancer, which has the fourth highest mortality rate in women with approximately 350 000 deaths in 2022, Pap smears are routinely used to detect aberrant cells, which could be a sign of precancerous lesions. However, the Pap smear has low specificity and sensitivity, and may result in inaccurate results.[31] Alternatively, colposcopy helps identify precancerous lesions that are imperceptible to the naked eye, improving the accuracy of histological sampling and diagnosis.[32] The visual inspection test with acetic acid has a higher specificity than the Pap smear, as an acetic acid solution can be applied directly to the cervix to detect underlying pathology. However, VIA has lower accuracy in menopausal women, and a higher rate of false positives is observed.[33] Finally, TCT is a liquid-

based cytological screening method that is more effective than Pap smear in detecting abnormal cervical cells and facilitates early detection and prevention of cervical cancer.[34]

Additionally, HPV screening methods, such as Hybrid Capture 2 (HC2) and Polymerase Chain Reaction (PCR)-based HPV screening, have been developed to reduce the false negatives observed with cytological screening. Hybrid capture 2 is an HPV test that consists of a probe that detects HPV infections from 13 high-risk strains; however, single strains cannot be identified, and a minimum of 5 000 viral copies are needed for a positive result.[35] Polymerase chain reaction-based screening detects HPV-DNA or messenger ribonucleic acid (mRNA) with high sensitivity from few viral copies, allowing for the detection of numerous HPV strains or the active transcription of E6/7, respectively.[36,37] HPV screening detects cervical cancer earlier than cytological screening, making it superior to cytological screening (Pap smear and VIA test), which could influence the prognosis of cancer.[12,38]

The guidelines for HPV screening from the World Health Organization (WHO) and Centres for Disease Control and Prevention (CDC) include routine screening for women only, as no tests are approved for screening men. If the Pap smear is negative, re-evaluation is recommended every 3 years for females aged 21–30 years, and Pap smear with PCR-based HPV testing is recommended every 3–5 years for females aged 30–65 years.[5,29] Lesions detected in the epithelium of the cervix have been classified into three groups: cervical intraepithelial neoplasia (CIN) 1–3. Low-grade CIN1 refers to flat warts that can produce newly formed viral particles, with low proliferation at the bottom third of the epithelium. High-grade CIN2 lesions consist of infected basal cells occupying two-thirds of the epithelium, while high-grade CIN3 lesions are precancerous.[2] Depending on the classification, women may undergo surgery to remove precancerous lesions. The prognosis for HPV infection remains good, as spontaneous clearance of the virus occurs within 12–24 months. However, 10% of HPV infections persist and can progress to cancer, which has a high mortality rate.

## Preventative and therapeutic management of HPV-infections

Currently, there is no treatment for HPV infections; however, prophylaxis is available to prevent infection and subsequent cancers. Therefore, the WHO launched a global strategy to eliminate cervical cancer as a public health problem by 2030, built around the 90-70-90 targets for vaccination, screening, and treatment: 90% of girls aged 15 years vaccinated, 70% of women aged 35–45 screened for HPV infections, and 90% of women with precancerous lesions and cervical cancer treated.[39] Cervical cancer is primarily prevented through HPV vaccination and secondarily through screening for the symptoms and diseases caused by HPV infection, such as warts and cancer.

### *Prophylactic vaccines*

The widespread use of preventative vaccinations has significantly reduced the prevalence of HPV infections and related diseases, as they result in high levels of neutralising antibodies against specific HPV strains.[2,40] Currently, three main prophylactic HPV vaccines are available: bivalent, quadrivalent, and nonavalent (Table I).[41] The bivalent vaccine (Cervarix, Cecolin, Walrinvax) targets HPV-16 and -18, while the quadrivalent vaccine (Gardasil, Cervavax) targets HPV-6, -11, -16, and -18. In South African schools, the vaccination programme consists of a single dose of Cervarix administered to girls aged 9–15 years, with increased dosing for immunocompromised individuals. The most recent nonavalent vaccine (Gardasil 9), which has largely replaced the quadrivalent vaccine, provides broader coverage against HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58.[41,42] The nonavalent vaccine targets HPV genotypes present in 90% of cervical, 23% of vulvar, 61% of vaginal, 21% of oropharynx, 25% of penile, and 79% of anal cancer cases.[43] However, approximately 28% of HPV-infected individuals were infected with multiple genotypes, which frequently included high-risk HPV-16, -18, and -59, probable high-risk HPV-44, and low-risk HPV-82. Moreover, 64% of the cases with multiple HPV genotypes had at least one HPV genotype not covered by any of the existing bivalent, quadrivalent or nonavalent vaccines.[44]

Prophylactic vaccines consist of a non-infectious recombinant vaccine derived from the L1 capsid protein and result in sustained immunity against HPV infections for approximately 12 years by producing antigen-specific antibodies and activating B cell immunity.[29,45] Vaccines are developed in bacteria, yeast, or insect cells and administered with an adjuvant that induces high levels of antibodies and immune response. Due to the fact that vaccines are based on the L1 protein, they only provide strain-restricted immunity rather than broader genotypic coverage.[46]

The WHO recommends one or two doses of HPV vaccines for girls aged 9–14, one or two doses for girls and women aged 15–20, and two doses with a 6-month interval for women over 21.[9] Although vaccination is generally not administered to males in developing countries, the decrease in HPV infections in girls and young women due to vaccination coverage is expected to provide herd immunity to males.[46] However, global vaccination rates are low due to cost, restricted access and limited knowledge and only 30% of the global target and 31% of countries in Africa have full HPV vaccine coverage.[29,46] Pan-gender vaccination programmes, which include vaccination of adolescent boys and girls, have been implemented in various developed countries to prevent HPV transmission and protect against penile and anal cancers in men.[47]

Furthermore, various factors influence vaccine coverage and efficacy, such as vaccination age, geographical location, and education. Data suggest that HPV vaccines are highly effective when administered to HPV-naïve patients before they become sexually active, while vaccinations after HPV exposure have only approximately 50–60% efficacy against targeted HPV genotype-related lesions (CIN2 and CIN3) or cervical cancer.[48] Second, the types of HPV infections vary between geographical regions, with HPV-45 and -31 frequently detected in most regions except Asia, resulting in discrepancies in vaccine efficacy.[46] Finally, women's knowledge of HPV transmission and prevention increases the

**Table I:** Key features of globally available and licensed prophylactic HPV vaccines

| Category | Mechanism of action | Name (Manufacturer) | Expression system | Eligibility and dosing schedule | Efficacy | Side effects | Clinical/ Experimental |
|---|---|---|---|---|---|---|---|
| **Bivalent HPV-16 and -18[5,9]** | L1 virus-like particle-based immunity targeting HPV-16 and -18[5,9] | Cervarix (GlaxoSmithKline)[47] | Baculovirus -Insect cell[5] | Males and females aged 9–14 years (1- or 2-dose schedule at 5–13 months apart)<br><br>Males and females 15 years and older (3-dose schedule at 0, 1–2.5 and 5–12 months)[9] | 70% protection against cervical cancer[46]<br><br>Strong protection against oral HPV-16/18[46] | Injection site pain and swelling<br><br>Systemic symptoms, such as fever, nausea, vomiting, dizziness, myalgia, and diarrhoea[46] | Food and Drug Administration (FDA), United States of America (USA) approved 2009[5,9] |
| | L1 virus-like particle-based immunity targeting HPV-16 and -18[5,9] | Cecolin (Xiamen Innovax Biotech Co., Ltd)[47] | *Escherichia coli*[5] | Females aged 9–14 years (2-dose schedule in 6-month intervals)<br><br>Females 15 years and older (3-dose schedule at 0, 1–2 and 5–8 months)[9] | 87.5% efficacy against high-grade cervical, vulvar and vaginal lesions[50] | Systemic symptoms include fever, nausea, vomiting, dizziness, myalgia, and diarrhoea. | National Medical Products Administration (NMPA)-China approved 2021[47] |
| | L1 virus-like particle-based immunity targeting HPV-16 and -18[5,9] | Walrinvax (Walvax, China)[47] | Yeast[5] | Females aged 9–14 years (2-dose schedule at 6-month intervals)<br><br>Females 15 years and older (3-dose schedule at 0, 2–3 and 6–7 months)[9] | 78.6% efficacy against high-grade cervical lesions[51] | Injection-site pain and swelling<br><br>Systemic symptoms, such as fever, nausea, vomiting, dizziness, myalgia, and diarrhea[51] | NMPA-China approved 2022[5,9] |
| **Quadrivalent HPV-6, -11, -16, and -18[5,9]** | L1 virus-like particle-based immunity targeting HPV-6, -11, -16, and -18[5,9] | Gardasil (Merck & Co.)[47] | Yeast[5] | Males and females aged 9–13 years (2-dose schedule at 6-month intervals)<br><br>Males and females 14 years and older (3-dose schedule at 0, 1–2 and 4–6 months)[9] | 70–75% protection against cervical cancer[46]<br><br>90% and 80% protection against vulvar and vaginal diseases[46] | Injection-site pain and swelling[46] | FDA, USA approved 2006[47] |
| | L1 virus-like particle-based immunity targeting HPV-6, -11, -16, and -18[5,9] | Cervavac (Serum Institute of India)[47] | Hansenula polymorpha[5] | Males and females aged 9–14 years (2-dose schedule in 6-month intervals)<br>Males and females 15 years and older (3-dose schedule at 0, 2 and 6 months)[9] | 93% efficacy against persistent HPV-16/18 infection[52] | Injection-site pain, headache [53] | Drugs Controller General of India (DCGI) approved 2022[47] |
| **Nonavalent HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58 [5,9]** | L1 virus-like particle-based immunity targeting HPV-6, -11, -16, -18, -1, -33, -45, -52, and -58[5,9] | Gardasil 9 (Merck & Co.)[47] | Yeast[5] | Males and females aged 9–14 years (2-dose schedule 6–12 months apart)<br><br>Males and females 15 years and older (3-dose schedule at 0, 2 and 6 months)[9] | 90% protection against cervical cancer[46] | Injection-site pain, dizziness, headache, syncope[54] | FDA, USA approved 2014[47] |
| | L1 virus-like particle-based immunity targeting HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58[5,9] | Cecolin-9 (Xiamen Innovax Biotech Co., Ltd)[5,9] | *Escherichia coli*[5] | Females aged 9–17 years (2-dose schedule)<br>Females 18 years and older (3-dose schedule) | Comparable immune response to Gardasil 9 after 3 years[55] | Injection-site pain and swelling, myalgia, fatigue, headaches[56] | NMPA-China approved 2025[57] |

acceptance and initiation of vaccinations.[49] Therefore, to sustain higher vaccine coverage, educational initiatives are required.

### *Therapeutic vaccines*

Therapeutic vaccines have been developed to treat cancers induced by high-risk HPV infections, aiming to generate cell-mediated immunity. These novel therapeutic vaccines target the E6 and E7 oncoproteins of high-risk HPV strains, which are the primary drivers of HPV-related oncogenesis.[2] Additionally, E2 could be an ideal drug target, as this protein acts as a translational repressor of E6 and E7 proteins. Four types of therapeutic vaccines have been developed and tested in genital neoplasia: vector-, peptide-, and protein-based, whole cell-based, and nucleic acid vaccines (Table II).[5]

Vector-based vaccines employ bacterial or viral vectors to deliver antigens and induce innate immune responses that mimic the natural course of infection. However, vaccine-related adverse effects, such as immune responses targeting the vector and high immunogenicity in patients with low immunity, limit the use of vector-based vaccines.[5,58] ADXS11-001, a vaccine composed of HPV-16 E7 carried by live-attenuated Listeria monocytogenes, resulted in a 34% overall survival in patients with refractory cervical cancer. Three vaccine-related serious adverse events were observed in phase II clinical trials and although phase III clinical trials were conducted, results have not been published.[59] MVA-E2, consisting of modified vaccinia viruses containing bovine E2 protein, had a 83% HPV DNA clearance rate and 89% overall efficacy in regression of CIN1 lesions.[60]

Peptide-based vaccines contain antigenic peptide segments, whereas protein-based vaccines are composed of antigenic proteins that are processed by dendritic cells and result in low T-cell immune responses.[58] Therefore, although these vaccines are safe, stable, and easy to produce, they are often combined with adjuvants to enhance immune response. ISA101, a peptide-based vaccine made of overlapping E6 and E7 proteins, was combined with CpG or GPI-0100 during phase II clinical trials and resulted in a polyclonal immune response that induces tumour regression in mice.[61] Furthermore, in patients with cervical cancer combination therapies of ISA101 and nivolumab resulted in a 33% response rate, while ISA101 and carboplatin-paclitaxel treatment resulted in tumour regression in 43% of patients.[62] However, patients with HPV-16 induced vulvar and vaginal precancerous lesions and advanced cervical cancer do not respond to ISA101 vaccines in combination with immune checkpoint blockades or chemotherapeutics.[62] The efficacy of PepCan, a peptide-based vaccine containing HPV-16 E6 peptides, was tested in phase II clinical trials resulting in a 45% regression rate in patients with high grade lesions.[63]

Whole-cell vaccines consist of dendritic cells that serve as adjuvants and are loaded with HPV E proteins. Dendritic cells loaded with HPV-16 and -18 E7 antigens were immunogenic in patients with CIN1/2; however, the manufacturing of whole-cell

**Table II:** Therapeutic vaccines targeting HPV

| Type | Mechanism of action | Name | Eligibility (Dosing schedule) | Efficacy | Study phase |
|---|---|---|---|---|---|
| Vector-based[5] | Live-attenuated listeria monocytogenes containing HPV-16 E7 fused with listeriolysin O[59] | ADXS11-001[5] | High-risk advanced cervical cancer (3 doses at days 1, 29 and 57)[59] | Overall survival rate of 35% in 12 months[59] | Phase III[5,59] |
| | Vaccinia virus containing bovine HPV-16 E2 protein[60] | MVA-E2[5] | Intraepithelial CIN2/3 lesions (females: 6 weekly intralesional doses, males: 5 weekly intraurethral doses)[60] | 83% HPV DNA clearance<br>89% elimination of CIN2/3 lesions in females<br>10% elimination of CIN2/3 lesions in males[60] | Phase III[5,60] |
| Peptide- or protein-based[5] | Nine E6 and four E7 HPV-16 derived peptides with Montanide ISA51 adjuvant[62] | ISA101[5] | HPV-16 solid tumours (two low-doses, 0 and 12 months) | Ineffective in patients with advanced cervical cancer | Phase II[5,62] |
| | HPV-16 E6 peptides and Candin adjuvant | PepCan[5] | High-grade cervical lesions (4 doses at a 3-week interval)[62] | Significant T-cell immunogenicity[62]<br>Viral loads significantly decrease[62] | Phase I[5,63] |
| Whole cell-based[5] | Dendritic cells loaded with HPV-16 and -18 E7[64] | Antigen-pulsed mature dendritic cell[5] | CIN1/2 lesions (5 doses administered on days 0, 21, 42, 63 and 84)[64] | Significant T-cell immunogenicity[64] | Phase I[5,64] |
| Nucleic acid-based[5] | Two DNA plasmids encoding HPV-16 and -18 E6/7 proteins[65] | VGX-3100[5] | High grade cervical lesions (3 doses at weeks 0, 4 and 12)[65] | Virologic clearance at 18 months[65] | Phase IIb[5,65] |
| | Messenger- RNA encoding HPV-16 E6 and E7 proteins[66] | mHPV[5] | 3 doses at 7-week intervals[66] | Significant T-cell immunogenicity[66] | Preclinical[5,66] |

vaccines is labour-intensive and expensive, which limits their use.[58,64]

Lastly, nucleic acid vaccines contain bacterial plasmids or mRNA sequences and work by introducing genetic information encoding specific antigens into host cells. This allows the host cell to express antigenic proteins and activate an immune response against them. VGX-3100 contains synthetic DNA plasmids encoding HPV-16 and -18 E6 and E7 proteins. During phase II clinical trials, VGX-3100 efficiently induced HPV-16 and -18 viral elimination at 18 months following vaccination and resulted in regression of CIN3 lesions comparable to the control group, which underwent surgical treatment.[65] DNA-based vaccines are stable and safe, but have low immunogenicity, while RNA-based vaccines packaged into vectors that induce sustained T-cell responses are unstable.[5] Therefore, RNA-based vaccines, such as the mRNA-HPV (mHPV) vaccine encoding HPV-16 and -18 E6 and E7 proteins, are packaged into lipid carriers. Vaccination with mHPV effectively suppressed tumour growth in mice models and resulted in robust T-cell immune responses in mice and rhesus macaques.[66]

A variety of therapeutic vaccines that have been evaluated in phase II/III clinical trials resulted in an overall regression of 54% of CIN2/3 lesions. However, because this response rate is substantially lower than the efficacy achieved with standard surgical excision, none of the therapeutic vaccines have been approved for clinical use.[67,68] Although patients with persistent HPV infections after treatment remain at a higher risk of recurrence, the modest efficacy of the therapeutic vaccines in clinical trials may not justify replacing highly effective surgical interventions.

## Strategies to increase global vaccination coverage

Future research is needed to develop financially feasible vaccines and improve vaccine formulations to produce high immunogenicity and broad-spectrum protection.[41,45] Current HPV vaccines, including bivalent and nonavalent vaccines, are stored at temperatures between 2 and 8°C, which could be a significant challenge in low-income countries with infrastructure and financial constraints. Several next-generation vaccines have been developed to facilitate vaccine access in low-income countries and provide broader protection against high-risk HPV strains and are candidates in advanced clinical trials.[57] These new vaccines include quadrivalent, nonavalent, 11-valent, and 14-valent L1-based formulations. Additionally, capsid protein L2-based vaccines, which allow long-term storage at room temperature and are broadly protective against various HPV strains, are under development. However, L2-based vaccine results in a low immune response and only provides protection for one year, therefore, various adjuvants, fusions and formulations are being explored to achieve a durable and adequate immune reaction response.[57]

Unlike prophylactic vaccines which prevent HPV infection, various therapeutic vaccines targeting E6 and E7 oncoproteins have been developed for cancer treatment. Multiple vector-, peptide- and DNA-based vaccines have established efficacy and immunogenicity, however, none have been licensed for clinical use.[42] These therapeutic vaccines have the potential to be used in combination with chemotherapy or radiation, and offer advantages such as disease-specific immune memory.[57]

Considering the high occurrence of HPV-related cancers in both men and women due to persistent HPV-infections, educational intervention and pan-gender vaccination programmes should be implemented globally to achieve better vaccination coverage.[46]

## Conclusion

HPV infection is a global health concern strongly related to various malignancies, including benign lesions such as warts and life-threatening genital cancers. Persistent infection with high-risk HPV leads to the expression of E6 and E7 oncoproteins, which disrupt the cell cycle of squamous cells by enhancing cell proliferation and inhibiting cell apoptosis. Therefore, the WHO has launched a global strategy to eliminate HPV-related cervical cancer through vaccination and screening. Prophylactic vaccines developed and approved to prevent HPV infections include bivalent, quadrivalent, and nonavalent vaccines consisting of virus-like proteins from viral capsid protein L1 of different HPV genotypes. Despite the efficacy of prophylactic vaccines targeting high-risk HPV strains, vaccination coverage remains low, and more than 80% of cervical cancer mortalities occur in lower-income countries. Additionally, research on viral capsid protein L2 vaccines with broad genotypic protection is underway, and efforts to increase the low immunogenicity of these vaccines remain essential to provide protection against HPV genotypes not covered by L1 virus-like particle vaccines. Various therapeutic vaccines targeting viral oncoproteins E6 and E7 are being investigated for mono- and combination therapy in cancer treatment. Vector-, peptide- and protein-, whole-cell-, and nucleic acid-based vaccines have demonstrated immunogenicity against high-risk HPV genotypes and partial efficacy in lesion regression; however, none have been approved for commercialisation. As most studies involving therapeutic vaccines have been administered to patients with advanced cervical cancer, further research and clinical trials are warranted to validate and improve the efficacy and safety of therapeutic HPV vaccines.

### *Conflict of interest*

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