

Review

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Review

Immune Landscape of Papillomavirus Infections: Innate Recognition, Adaptive Immunity, and Immune Evasion

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Abstract

Human papillomavirus (HPV) infection remains a major global health concern due to its strong association with cervical and other anogenital and oropharyngeal cancers. The outcome of HPV infection is largely determined by complex interactions between the virus and host immune responses. This review summarizes current knowledge on the immune landscape of HPV infection, focusing on innate immune recognition, adaptive immune responses, and viral immune evasion strategies. HPV is sensed by host pattern recognition receptors, yet it efficiently suppresses interferon signaling and cytokine responses to establish persistent infection. Adaptive immunity, including HPV-specific CD4⁺ and CD8⁺ T-cell responses and neutralizing antibodies, plays a critical role in viral clearance, while defects in these responses contribute to persistence and disease progression. The virus employs multiple immune evasion mechanisms, such as downregulation of antigen presentation and modulation of cytokine signaling, facilitating immune escape and oncogenesis. The review also highlights immune correlates of protection, vaccine-induced immunity, and emerging immunotherapeutic strategies targeting HPV-associated diseases. A comprehensive understanding of HPV–host immune interactions is essential for optimizing vaccine design, improving therapeutic interventions, and reducing the global burden of HPV-related malignancies.

Keywords: human papillomavirus (HPV); innate immunity; adaptive immune response; immune evasion; HPV vaccines and immunotherapy

1. Introduction

Importance of Understanding HPV Immunity

The study of Human Papillomavirus (HPV) immunity is of critical significance because it has direct implications on the prevention of the disease, diagnosis, and therapeutic development. Recent studies have emphasized the complicated interaction between HPV infection and the host immune responses wherein there is a need to have a holistic view of the immune responses that are involved in HPV-related pathologies.

The initial defense against HPV invasion is innate immunity in which recent discoveries have highlighted the significance of the innate immune response in the early response to infection. The innate immune activation that takes place in response to HPV infection is described by Fu et al. (2025) and helps to understand the mechanisms through which HPV avoids the immune system and advances cervical lesions [1]. This highlights the need to learn about innate immune responses so as to devise effective interventions.

Additionally, the application of immune memory especially competent immunity has been under focus as a possible paradigm shift in the host defense mechanisms. Bahl et al. (2024) also

introduce the effect of infection-induced competent immunity that may redefine our perception of immune memory beyond adaptive responses and how the biochemical and cellular nature of this occurrence affects repeated disease exposures [2]. This observation implies that one potential direction of improving disease control in HPV would be to exploit competent immunity.

Immune responses are important not only in cervical pathology, but also in other conditions that are related to HPV, like oral epithelial dysplasia. Abilaji et al. (2025) point out the new findings regarding HPV as the cause of oral epithelial dysplasia and the significance of molecular tests of HPV in diagnostics and the prospect of using immunotherapy in the treatment of such dysplasia [3].

Immune responses are also affected by the interaction of HPV infection and the microbiome of the host. Parvez et al. (2025) examine the vaginal microbiome of women infected by various genotypes of HPV and identify the predominant types of bacterial taxa that might regulate immune response and affect infection maintenance or elimination [4]. In the same way, Che et al. (2025) discuss the effects of immune deficiencies, including those after hematopoietic stem cell transplantation, on microbiome disturbance, including diverse and oncogenic HPVs, and this way of the connection between immunity, microbiota, and HPV persistence are highly intricate [5].

New immunological-based therapeutic approaches against HPV-associated diseases are also based on immune knowledge. Zhu et al. (2025) concentrate on the cyclic GMP-AMP synthase - stimulator of interferon genes (cGAS-STING) signaling pathway which is involved in HPV infection and cancerous cells related to HPV and suggest it as a potential therapeutic target [6]. Also, as Bhaliya et al. (2025) explain, HPV-targeted vaccines and immunotherapies are relevant in treating lung cancer, and it is necessary to understand the HPV immunity to develop efficient treatment [7].

Lastly, the knowledge of HPV immunity is relevant to the broader aspects of vaccine development and the vaccination strategies of the population. Guillaume et al. (2025) examine the cultural and perception drivers of HPV vaccination intentions in immigrant women, thus signifying the sensitivity of the understanding of the vaccine acceptance of awareness and immune-related risk perception [8].

Implications for Vaccine and Therapeutic Development

The innovation of vaccines and therapeutics against human papillomavirus (HPV) has great potential to prevent cancer and treatment of HPV-related malignancies like cervical cancer. Recent studies focus on both prophylactic and curative approaches, and it is important to increase vaccine specificity, delivery systems, and immune responses.

The development of vaccine platforms is at the core of enhancing interventions on HPV-related cancer. Lei et al. (2025) emphasise on the need to overcome the barrier of effective antigen identification and immunosuppressive tumor microenvironment by innovative delivery systems and neoantigen discovery [9]. Likewise, Nakahashi-Ouchida et al. (2025) report the possibilities of mucosal immunity with nasal delivery systems based on the use of cationic nanogels on HPV16 E7 that could help prevent the development of cervical cancer due to the onset of local immunity [8–10].

HPV vaccines of therapeutic nature are now under investigation for their ability to treat already existing lesions and cancer caused by HPV. Zheng et al. (2025) summarize medical advances in treating cervical intraepithelial neoplasia and cervical cancer using therapeutic vaccines, but note that they have been used in combination with chemotherapy, radiotherapy, or immune checkpoint inhibitors [11]. Zhu et al. (2025) add to and propose additional work by developing a multi-epitope protein vaccine targeting HPV16 E6 and E7, which produces strong tumor regression and cytotoxic immune responses in preclinical models, demonstrating a promising therapeutic effect [12].

The immunologic response to HPV infection and vaccination is a crucial area of study that should be leveraged to optimize vaccine development. Kiamba et al. (2025) emphasize the need to understand natural and vaccine-induced immunity and pay particular attention to immunogenicity pathways that may be manipulated to improve the performance of vaccines [13]. This is supplemented by other immune activational studies, including the one by Shirazi et al. (2025) which

showed that tumor growth in murine models could be inhibited through the combination of immune activational HPV16 E7 mutant protein with adjuvants such as imiquimod [14].

New strategies are also using the power of immunoinformatics and the prediction of epitopes to come up with targeted vaccines. Dai et al. (2025) have used integrated immunoinformatic profiling to determine high-affinity epitopes of HLA-I-restricted in HPV16 E6/E7 oncoproteins that can be used to design precision multiepitope vaccines [15]. These approaches will maximize the specificity and effectiveness of therapeutic vaccines against HPV induced cancers.

Moreover, HPV-targeting vaccines have the potential to treat more cancer types than cervical cancer. Bhaliya et al. (2025) comment on the growing evidence indicating that high-risk HPV infection is associated with lung cancer, which might mean that HPV-targeted immunotherapy can be used in oncology with a broader scope [7]. This stresses the need to keep researching the vaccine platforms that can treat more malignancies associated with HPV.

2. Innate Immune Responses

HPV Viral Sensing and Pattern Recognition Receptors (PRRs)

Pattern recognition receptors (PRRs) recognition of viral pathogens is a major feature of an innate immune response, such as human papillomavirus (HPV) infection. Despite the fact that the given documents are not directly addressing the issue of HPV, they all emphasize the various ways in which the PRRs will recognize viral components and trigger antiviral responses in a variety of organisms and cell types.

The Dome receptor has been reported to be a direct sensor of viral envelopes in insects, especially the detection of double stranded RNA viruses (dsRNA) and triggering the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway leading to the activation of antiviral effectors including viperin [16]. That finding highlights the ability of given PRRs to bind directly to viral structural proteins, which then causes downstream immune response. On the same note, Toll-9 has been observed to play a major role in antiviral immunity in *Drosophila*, and its stimulation induces RNA interference (RNAi) which is a major antiviral effector in invertebrates [17].

Toll-like receptors (TLRs) in the mammalian systems are critical in sensing viruses. TLR9 is specifically an unmethylated Cytosine-phosphate-Guanine (CpG) motifs receptor, and design of very strong TLR9 antagonists demonstrates the value of controlling this pathway as a therapeutic activity [18]. Furthermore, the TLR7 and TLR8 sense viral RNA resulting in the synthesis of type I interferons (IFNs), which play a significant role in antiviral competence and are also used in cancer immunotherapy [19]. TLR pathways activate and induce interferons and other cytokines which sets up an antiviral state.

An additional important PRR-mediated sensing mechanism is the cyclic GMP-AMP synthase - stimulator of interferon genes (cGAS/STING) pathway which is critical in the case of macrophages. A case in point is that African swine fever virus (ASFV) upgrades CD14-dependent phagocytosis through cGAS/STING/ nuclear factor (NF-KB) pathways, which facilitate viral transmission and inflammatory reactions [20]. This exemplifies the possibility of viruses to control PRR signaling in order to propagate itself and avoid reactions of the immune system.

In addition, innate immune homeostasis encompasses modulatory elements like the Med23, which inhibits the expression of Retinoic Acid-Inducible Gene I (RIG-I) and hence antiviral signaling is muted [21]. This underscores the complicated control of the PRR pathways to achieve immune homeostasis and successful viral clearance.

Cytokine and Interferon Response

The existing literature emphasizes the intricate cross-talk that exists between cytokine and interferon responses in immune pathways, including recent findings as to how these are subject to regulation during viral infections or immunity challenges. While most of the included publications were related to different pathogens and immune mechanisms, together they identify critical features

concerning cytokine and interferon response, which could be inferred for studies involving HPV immunity.

Thakur et al. (2024) show that SARS-CoV-2 Nsp14 and other viral proteins can modulate cytokine secretion by inducing the activity of several signaling pathways, in particular nuclear factor- κ B (NF- κ B) and mitogen activated protein kinases (MAPKs) (ERK, p38, JNK), whereas facilitating the downregulation of interferon receptor expression [22]. This indicates that gain of benefit for viruses from cytokine signaling may be a mechanism common to infection and survival, which may have implications for HPV, where several studies indicate that this virus has ways of modulating the host immune responses to ensure maintenance of the viral nucleic acids within cells.

The researchers (Kirchhoff et al., 2024) recognized heterogeneous nuclear ribonucleoprotein M (hnRNPM) and embryonic lethal, abnormal vision)-like 1 (ELAVL1) as positive regulators in the type I interferon induction that is downstream of the nucleic acid sensors cGAS and retinoic acid inducible gene I (RIG-I) [23]. Their results emphasize on the role of host cellular factors in interferon stimulation and antiviral protection. This regulatory axis can be specifically applicable in HPV infection whereby the virus is often capable of escaping immune surveillance through interference with interferon signaling cascades.

Liu et al. (2025) also discuss the modulation of the cytokines profiles by the environmental factors, including exposure to fluoride. Their analysis indicates that fluoride inhibits the production of the pro-inflammatory cytokines, such as IFN- γ , IL-2, and IL-12, whereas it enhances the percentage of regulatory T cells [24]. It means that there are external factors that can modify cytokine reactions and it could lead to the implementation of the immune system to respond to the HPV infection or to the pathologies.

Although Siddig et al. (2025) concentrate on the subject of Marburg virus, the review points out the significance of immune evasion and response in pathogenesis of viruses (such as cytokine and interferon pathways) [25]. This information can be applied to HPV which uses immune evasion to survive, in many cases through regulation of cytokine response and interferon response.

Regarding immunomodulation, Wang et. et al. (2025) examine how the tumor growth is connected with decreased IFN- γ signaling, and strongly support that defective interferon responses may contribute to tumorigenesis [26]. This is of particular relevance in HPV-associated cancers, where decreased interferon activity may facilitate immune evasion and tumorigenesis.

Additionally, viruses such as avian influenza's NS1 protein can suppress interferon responses through engineered cell lines [27]. This is indicative of the viral mechanism that block interferon (IFN) responses, a response that HPV could use to avoid immune surveillance.

Zhang et al. (2025) summarizes the role of innate immune sensors like STING in inflammation and cancer, stating that activation of STING leads to inflammatory responses, thereby affecting the outcome of diseases [28]. Since interferon responses are usually mediated by STING-dependent pathways, knowledge of this will enhance understanding of how HPV might be able to manipulate innate immunity in favor of either persistence or oncogenesis.

Hang et al. (2025) shows that nanomaterials can activate STING, resulting in immunogenic cell death and enhanced antitumor immunity [29]. Such a strategy may be explored for therapeutic interventions to enhance interferon responses against HPV-associated lesions or cancers by targeting innate immune pathways.

3. Adaptive Immunity

Cellular Immunity: CD4+, CD8+ T-Cell Roles in HPV Infection

The role of CD4+ and CD8+ T cells in cell-immunity has been elaborately studied in the light of several viral infections, including SARS-CoV-2 and other viruses. Though the documents to be discussed mainly deal with SARS-CoV-2, specificities of T cell receptor (TCR), epitope specificity, and immune responses can be helpful in formulating parallels for the understanding of T-cell functions related to HPV infection.

Fahnøe et al. (2025) highlight the heterogeneity in epitope specificity among SARS-CoV-2-specific CD4+ and CD8+ T cells, emphasizing immunodominant responses and the potential for long-lasting T cell immunity [30]. This suggests that similar mechanisms of epitope recognition and TCR diversity could be relevant in HPV infections, where CD4+ T cells are crucial for orchestrating immune responses and CD8+ T cells are vital for cytotoxic clearance of infected cells.

Xiao et al. (2025) bring into focus the relevance of HLA-restricted CD8+ T-cell epitopes in the context of SARS-CoV-2, particularly with regard to variants such as Omicron [31]. This emphasizes the importance of epitope presentation in generating strong CD8+ T-cell responses, a notion that is equally valid in HPV, wherein epitope specificity is crucial for immune clearance and vaccine design.

In their study, Kawakita et al. (2025) examined certain adjuvants that would boost cellular immunity, including CD4+ and CD8+ T-cell responses, in context with the vaccines for SARS-CoV-2 [32]. They suggest that such approaches to enhance T-cell responses may also find application in the immunotherapy of HPV, in which strong T-cell activation is a prerequisite for controlling chronic infections.

A study by Xu et al. (2025) indicate that immune responses induced by vaccination can definitely be improved by CD4+ and CD8+ T-cell activation through heterologous prime-boost regimens and their inherent improvement of the response [33]. This may be useful with regards to HPV vaccines that would induce strong cell-mediated clearance of infected cells.

In addition, Liu et al. (2025) focus on the cellular immune responses in patients with advance infections, highlighting the importance of T-cell immunity in controlling viral persistence and infectivity [34]. These investigations mainly concerned Omicron but further underscore the important role of CD4+ T cells in sustaining cytotoxic responses and maintaining immune memory, equally important in the management of HPV infection.

Galuzo et al. (2025) showed innate immune signals could actually modulate T-cell activation and differentiation [35]. C-Type Lectin Domain Containing 5A (CLEC5A) activation in monocytes would enhance vaccination-induced adaptive T-cell responses, but innate pathways seem to modulate T-cell efficacy. Such mechanisms may be effective in HPV, wherein innate signals will determine the quality of T-cell responses.

As mentioned by Zhang et al. (2025) cellular immune impairment among immunocompromised individuals emphasizes the significance of functioning CD4+ and CD8+ T cells in the control of viral infections [36]. In the case of HPV, the compromised T-cell responses are associated with persistent infection and malignancy progression, further indicating that effective cellular immunity is necessary for the viral clearance.

Humoral Immunity and Neutralizing Antibodies in HPV Infection

From available literature, it appears that humoral immunity and neutralizing antibodies are crucial for the response against viral infections, and that this information would also apply to HPV. Most studies cover viruses such as SARS-CoV-2 and HIV, but the principles guiding humoral immune responses- such as antibody production, neutralization capability, and germinal center responses- are pertinent to the study of HPV immunity.

Benlarbi et al. (2025) furnish an elaborate examination of longitudinal humoral responses following infection with SARS-CoV-2 and point out the importance of antibodies directed against viral spike proteins, along with their neutralizing properties against the virus [37]. The study underlines the fact that in effective humoral immunity there must not only be targeted antibodies but also functional ability to neutralize pathogens that one receives against HPV: neutralizing antibodies are a prerequisite of protection.

Deng and colleagues demonstrate that vaccine platforms causing immune cell recruitment and germinal center activation can boost and prolong humoral responses [38]. Their work with a hydrogel vaccine platform against rabies illuminates how germinal center activation is necessary for lasting antibody responses-a principle that can extend to HPV vaccine development, in which strong germinal center responses are required to yield high-affinity neutralizing antibodies.

Chairunnisa et al. (2025) concerning the immune response generated by virus-like particles (VLPs) of HPV virus, which can induce specific antibody responses in mice, are determined by ELISA and neutralization assays [39]. The results support the idea that VLP-based vaccines can elicit neutralizing antibodies that are effective in preventing HPV infection, which correlates to the general understanding that VLPs are extremely immunogenic in inducing humoral immunity against infection.

Ewaisha et al. (2025) working on the humoral immune response to HPV in women find that very large numbers of individuals with antibodies to the L1 or L2 protein of HPV carry those antibodies specific to only one HPV type [40]. This suggests that a natural infection induces a type-specific antibody response that may have different neutralizing abilities. The type-specific neutralizing antibodies were of importance in natural immunity and vaccine design.

Kiamba et al. (2025) review immune responses to HPV infection and vaccination, emphasizing that current prophylactic vaccines elicit strong humoral responses, particularly neutralizing antibodies, which are key to preventing infection [13]. They also highlight the need for therapeutic vaccines that can induce effective humoral immunity in already infected individuals, pointing to the potential for neutralizing antibodies to contribute to disease control.

While most papers analyze SARS-CoV-2, Yin et al.(2025) and Jeworowski et al.(2025) analyze humoral responses in other contexts such as pregnancy or vaccination, indicating that humoral immunity is not only long-lasting but also adaptable in different physiological conditions [41,42]. Here, they emphasized that neutralizing antibodies are fundamentally important in the development of long-term immunity applies directly to the HPV vaccine strategies that aim to provide long-lasting protection.

At last, Webb et al. (2025) examined the heterogeneity of humoral responses in HIV controllers, emphasizing that, in addition to neutralization, Fc-mediated antibody functions also contribute to viral control [43]. This extends our understanding of humoral immunity further against HPV, whereby neutralizing antibodies are a major player, but other antibody functions may be involved in immune protection.

4. Immune Evasion Strategies

Downregulation of Antigen Presentation

Multiple studies showed that HPV downregulation of antigen presentation is a crucial mechanism in immune evasion and establishment of persistent infection. Maleka et al. (2025) highlight that oncoproteins E6 and E7 of high-risk HPV directly disturb the regulation of MHC class I molecules so that granzyme-mediated cytotoxicity is impaired, resulting in immune escape and carcinogenesis [44]. Thus, disruption of MHC-I expression prevents recognition of HPV-infected cells by cytotoxic T lymphocytes, thereby contributing to the persistence of HPV infection and eventual progression to malignancy.

Moreover, they elaborate on how HPV oncoproteins, particularly E5, E6, and E7, actively disrupt the tumor immune microenvironment in cervical cancer by impairing antigen presentation pathways. These viral proteins hinder interferon signalling and activate immune checkpoints, engendering an immunosuppressive tumor immune microenvironment (TIME) supportive of immune escape. This suppression of antigen presentation machinery is a major determinant for immune surveillance failure during HPV-associated carcinogenesis.

The mechanisms of immune evasion through antigen presentation downregulation are not unique to HPV but are also observed in other viral infections. Krenzlin et al. (2025) discuss how cytomegalovirus (CMV) employs viral regulators of antigen presentation (vRAP) to downregulate MHC-I molecules, facilitating immune escape in glioblastoma models [46]. This parallel underscores the importance of viral strategies targeting antigen presentation pathways across different pathogens.

The barrier of proper antigen presentation may alter the control of the immune response. Steiner et al. (2025) describe how interaction with membrane-associated antigens may impair B cell ability to

capture and present soluble antigens containing T helper epitopes by downregulating IgM and IgD [47]. While this study addresses the functions of B cells, it emphasizes the far-reaching consequences of modulation of antigen presentation during infections.

Primarily in terms of therapeutic intervention, comprehension of downregulation of antigen presentation mediated by HPV is important [48]. Studies by Xu et.al. (2025) discussed seeking a possible intranasal HPV vaccine delivery route to enhance mucosal immunity and even overcome some immune evasion mechanisms through localized immune responses [48].

Modulation of Cytokine Signaling

HPV infection is known to modulate the cytokine signaling, which is a complicated process of interactions between multiple immune pathways and cells. Recent research reveals the importance of the response of cytokines in defining the immune during HPV persistence and development to cervical cancer. Cervicovaginal microbiome, which is the subject of discussion in the article by Alizhan et al. (2025) regulates local immunity and can potentially affect the cytokine profiles, which, in turn, have an impact on the outcomes of HPV infection [49]. This interaction implies that both microbial diversity and immune responses are two factors that are interconnected and may regulate cytokine signaling pathways that are applicable to HPV clearance or persistence.

Transcriptomic studies made in single cells allowed gaining more intimate understanding of the cellular environment of HPV-related lesions in the cervix. Fan et al. provided research that employed Single-Cell RNA Sequencing (scRNA-seq) to find particular populations of keratinocytes in early cervical squamous cell carcinoma and found gene expression patterns that could impact cytokine-driven immune response [50]. On a similar note, Zhou et al. summarized the mechanisms by which HPV oncoproteins alter cytokine signaling pathways, such as interferon signaling and antigen presentation, to build an immunosuppressive tumor microenvironment (TME) [51]. The immune evasion through these disruptions supports the significance of modulation of cytokines in pathogenesis of HPV.

Cytokine pathway therapeutic approaches are coming up as potential frontiers. Barik et al. (2025) have explained the dual character of TGF- β in immunity and pathogenesis, and they have stated that the targeted control of the TGF- β signaling can improve immune elimination of HPV-infected cells and reduce tissue damage [52]. This is in line with the bigger goal of cytokine signaling modulation to repair effective immune responses. Also, the anti-inflammatory cytokine IL-37 was demonstrated by Qi et al. (2025) to suppress inflammatory processes through the NF- κ B pathway, which suggests that cytokine-based treatment has a potential to suppress inflammation caused by HPV infection [53].

Viral mechanisms of cytokine signaling during HPV infection are also complicated by its viral mechanisms of evading immune responses. Oncoproteins of HPV, such as E5, E6, and E7 disrupt cytokine-mediated pathways, such as interferon responses and immune cell activation as a summary of the findings by Zhou et al. (2025) [51]. Such mechanisms also play a role in immune evasion and chronic infection and it is important to note that therapeutic interventions are required to regulate cytokine signalling and circumvent immune suppression caused by HPV.

5. Immunity and Disease Progression

Clearance Versus Persistence of HPV Infection

The literature about HPV infection focuses on the difference between clearance and persistence that are the determinant factors of progressing to HPV-related lesions and cancer. A number of studies emphasize the epidemiological attributes of HPV persistence, especially in the high-risk groups. Huang et al. did a retrospective cohort study in China and found that the HPV infection tends to be persistent over time with the persistence being a major risk factor in the development of cervical carcinogenesis [54] in gynecology outpatients. These results provide significance to comprehending

those factors impacting whether HPV infection is eliminated or remains, particularly because the oncogenic potential is associated with persistent infection.

Alizjan et al. (2025) examined the role of host factors and microbiota in HPV persistence by synthesizing the interaction between the microbiome of the cervicovaginal tract and local immunity [55]. They argue that microbial diversity and immune responses can regulate the effect of HPV infection, and this can influence clearance/persistence probability. This shows that the composition of microbiome and the local immune environment are part of the natural history of HPV infection.

The HPV infection dynamics are of specific interest in immunocompromised populations, i.e., in people with HIV. A high prevalence of HPV infection (86.4%) was reported by Sambo et al. (2025) in individuals who have HIV, and a significant proportion of high-risk genotypes [56]. Despite the fact that the study has tried mainly on prevalence, the high rate of infection is an indication that clearance is not easily realized even in immunocompromised individuals which could result in persistent infections and consequent lesions.

Treatment modalities involving therapeutic interventions that encourage HPV clearance have been studied in interventional studies. Porcaro et al. tested a dietary supplement based on Epigallocatechin Gallate (EGCG), folic acid, vitamin B12, and hyaluronic acid, the results that revealed that this treatment might enhance HPV clearance and reduce persistence [57]. In like manner, Chen et al. and Li et al. also considered photodynamic therapy (PDT) methods that show that Aminolevulinic Acid-Photodynamic Therapy (ALA-PDT) does not only target cells with HPV infection but can also promote the elimination of the virus, thus preventing persistence [58,59]. According to these studies, therapeutic interventions may have a role in modifying the natural history of HPV infection, and this may alter the outcome to the clearance.

The difference between clearance and persistence is also useful when it comes to lesion management. Wang et al. [60] studied photodynamic therapy as compared to surgical excision of high-grade lesions, which suggests that the effective modes of treatment can be of help in addressing the persistent infection and related lesions. Their effectiveness in eliminating HPV and inhibiting progression highlights the possibility of the treatment to be used in treating persistent infections.

Immune Correlates of Protection of HPV Infection

The use of immune correlates of protection (CoP) on HPV infection is an important field of study, and there is ongoing research to elaborate on immune responses that promote effective and long term immunity. The article by Lehtinen et al. (2025) has a detailed report on the current progress and obstacles in the definition of HPV vaccine induced CoP basing on the experience of hepatitis B virus (HBV) vaccination strategies [61]. They indicate the number of protective antibodies against HBV (10 mIU/mL) as a reference point and the significance of uniform serological tests and prolonged antibody testing as a measure of breakthrough infection [61].

The responses to HPV vaccination (antibody responses) are of central importance in the present knowledge, and research has shown that antibodies developed after the vaccine are the major part of the protective immunity. Review by Kiamba et al. (2025) on immunogenicity of HPV vaccines indicates that vaccines made up of subunits are associated with good-protective antibody responses [62]. The review however also indicates that other immune pathways than the antibody titers may be involved, showing that it is important to investigate further immune mechanisms that can help to provide the protection [62].

Periodicity of the vaccine-induced immunity is also significant. According to Zhao et al. (2025), the immune response may persist as long as 10 years following vaccination [63]. Their results are in support of protective antibodies which persist over time, which adds value to the sustained humoral responses in sustaining immunity against HPV [63]. This kind of data on a long-term basis is critical in determining standard CoP benchmarks.

In addition to the humoral immunity, cell-mediated immune is also being accepted as significant in protection. Zhu et al. (2025) show that multi-epitope therapeutic vaccine against HPV16 E6 and E7 could induce cytotoxic T lymphocytes and efficacy memory T cells resulting in a substantial tumor

regression in preclinical models [64]. This highlights the possibility of T-cell responses being a component of the immune correlates of protection particularly in the treatment scenarios [64].

The complexity of the immune responses is further exemplified by the results of Rubio-Casillas et al. (2025), who emphasize on the Fc effector functions of antibodies, i.e. phagocytosis, as critical to the protection against SARS-CoV-2 [65]. As much as they focus on COVID-19, the statement that antibody quality, in addition to quantity, might have a substantial role in the protective efficacy is applicable to HPV too, with the idea that Fc-mediated functions are potentially high-profile as far as immunity caused by the HPV vaccine is concerned [65].

Considering the predictive modeling, Hao et al. (2025) propose a statistical model that estimates the degree of immune protection using the information about the population, which takes into consideration immune waning and several outcomes [66]. These models may be adapted to HPV in order to learn more about the correlates of protection and influence vaccination strategies [66].

6. Vaccine-Induced Immunity

Mechanisms of Immune Priming in HPV Infection

Recent research indicates that there is complex interplay between viral factors and host immune responses in the mechanisms of immune priming in HPV infection. The capability of the virus to evade the immune response is one of the factors, especially by down regulating major histocompatibility complex (MHC) class I molecules, which inhibits cytotoxic T cell immune response and allows persistent infection [67]. The role of this immune evasion mechanism in the study of HPV infection control highlights the significance of getting familiar with the manner in which HPV can affect host immune systems to acquire and perpetuate infection.

More information on the mechanisms of immune priming is seen by research studies into cellular and molecular response. As an example, single-cell RNA sequencing (scRNA-seq) has been used to describe the tumor microenvironment in HPV-related cervical cancer that included heterogeneous types and states of cells that could induce immune priming [68]. This is because such detailed cellular profiling increases our knowledge of how immune cells may be activated or suppressed in early HPV infection and progression.

Also, viral oncogenes have been associated with the effect of HPV on cellular processes in relation to immunoregulation. Specifically, HPV E7 protein was found to suppress immune responses in keratinocytes by regulating the activation of HtrA serine peptidase 1(HTRA1)-mediated mitophagy that can be involved in immune evasion and the establishment of persistent infection [69]. This implies that HPV has the ability to tune intracellular pathways to suppress immune activation, and hence regulation of immune priming.

Immune priming also depends on the fact the virus is integrated into the host genome, the process that results in genome reshaping and can change immune recognition mechanisms. The process of HPV integration consists of several steps, such as viral invasion and immune evasion with the end result of the persistence of infection and possible carcinogenesis [70]. These stages are important in understanding the initiation or inhibition of immune priming during HPV infection.

In addition, viral factors alone are not only involved in immune priming in HPV infection but also host immune modulation. As an illustration, crosstalk of immune cells involved in regulation of immune responses has been examined in the case of bacterial co-infections, which may alter HPV clearance and immune priming efficacy [71]. The complexity of the immune priming mechanisms is pointed out by such interactions.

Long-Term Protection Data of HPV Infection

The long-term defense, which is the result of HPV vaccination, is the burning field of research, and the recent studies are valuable in terms of analyzing long-term aspects of immune responses and their adequacy. Oswald et al. (2024) created a mathematical model to determine the effect of HPV vaccine uptake on dynamics of transmission, where it was found that there are both HPV-free and

endemic equilibrium states, and thus the significance of sustained vaccination efforts to control HPV over the long run [72].

An example of the published empirical data on the effectiveness of vaccines over time is the study by Zhao et al. (2025), that showed a follow-up of up to 10 years of an observational extension trial among women who received the HPV-16/18 bivalent vaccine. Their results reveal enduring immunogenicity and efficacy which shows that protection due to vaccines may last at least one decade after the vaccination [73]. In the same way, Wiek et al. (2025) examined the antibody levels before incident HPV18/45 infections, which gave evidence that increased anti-HPV18 IgG levels were correlated with decreased risk of second infection and thereby assist in support of the role of enduring antibody levels in long-term protection [74].

The systematic review published by Harper et al. (2025), summarizes the information about the efficacy, effectiveness, and durability of licensed HPV vaccines and underlines that currently the evidence provides strong protection against infection, precursor lesions, and cervical cancer [75]. Nonetheless, the review also mentions that data concerning the exact length of immunity stay insufficient, which points to the necessity of the further surveillance and investigation [75].

Mathematical modeling research also leads to the comprehension of protection in the long-term. Choi et al. (2025) employed a dynamic model of transmission that has been calibrated using the population data on Japan to estimate the long-term effects of the 9-valent HPV vaccine, which includes the decrease in cervical cancer and genital warts in a 100-year horizon [76]. According to their estimations, they imply long-term gains even though the amount of time that a person would use the immunity was not directly mentioned [76].

Hasan et al. (2025), investigate the role of natural and vaccine-based immunity in the dynamics of HPV transmission and because of this, they added exogenous re-infection into their model [77]. They suggest that natural immunity is ineffective to protect over time due to which vaccination is critical to herd immunity and the decrease in persistent infections [77]. On the same note, the article authored by Zhang et al. (2025) points out that although vaccination lowers HPV rates, there exists a risk of type substitution and modification of sexual behaviors, and hence, there is a need to monitor the situation over a long term, in order to comprehend long-term epidemiological effects [78].

Antibody titer, which is known as Correlates of protection, are important in assessing long term immunity. Berry et al. (2025) were able to show that HPV type-specific antibody binding concentrations are associated with incident and persistent case protection, indicating that immunogenicity markers are good proxies of long-term vaccine protection [79]. This is in agreement with the results of Wiek et al. (2025), who attributed antibody titers to the future risk of infection, which further adds to the value of a sustained antibody response on long-term protection [74].

7. Conclusions and Future Perspectives

The existing situation in HPV study gives prominence to the complex approach to the research of HPV and its associated diseases with a further focus on the novel screening techniques, vaccination approaches, and the biological processes of HPV-related carcinogenesis. The future of this area is set to deal with the prevailing barriers, broaden the scope of specific interventions, and enhance knowledge of the mechanisms.

New studies suggest the promise of home-based urine self-collection as a screening method of cervical cancer, particularly in those groups that have limitations to conventional clinician-based testing. Guetterman et al. (2025) show that these methods may have a beneficial impact on screening intentions in the future among women in the MENA region and this would provide a promising line of research on enhancing screening uptake and reducing disparities [80].

Simultaneously, it is also important to learn more about the epidemiology of HPV in children. Tomecka et al. (2025) also show that HPV DNA can be quite common in children and adolescents and it has various clinical features and vertical transmission was revealed [81]. The findings highlight the significance of early detection and intervention methods that might guide future studies on the dynamics of HPV transmission and prevention methods at an early age.

The acceptance of vaccines and decision-making processes remain some of the major topics. Cooper et al. (2025) summarize the qualitative data on the determinants of HPV vaccination among teenagers and caregivers, with specific emphasis on the contribution of perceptions, experiences, and social factors to it [82]. In a similar fashion, Oyediji et al. (2025) examine the perceptions of young adults, determining that the recommendations of healthcare providers and the support of family members are the facilitators that may be used to create individual communication tactics to increase the likelihood of taking the vaccine [83].

To discuss the issue of vaccine-related perceptions, Wang et al. (2025) analyze the effects of sex-biased information on the intentions of male college students to inoculate against vaccines, which expands the scope of behavioral theory application, such as the Theory of Planned Behavior (TPB) [84]. These observations indicate that effective health communication campaigns are important in enhancing the vaccination rates among the genders.

The influence of HPV vaccination programs on screening behaviors is also another important factor. Shpendi et al. (2025) state that future research should focus on the creation of interventions that improve reflective motivation because vaccinated cohorts will reach the age of screening [85]. The knowledge of the role of immunization on screening attendance will be essential in enhancing the cervical cancer prevention measures.

Biological studies are still in the process of unravelling the complicated mechanisms of HPV-associated carcinogenesis. Tao et al. (2025) pay attention to microbial and metabolic dysbiosis in cervical cancer and suggest a multi-targeted precision medicine framework although the problem is still limited [86]. These insights of a mechanistic nature would open up new treatment targets and precision in treatment

Moreover, the experience gained during the LMIC vaccination campaigns, like Nigeria, will be useful in future work. Kubura et al. (2025) raise some stakeholders views and ways to reduce obstacles and underline the necessity of interventions that are specific to the context and the involvement of communities in increasing the level of HPV vaccination [87].

Studies on HPV-related cancers of the oropharynx are also still relevant. Zhang et al. (2025) point out research hotspots and differences in regions, indicating that further research efforts should encompass outcomes, dysphagia, and impacts on the region to guide the research priorities on a global scale [88].

Last, but not least, new methods of enhancing the accessibility of HPV screening among vulnerable groups become a matter of interest. The article by Gaydos et al. (2025) shows how the deliberative democracy approaches in LMICs, like Nigeria, are adapted to create sustainable screening programs, which reveals that the participatory and culturally responsive interventions are crucial to the success of the future interventions [89].

Conclusively, future studies on HPV are expected to aim at increasing the screening modalities that are available, learning more about behavioral determinants of vaccination, clarifying biological processes of HPV-caused carcinogenesis, and using context-specific interventions. Such initiatives will play a vital role in minimising disease burden of HPV in the entire world and equitable health outcomes.

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