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HPV Pathogenesis, Vaccines Mechanisms, and Prevention Strategies

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Abstract. Cervical cancer has become a critical health menace to females, with half of which are caused by Human papillomaviruses. To prevent HPV infection and cervical cancer, HPV vaccination is the most effective known preventative measure. This article introduces the classification and pathogenic mechanisms of HPV, analyzes the transmission methods of various HPV types, and provides a detailed explanation of the roles played by the E6/E7 proteins in cell cycle dysregulation and immune evasion. In addition, the paper examines the immune processes following HPV infection, the working principles of HPV vaccines, and the protective efficacy and suitable target populations for different types of vaccines. Finally, it analyses the current challenges facing HPV vaccines and future development directions in light of the global vaccination landscape. Therefore, this paper aims to provide a more scientific basis for the prevention of cervical cancer and instructions for the formulation of relevant vaccine strategies through a comprehensive analysis of the biological mechanisms of human papillomavirus and the basic principles of HPV vaccines.

Keywords: Cervical cancer; HPV vaccine; p53 protein; Vaccination strategy; HPV detection.

1. Introduction

According to the WHO (2023), there are approximately 630,000 cases of human papillomavirus-associated cancers per year. Among all the cases, cervical cancer accounts for the majority (approximately 340,000 cases per year), which explains why cervical cancer is one of the most frequent cancers and influences females worldwide. Cervical cancer incidence is highest in sub-Saharan Africa (>40/100,000 persons/year) and lowest in Europe and North America (<10), but oropharyngeal cancer is rising significantly in developed countries.[1] Such data are related to the prevalence of HPV infection since persistent infection with high-risk types of human papillomavirus is the leading factor in cervical cancer. Areas with high HPV infection rates are Africa (24% of women carry HPV), Latin America (16%), and parts of Asia (India, 1/4 of the global burden). In several developed countries, such as the United States, for example, about 42% of adults have been infected with HPV, and the rate of infection in adolescents has declined due to vaccination. The peak age group for HPV infection is usually women under 25 years old (in the early stages of sexual activity), and the infection rate can be 20-30%, but most of them clear up naturally within 1-2 years. However, women over 30 years of age are at a higher risk of persistent infection, with a rate of persistent high-risk infection of about 10% and an increased risk of cancer.

Human papillomavirus is one of the most common sexually transmitted viruses, and around 80% of sexually active people will be infected with at least one HPV type in their lifetime. There are more than 200 subtypes of HPV, which are categorized into four main genres: low-risk skin types, low-risk mucosal types, high-risk skin types, and high-risk mucosal types. For low-risk HPV types (types 6/11), the symptoms they cause are primarily benign wart-like lesions. For example, genital warts take the form of cauliflower-like, papular, or flat, bulbous organisms that are soft and can be single or clustered. These types of genital warts often grow on the vulva, penis, perianal area, vagina, or mouth. Other common types of warts are flat warts on the skin, plantar warts on the soles, and laryngeal papillomas (mainly in children, rare but recurrent). For high-risk HPV types (types 16/18/31/45), they are highly likely to cause cancer-related symptoms. In the early stages of cancer, there are usually no symptoms or only minor abnormalities, including bleeding after sexual intercourse, increased vaginal discharge. In advanced stages of cervical cancer, for example, symptoms such as irregular vaginal bleeding, foul-smelling discharge, pelvic pain, and even blood in the urine (bladder invasion), bowel

obstruction (rectal compression), and weight loss can occur if symptoms metastasize. HPV-induced oropharyngeal cancers usually cause sore throat, difficulty swallowing, and a lump in the neck, while anal cancers cause bleeding, itching, and a sensation of a lump.

After entering the 21st century, the invention of the HPV vaccine has become one of the most important breakthroughs in global public health, which has significantly decreased the incidence of HPV-associated diseases, including cervical, oropharyngeal, and anal cancers, and driven changes in cancer prevention strategies worldwide. Some countries have developed herd immunity to HPV, reducing overall HPV transmission. The success of the HPV vaccine demonstrates that science-driven immunisation strategies can significantly reduce the global burden of disease, and continued expansion is necessary to reach the entire population.

2. Discovery and Taxonomy of (HPV)

HPVs are tiny, non-enveloped, double-stranded DNA viruses belonging to the family Papillomaviridae.[2] The history of HPV discovery and research dates back to the early 20th century. In 1956, German scientist Harald zur Hausen first proposed a possible relationship between the human papillomavirus and cervical cancer. His hypothesis was based on the discovery that an unknown pathogen, different from other known viruses, was present in cervical cancer patients. However, at the time, there were no technical means to confirm this hypothesis. It was not until the 1970s that scientists were able to isolate and characterize HPV from the tissues of cervical cancer patients, and the key breakthrough was the use of electron microscopy to observe the presence of viral particles. Since then, a series of studies have further confirmed the close connection between HPV and cervical cancer, especially high-risk types of HPV. As technology continued to advance, scientists began to classify and characterize HPV. By comparing virus samples from different patients, they discovered that HPV can be categorized into multiple subtypes. To date, more than 200 subtypes of HPV viruses have been identified, and their taxonomic and evolutionary characteristics have resulted in a high degree of diversity in their pathogenicity. The classification of HPV subtypes is mainly based on their gene sequence differences. The L1 coat protein gene is the main criterion for HPV classification. If the sequence similarity is <90%, then it is defined as a different type; similarity in the interval of 90%-98% is known as a subtype, and if the similarity is >98%, then it is a Variant. Among the approximately 200 subtypes, high-risk types 16, 18, 31, 33, 45, 52, 58, etc., are prone to cause cervical cancer and oropharyngeal cancer, while Low-risk types 6 and 11 cause genital warts and laryngeal papillomas. According to WHO statistics, the carcinogenic subtypes are HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59; the subtypes which may cause cancer are HPV 68 and 73; the potentially oncogenic subtypes are HPV 26, 53, 66, 67, 70, 82.

3. Transmission Mechanisms of Human Papillomavirus

The transmission of HPV is not limited to sexual contact but also includes skin-to-skin contact, mother-to-child transmission, and other modes of transmission. The sexual contact transmission is the central method of HPV transmission, with vaginal intercourse, anal intercourse, and oral intercourse leading to cervical, anal, and oropharyngeal cancers, respectively.[3] Even though condoms do reduce the probability of contact infection by physically isolating viral particles in genital secretions during transmission, they still do not completely block it, as the virus can be present in uncovered areas of the scrotum or perineum. If transmitted by direct skin-to-skin contact, HPV will enter the basal cells through small skin breaks. As the cell proliferates and matures, the HPV virus replicates and assembles, thereby injecting its genetic information into the host's skin cells. As the cells divide, more and more cells become infected by HPV, and the HPV virus gradually enters the stratum spinosum and stratum corneum of the skin, triggering cancer. Mother-to-child transmission is a vertical route of transmission in which a newborn may become infected via the placenta, causing fetal congenital warts. Or laryngeal papilloma via the birth canal. Therefore, it is recommended that

pregnant women should be screened for cervical cancer and follow up for high-risk infections. Regular laryngoscopy is also needed in newborns to avoid airway obstruction through early intervention.

4. Mechanisms of HPV Infection and Replication

HPV viruses are composed of DNA and capsid proteins, of which the nucleic acids are closed-loop DNA genomes that can be separated into the following three genomic regions: the early coding region, which encodes non-structural proteins; the late coding region, which encodes viral particles and structural proteins needed for viral transmission; and the long regulatory region, which contains the early promoter and regulates disease transmission; the late coding region - encodes structural proteins required for viral particles and viral transmission; the long control region - contains early promoters, regulatory elements that regulate the transcription of viral and cellular proteins. HPV replicates and reproduces only in specific areas, namely the skin surface and mucous membranes. The area of the cervix where the squamous epithelium meets the columnar epithelium is a susceptible area for HPV.[4] When HPV infects a host cell, it can exist in a free state or integrate with the host cell's chromosome and remain there for an extended period. HPV primarily infects the basal cells of the skin or mucous membranes, especially those exposed at the site of injury. The protein L1 on the viral capsid recognizes receptors on the host cell surface. After binding to the receptor, the virus accesses to the cell through endocytosis, either via clathrin-mediated or caveolin-mediated pathways.[5] When the virus successfully gets into the cell, it undergoes a series of conformational changes, and the capsid protein L2 exposes a nuclear localisation signal, which guides the viral genome to the nucleus of the host cell through the nuclear pore complex.[6] This process is entirely dependent on the host cell's nuclear translocation mechanism.

The HPV genome is divided into early and late regions. HPV expresses genes early in the cell to maintain replication. E1 and E2 proteins are expressed first. E1 is a deconjugating enzyme that binds to the viral replication start point and recruits host DNA polymerase to initiate viral DNA replication. E2 proteins primarily regulate the function of E1 and inhibit the overexpression of early viral genes. E6 and E7 proteins, which are two oncogenic proteins, are subsequently expressed. E6 is used to degrade p53 and inhibit apoptosis. At the same time, E7 releases the E2F transcription factor by binding to the pRB protein, which drives the cell cycle into the S stage and facilitates viral replication. As a result, HPV utilises the host cell's DNA polymerase for rolling-circle replication, amplifying the copy number of the viral genome.

In contrast, replication depends on the nucleotides and energy of the host. In contrast, late viral gene expression primarily relies on the synthesis of structural proteins. After viral DNA is replicated to a certain extent, it initiates the expression of the L region. It synthesises the major capsid proteins L1 and minor L2 proteins. The coated assembly of the nascent virus begins with the assembly of the procapsid in the nucleus, facilitated by the L1 pentamer and the L2 protein. Subsequently, the viral DNA is packaged into the coat to form a complete viral particle.

The HPV is released not by lysing the cell but through a cellular differentiation-dependent release mechanism. Infected epithelial cells gradually differentiate and migrate to the surface, where the virus completes its final assembly in the granular layer or stratum corneum. The virus is released by keratinocyte shedding or transmitted by cell-to-cell contact. The released virus can infect neighbouring cells or be transmitted to a new host by mucosal or dermal contact. In general, HPV infection follows the sequence of "receptor binding, endocytosis, genome entry, early gene expression, DNA replication, late gene expression, capsid assembly, and finally release" and relies on host cellular mechanisms to complete its life cycle. Its latent infection and oncogenicity are mainly derived from the regulation of the cell cycle by the E6 and E7 proteins. Therefore, the carcinogenic potential of HPV is primarily attributed to two early proteins, E6 and E7. These two proteins interfere with the function of key host cell tumour suppressor proteins p53 and pRB through precise and complex

molecular mechanisms, leading to cell cycle dysregulation, apoptosis imbalance, and tumor progression.

The p53 protein, as a tumor suppressor, participates in multiple signal transduction processes within cells, including cell proliferation and DNA repair. When necessary, it can terminate cellular processes and induce apoptosis. Hence, the silencing or mutation of the p53 gene can disrupt intracellular signal transduction pathways, leading to uncontrolled cell growth and apoptosis, thereby inducing cellular carcinogenesis. When DNA damage is not severe, the expression level of p53 protein increases, causing damaged cells to arrest at the G1 checkpoint for DNA repair, thereby retaining the intact cellular genome. If DNA repair does not succeed, the p53 protein inaugurates the apoptosis pathway, inducing cellular senescence and apoptosis, thereby diminishing the probability of genomic mutations occurring. The HPV virus protein E6 interferes with the function of the p53 protein, inducing its degradation in the proteasome-dependent system, significantly reducing the level of p53 protein in cells, and this prevents cells from effectively repairing DNA damage or undergoing apoptosis, allowing mutated cells to continue to survive and proliferate, greatly increasing the possibility of cellular carcinogenesis.[7]

pRB is an important tumour suppressor protein that regulates the transition of cells from the G1 stage to the S stage. Its primary function is to bind with the E2F transcription factor, inhibiting its activation of cell cycle-promoting genes and maintaining cells in a non-proliferative state. Additionally, pRB participates in regulating processes such as DNA replication and apoptosis. In cells infected by HPV, the expression of the E2 gene is suppressed, while the E7 viral protein is continuously overexpressed. The overexpressed E7 protein can bind with the pRB protein, thereby inhibiting its binding with the E2F factor, leaving E2F in a free, activated state within the cell. This process enables cells to progress into the S phase even under conditions of DNA damage, resulting in continuous proliferation and the accumulation of mutated genes, which ultimately leads to carcinogenesis in infected cells. The E7 protein forces cells to enter the DNA synthesis phase even when they are not fully prepared, increasing the risk of gene mutations and chromosomal instability.

During persistent HPV infection, both E6 and E7 proteins can lead to abnormal methylation levels of host genomic DNA or HPV genomic DNA.[8] Following the integration of high-risk HPV into the host genome, the DNA methylation status of 11 host genes undergoes significant changes, thereby affecting their expression levels. Additionally, HPV's E6/E7 proteins may indirectly promote the silencing of key genes by influencing the expression or activity of DNA methyltransferases (DNMTs), further facilitating malignant transformation. For example, the HPV16 E7 protein can upregulate DNMT1 activity, leading to the methylation of the CDH1 promoter and reduced expression levels of E-cadherin, which is encoded by the CDH1 gene. This methylation induces cervical cancer cells to undergo migration, invasion, and epithelial-mesenchymal transition. The E6/E7 proteins of HPV18 can inhibit DN-MT3a expression through the Enhancer of Zeste Homolog 2 , thereby suppressing methylation of the Tim-3/galectin-9 promoter, activating the Tim-3/galectin-9 pathway, and causing immune escape in cervical cancer cells.

What is certain is that HPV-induced cancers do not occur immediately, but rather in a multi-stage process involving the gradual accumulation of mutations and evasion of regulatory mechanisms. The first stage involves cell cycle disruption: the sustained expression of E6/E7 interferes with the cell's control over proliferation, causing it to enter a state of continuous division. Additionally, due to the absence of p53 and pRB regulation, DNA replication errors occur frequently, leading to a decline in genetic stability. The second stage is apoptosis inhibition: in addition to degrading p53, E6 also upregulates anti-apoptotic proteins, blocking the apoptosis pathway, resulting in damaged cells unable to be cleared and accumulating more mutations. The third stage is angiogenesis: E6/E7 can indirectly induce the expression of vascular endothelial growth factor, prompting the formation of new blood vessels. This expression provides the cancerous tissue with more nutrients and oxygen, thereby facilitating tumour growth and metastasis. The final step is immune evasion: HPV-expressed proteins can downregulate MHC I molecules, reducing the immune system's capability to recognize

infected cells. Thus, prolonged infection exacerbates the accumulation of cellular mutations, creating an 'immune sanctuary' for carcinogenesis.

5. HPV detection methods

At the beginning of the twentieth century, Dr George Papanicolaou began to specialise in the cytopathology of the human reproductive system. He discovered that by looking at swabs on smears of vaginal secretions from women under a microscope, he was able to distinguish between normal and malignant cervical cells. This process is now known as a Papanicolaou smear. The Pap smear is usually sampled from the squamocolumnar junction area, which is the most common site of cervical carcinogenesis.[9] In women who have had cervical surgery or after menopause, cells from the opening of the cervical canal are also sampled. Traditional Pap smears use a wooden or plastic spatula as the collection tool, while cervical brushes are used for collecting cells from the cervical canal. Although the Pap smear is very simple to perform, this test is prone to false-positive or false-negative misdiagnosis and is unable to locate specific lesions accurately. Therefore, after a Pap smear, the patient will be asked to undergo a colposcopy.

Colposcopy is another diagnostic microscopy. The colposcope is an optical instrument capable of optical magnification and is primarily used to perform diagnostic visual examinations of cervical epithelial tissue. By using a colposcope, the entire cervical area can be magnified up to 30 times, allowing for more detailed visual observation. During colposcopy, the cervix is inspected after applying a 3-5% acetic acid solution, causing squamous cells with comparatively large and dense nuclei, like migratory cells, dysplastic cells, and HPV-infected cells, to show white. These phenomena are known as ‘acetylation’. Moreover, aberrant blood vessels and vascular patterns are more easily visible under this white background. [10]Likewise, dysplastic lesions will be more easily visualised by applying Lugol's iodine to the cervix. Lugol's iodine is a chemical substance that turns brown or black when it comes into contact with glycogen in normal, mature squamous epithelium. Pre-cancerous lesions and cancers contain little glycogen due to the presence of poorly differentiated cells, and therefore, they gradually turn shades of yellow after Lugol's iodine is applied.[11]

The detection of HPV nucleic acid is also essential for cervical cancer screening. HPV nucleic acid testing methods can be categorised into two main types based on the detection principle, namely signal amplification technology and target amplification. Signal amplification refers to a method that detects nucleic acids mainly through the hybridisation of specific probes with nucleic acids and cascade amplification of chemiluminescent signals. It mainly includes the hybridisation capture chemiluminescence method and the enzymatic signal amplification method, among others. The target amplification method is the most widely utilized approach for detecting nucleic acids, primarily through polymerase chain reaction (PCR) amplification combined with other techniques.

Recently, new methods for detecting HPV have also been developed. Zhan's team has developed a novel HPV-DNA detection technology that combines DNA tetrahedron-modified magnetic beads with the CRISPR-Cas12a system. This method uses three metal-labeled probes (gold, silver, and platinum) corresponding to the three high-risk types HPV-16/18/52. When target DNA is detected, the CRISPR-Cas12a system is activated, cleaving the single-stranded DNA connected to the metal label and releasing the metal signal. The signal is then precisely detected using a high-sensitivity ICP-MS mass spectrometer. The innovation of this technology lies in the use of DNA tetrahedral structure-modified magnetic beads, which significantly enhance probe binding efficiency while achieving three-level signal amplification, resulting in a detection sensitivity of 218 fM. This technology exhibits high specificity, strong interference resistance, and outstanding performance in clinical applications, providing a more precise and efficient solution for HPV screening.[12]

In addition, Leung's team developed an HPV circulating tumor DNA (ctDNA) detection platform based on high-throughput sequencing of HPV. This technology uses a hybridization capture strategy to target and enrich complete HPV genomic sequences in plasma, combined with deep sequencing analysis, achieving several technical breakthroughs. In terms of detection performance, its sensitivity

reaches 0.03 copies/mL of plasma, enabling simultaneous HPV genotyping and ctDNA fragmentomics analysis. It demonstrates 100% sensitivity and 67% specificity in predicting tumor recurrence. It offers higher detection sensitivity than traditional digital PCR technology, capable of detecting low-concentration samples that are negative by dPCR and providing multi-dimensional molecular feature information. Therefore, it provides a new method for the early diagnosis of HPV-related malignant tumors and aims to enable dynamic monitoring during treatment.[13]

6. The HPV was cleared by the immune system

Vaccines are an effective means of preventing HPV infection. To better understand the mechanism of the HPV vaccine, it is helpful to briefly introduce the human immune system briefly. The immune system is the body's defence system against pathogens, consisting mainly of immune organs, immune cells, and immune molecules. There are two significant types of immunity in the human body: innate immunity and adaptive immunity. The innate immune system can respond rapidly and is non-specific. The main components of the innate immune system include the skin and mucosal barriers, as well as phagocytes such as neutrophils and macrophages. The innate immune system effectively blocks pathogen invasion, identifies and phagocytoses invading pathogens, and releases inflammatory factors to activate other immune cells. However, it cannot recognise specific pathogens and lacks immune memory function, so when the innate immune system cannot withstand pathogens, the adaptive immune system takes over. Adaptive immunity, although slower to respond, possesses strong specificity and immune memory. The two types of cells responsible for adaptive immunity are B lymphocytes and T lymphocytes. B lymphocytes primarily mediate humoral immunity; after recognising antigens, they differentiate into plasma cells and produce antibodies in response. Antibodies typically complement pathogens, enabling them to neutralise toxins by binding to pathogens and marking them for phagocytosis by phagocytes. T lymphocytes primarily mediate cellular immunity. They can recognise infected or abnormal cells. T-killer cells can immediately remove infected cells, while T-helper cells can activate B lymphocytes and macrophages by releasing cytokines.[14]

After HPV infects the human body, the immune system recognises and fights HPV in two stages: the innate immune response and the adaptive immune response. The cells related to the innate immune response against HPV are natural killer (NK) cells, which are commonly found in virus-related lesions and precancerous lesions. Nevertheless, it has been observed that cancerous lesions are resistant to NK cell attacks, while the activity of immune-stimulating cytokines is reduced and restricted.[15] Therefore, the adaptive immune response, which produces antibodies and memory cells, is a more critical stage. After HPV infection of basal cells, the L1 and L2 capsid proteins on the viral particles are recognised by particular antigen-presenting cells (APCs), such as dendritic cells (DCs) or Langerhans cells (LCs). These APCs take up and process viral antigens, then present them on MHC molecules to $CD4^+$ T cells or CD8+ T cells. Co-stimulatory signals activate $CD4^+$ T helper cells (Th cells) after recognising antigens and subsequently differentiate into Th1 cells to generate cytokines such as IFN-γ and IL-2, thereby enhancing cytotoxic T cell (CTL) responses. Concurrently, $CD4^+$ Th cells can also differentiate into Th2 cells, which secrete cytokines such as IL-4, IL-5, and IL-6, thereby improving the differentiation of B cells into plasma cells and the production of antibodies. $CD8^+$ CTLs recognise HPV antigens presented on virus-infected epithelial cells and secrete perforin and granzyme to induce target cell apoptosis. B cells activated by cytokines can differentiate into plasma cells and produce neutralising antibodies. IgG antibodies produced by B cells can bind to the L1 capsid protein of HPV, preventing it from binding to receptors on the surface of host cells, neutralising viral particles, and preventing them from entering epithelial cells. In addition, IgG antibodies can also enhance the clearance capacity of macrophages through Fc receptor-mediated phagocytosis. Another portion of B cells form memory B cells, which provide a rapid response in the future. When reinfected, memory B cells can rapidly differentiate into plasma cells and produce large amounts of antibodies quickly.[16] The HPV vaccine induces immunity and mimics natural immunity

through the above process. Taking the nine-valent vaccine, which is based on virus-like particles constructed from the L1 protein and does not contain viral genomes, as an example, the nine-valent vaccine can induce a strong humoral immune response, produce many neutralising antibodies, and induce memory B cells, providing the human body with long-term protection.

7. The HPV vaccine protects by inducing immune memory

The HPV vaccine is a preventive vaccine based on virus-like particle (VLP) technology. Its production process utilizes recombinant DNA technology to efficiently produce the HPV major capsid protein L1 through a yeast expression system. These L1 proteins possess self-assembly properties, enabling them to form VLPs structurally highly similar to natural HPV viral particles. They are completely non-infectious and non-oncogenic due to lacking viral genomic DNA. Following vaccination, VLPs can be recognized by antigen-presenting cells, inducing the body to produce high-titer neutralizing antibodies. These antibodies can specifically bind to HPV viral particles, blocking their interaction with host cell surface receptors, thereby effectively preventing viral infection. Clinical studies have confirmed that the humoral immune response induced by the vaccine is significantly stronger than that produced by natural infection, and vaccinated individuals can develop long-term immune memory. Therefore, the vaccine achieves over 90% efficacy in preventing HPV-related high-grade cervical intraepithelial neoplasia and genital warts.[17]

Currently, the HPV vaccine is the most useful means to hinder diseases caused by HPV. An international, randomised, controlled trial conducted among female adolescents and adult women aged 15 to 26 years demonstrated that the vaccine efficacy in preventing cervical precancerous lesions was at least 96%, as the HPV types aimed by the vaccine were effective in the study population.[18] The three most common types of HPV vaccines are bivalent, quadrivalent, and 9-valent. The bivalent HPV vaccine contains the antigens of L1 VLP of high-risk HPV types 16 and 18, which are bonded with about 70% of cervical cancers. It effectively prevents cervical cancer, vaginal cancer, and vulvar cancer triggered by HPV types 16 or 18. Therefore, it is typically recommended for women aged 9 to 25. The quadrivalent HPV vaccine effectively prevents high-risk HPV types 16 and 18, as well as low-risk HPV types 6 and 11, which are associated with around 90% of genital warts. Unlike the bivalent vaccine, the quadrivalent vaccine is suitable for both men and women aged 9 to 26. Vaccination for men can prevent genital warts and anal cancer, while vaccination for women can prevent both cervical cancer and genital warts. Therefore, the quadrivalent vaccine offers broader preventive effects and is particularly suitable for those at risk of sexual activity or with a history of warts. The nine-valent HPV vaccine provides protection against seven high-risk HPV types 16/18/31/33/45/52/58, which account for approximately 90% of cervical cancer cases, as well as two low-risk HPV types—6 and 11—that cause genital warts. The nine-valent vaccine is suitable for males and females aged 9 to 45. It provides the most comprehensive protection against cervical cancer and related lesions and is considered the optimal HPV vaccine currently available. The high coverage rate of the nine-valent vaccine can significantly reduce the burden of related cancers at the population level.[19]

8. Current status and challenges of HPV vaccination

By the end of November 2022, 125 countries had included the HPV vaccine in their domestic vaccination programmes, with approximately 24% of countries also providing coverage for male vaccination. According to World Health Organisation data, the first-dose vaccination rate for 15-year-old girls worldwide increased from 20% to 27% between 2022 and 2023, but this remains significantly below the WHO's 90% target for 2030. Additionally, HPV vaccination coverage exhibits significant regional disparities, with first-dose coverage rates of 85% and 77% in the Americas and Europe, respectively, while low- and middle-income countries lag far behind at less than one-third.[20] To reduce this inequality in HPV vaccination, a single-dose HPV vaccine strategy is being promoted.

Because fewer doses are required to complete the vaccination, the pressure of vaccine shortages can be alleviated, allowing those who need it most to receive the vaccine. This approach reduces the overall cost of implementing vaccination programmes, enabling more people in low- and middle-income countries to be vaccinated.[21]

According to the results of a randomized controlled clinical trial conducted by Iversen et al., the 9-valent HPV vaccine demonstrated significant immunogenicity advantages when administered in a two-dose schedule in adolescents aged 9–14 years. The study showed that the two-dose regimen achieved a pre-specified non-inferiority criteria for antibody titers across all HPV types, and the geometric mean antibody titers (GMT) in the adolescent group were comparable to or even higher than those in the three-dose regimen group of women aged 16–26 years. This regimen significantly improved vaccination adherence while simplifying the vaccination schedule, with a seroconversion rate exceeding 98%, and demonstrated a 23–35% reduction in vaccination costs in a cost-effectiveness analysis. This study provides important scientific evidence supporting the WHO-recommended two-dose HPV vaccination strategy for adolescents, driving adjustments to immunization programs in over 45 countries worldwide. Five-year follow-up data further confirmed that this regimen maintains durable immune protection, with a GMT decline rate below 15%.[23]

The UK's policy on whether males should receive the HPV vaccine has undergone a significant shift. In 2017, the UK Joint Committee on Vaccination and Immunization recommended against including boys in the HPV vaccination program, citing insufficient cost-effectiveness.[24] However, in 2018, the English Department of Health revised its policy and decided to offer HPV vaccination to boys aged 12 to 13.[25] This shift was based on the following considerations: first, expanding the scope of vaccination would help achieve more comprehensive herd immunity protection; second, it would prevent HPV-related diseases in men; and third, it would effectively fill the immunity coverage gap caused by vaccinating only women. This policy change not only reflects the evolution of public health strategies but also demonstrates recognition of gender equality in vaccination rights.

Additionally, HPV vaccines may increase the risk of certain immune system disorders. The most common autoimmune diseases include musculoskeletal disorders, central nervous system disorders, and endocrine system disorders.[22] Regarding the future development trends of HPV vaccines, governments around the world should continue to promote the inclusion of HPV vaccines in national immunisation programmes, using government procurement and subsidies to reduce costs. At the same time, they should enhance the research and development of nine-valent and next-generation multivalent vaccines to effectively address supply bottlenecks. In addition, they should promote vaccination strategies for different gender groups to eliminate gender inequality and thereby enhance public awareness.

9. Conclusion

This paper explores the relevance between HPV and cervical cancer, discussing the classification of HPV, the infection mechanisms, transmission routes, and the carcinogenic processes which HPV induces. HPV infection is the dominant cause for cervical cancer, with its carcinogenicity primarily stemming from the interference of the viral early proteins E6 and E7 with the host's tumour suppressor genes p53 and pRB. Given that vaccination is the primary way of preventing HPV infection, the article further reviews the current types of HPV vaccines, their mechanisms of action, immunological principles, and target populations. Based on the global vaccination landscape, it analyzes the challenges and difficulties encountered in vaccine rollout. In spite of the vaccine's high efficacy, vaccination rates in developing countries are still far below the World Health Organisation's target figures, posing a significant challenge to global public health. This paper aims to enhance the public's systematic comprehension of the pathogenic mechanisms of HPV and the immunological mechanisms of vaccines, while also promoting the global popularisation of HPV vaccines. Future research should focus on the role of HPV vaccines in distinct gender and age groups. It should also

strengthen studies on the protective effects of vaccines against HPV-related non-cervical cancers, thereby achieving broader preventive coverage and health intervention goals.

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