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Review

Detection of HPV Infection and the Current Status of Vaccine Research: A Review

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Abstract

Objectives: Purpose of this narrative review is to comprehensively summarize and compare the methods of human papilloma viruses (HPV) detection to provide a reference for clinical selection. And it also concludes the research progress of preventive HPV vaccines and therapeutic HPV vaccines to provide new ideas for the future development of HPV vaccines. **Mechanism**: A comprehensive search of published relevant articles was conducted. Multiple database were searched including PubMed, SCOPUS, and Ovid. Searches included the key terms: human papilloma viruses (HPV), HPV infection, epidemiology, HPV vaccine, cervical cancer (CC) screening, detection technology. **Findings in Brief**: HPV is a sexually transmitted virus and also a common cause of female reproductive tract infections. HPV has been reported to be associated with approximately 5% of human cancers worldwide, among which high-risk HPV (HR-HPV) infection is the most closely related to cervical cancer. The advantages of using HPV testing for cervical cancer screening are the high long-term negative predictive value (NPV), the high sensitivity (90–95%) for cervical intraepithelial neoplasia (CIN) 2 or 3, and the significant reduction in CIN2/3 and cancer in test-negative women over long term follow-up. The current detection of HPV infection is mainly for HPV DNA, RNA and oncoprotein, and vrious methods have their own features. Currently, there is no treatment for an HPV infection, so prevention is the key to cancer reduction. HPV vaccine is an important means to reduce the incidence rate of HPV infection and HPV related cervical cancer. **Conclusions**: With the development of assay technology, assays with low cost, high versatility and operability will be needed in the future. The HPV vaccine, as a primary prevention measure for cervical cancer, has achieved significant results in preventing HPV infection and reducing the incidence of reproductive tract diseases. In the future, it is expected that the HPV vaccine will make significant breakthroughs in the treatment of current HPV infections and cervical cancer.

Keywords: human papilloma viruses; screening; vaccines; cervical cancer

1. Human Papilloma Viruses Screening

There are 280 human papilloma viruses (HPV) subtypes and more than 200 species that can infect humans [1,2]. Eighty-five to 90% of high-risk HPV (HR-HPV) infections are eliminated spontaneously within 6 months to 2 years, with the remainder being persistent [3]. Persistent HR-HPV infection is an important factor in promoting the development of cervical intraepithelial neoplasia (CIN) to invasive cervical cancer (ICC). Other high risk factors include early and multiple partner sexual activity [4]. It has been demonstrated that Chinese women are predominately infected by HPV 16, followed by HPV 52 and 58 [3].

HPV is a nonenveloped circular double-stranded DNA virus. The HPV viral genome can be divided into three regions: early coding region (E region) which mainly encodes non-structural proteins including E1, E2, E4, E5, E6, and E7; late coding region (L region) which mainly encodes the structural proteins required for virions and virus transmission; and long control region (LCR) which contain early promoters and regulatory sites that regulate the transcription of viral and cellular proteins [5]. E1 and E2 proteins initiate viral DNA replication and act as transcriptional activators [6]. E5 protein induces immune evasion, which leading to enhanced cell proliferation [7]. E6 protein combines with tumor suppressor protein p53 and can induce the degradation of p53 protein [8,9]. The E7 protein combines with retinoblastoma protein (pRb) and can degrade the pRb through the ubiquitin-proteasome pathway [10–12]. Research has confirmed that E7 is the key to HPV16 related carcinogenesis [13].

HPV can be divided into two groups: low risk types that cause genital warts and high risk types that are associated with invasive cervical cancer. The World Health Organization (WHO) defines 12 types of HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) as a category 1 high-risk carcinogenic type, with HPV 68 possibly being carcinogenic (category 2A) [14]. It has been demonstrated that there are significant differences between high-risk HPV and low-risk HPV in promoter location, promoter regulation and messenger RNA (mRNA) splicing mode, which affects the expression of E6 and E7 genes [15]. Of the high-risk HPV types, HPV 16 and 18 are responsible for

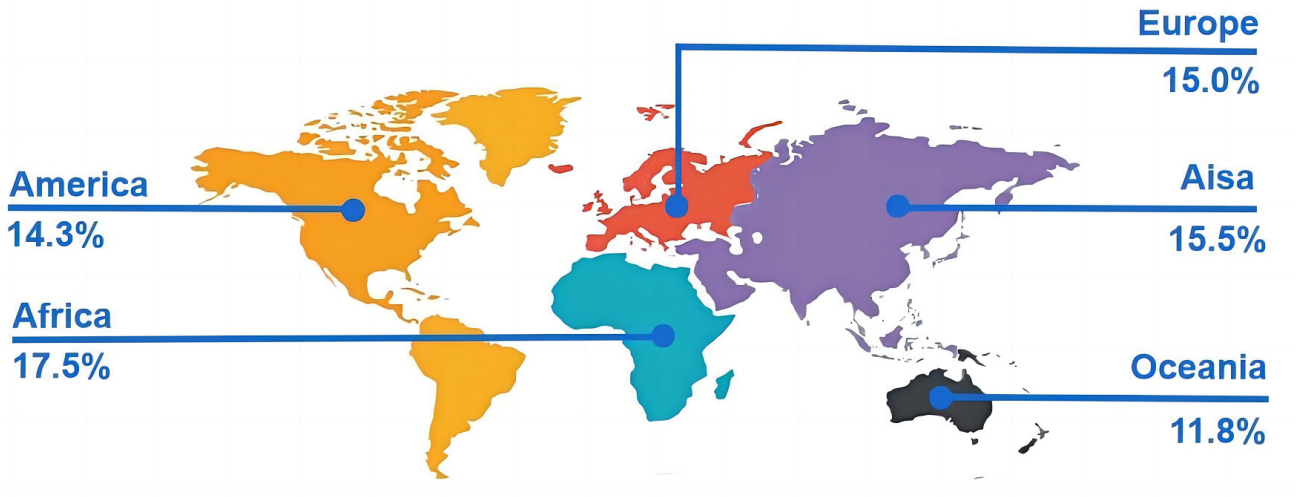

Fig. 1. Percent prevalence of HPV grouped by continent.

approximately 90% of all cervical cancers. HPV infection and replication occurs in host mucosa and skin epithelial cells. HPV enters epithelial cells by taking the full advantage of the epithelial cell self-division and renewal. HPV that enters into epithelial cells integrates genes into cells and participates in the formation of cervical lesions [16].

HPV is mainly transmitted through sexual intercourse. Surveys reveal that the worldwide HPV infection rate in 2020 is 15.6% with great geographic variation [17]. Among the five continents, Africa (17.5%) and Asia (15.5%) had the highest HPV infection rates among women, followed by Europe (15.0%), America (14.3%) and Oceania (11.8%) [17] (Fig. 1). The HPV infection rate in women in developing regions (16.4%) is higher than that in developed regions (11.6%) [18]. The HPV infection rate in men is similar to that in women (3.5%–45.0% *vs*. 2.0%–44.0%) [19]. The five most prevalent popular HPV types in the world are HPV16, 18, 52, 31 and 58 [15].

HR-HPV infection has attracted a great deal of attention because of its close relationship with CIN and cervical cancer (CC). Previously, HPV screening was only used to triage patients in cases of abnormal cytology, but current research has found that using HPV screening as the first choice for primary cervical cancer screening can yield higher accuracy rates than cervical cytology [20]. HPV screening is more sensitive in detecting CIN2+ cases. Currently, HPV testing is mainly used for co testing with cytology but can be used for primary screening for cervical cancer. It can be used to evaluate patients with abnormal cytology as well as for follow-up after treatment of precancerous lesions. According to the structural characteristics of HPV, the current clinical testing of HPV is mainly for HPV DNA, RNA and oncoproteins, as shown in Table 1.

2. HPV DNA Detection

2.1 Second-Generation Hybridization Capture Technology (HC-2)

HC-2 is a qualitative nucleic acid hybridization assay that uses a synthetic RNA probe complementary to the viral genome sequence to provide comprehensive detection of 13 HR-HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) by signal amplification [21]. HC-2 is the first method approved by the US Food and Drug Administration (FDA) to detect HPV DNA clinically. It is commonly used to detect HPV DNA and is often used as a reference comparison for other detection methods [22] to obtain higher efficiency and accuracy. It can only report the presence of infection but does not identify the type or whether there are multiple infections [23]. A meta-analysis of HC-2 detection demonstrated that the sensitivity and specificity of HC-2 detection for cervical cancer were 83% and 71% respectively [24]. Another study [22] showed that HC-2 has higher sensitivity compared with cervical cytology screening. However, the limited specificity of the HC-2 test makes it susceptible to over-testing and over-treatment in clinical practice.

2.2 Real Time Fluorescence Quantitative Polymerase Chain Reaction (PCR) Detection Method

Compared with HC-2 detection, PCR detection can specifically detect HPV 16 and 18 infection along with 12 other types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) of high-risk HPV. However, it has the disadvantage of being complex and expensive to perform, and the multiple types of HPV infections require separate testing. Currently, the kits used for clinical detection include Cobas 4800 HPV detection, Abbott Real Time HR-HPV detection, and BD Onclarity HPV Assay. Cobas 4800 is simple and convenient to operate, and is widely used in clinical practice. One study showed that the sensitivity and specificity of HC-2 and Cobas 4800 in diagnosing CIN2 were 95.2% *vs*. 93.7% and 72.4% *vs*. 77.2% respectively [25].

Table 1. Clinical characteristics of the different assays for HPV infection.

HPV assay	Target	Common types of reagents	Separate genotyping	Sensitivity/specificity	Advantages	Disadvantages
HC-2	HPV DNA	-	No (13 HR-HPV types)	83%/71% for cervical cancer	higher efficiency and accuracy	only report whether it is infected, cannot know the accurately type or multiple infection
PCR	HPV DNA	Cobas 4800 test Abbott Real Time HR-HPV test BD Onclavity HPV assay	16, 18 and 12 other HR types (Abbott Real Time HR-HPV test and Cobas 4800 test) 16/18/31/45/51/52; 33/58; 56/59/66; 35/39/68 (BD Onclavity HPV assay)	93.7%/77.2% (Cobas 4800 *t*-est compared with HC-2 in diagnosing CIN2)	specifically detect HPV 16 and 18 infection and other 12 types of HPV infection	complex and expensive to perform
Enzymatic digestion signal amplification technology	HPV DNA	Cervista HPV HR test	A5/A6:51/56 /66 A7:18/39/45/59 and 68 A9:16/31/33/35/52 and 58	The agreement was 91.7% compared with HC-2	qualitatively detect specific 14 HR-HPV types	expensive
In Situ Hybridization	HPV DNA	No commercial product were found and Just use in research laboratory	Detect different types according to clinical needs	100%/83%	High specificity	too laborious and clinically insensitive
HPV E6/E7 detection	HPV mRNA	Aptima HPV (AHPV) Aptima HPV 16/18/45 Genotype (AHPV GT)	No (14 HR types in bulk). Separate typing of 16; 18:45 available as a separate reflex test	83–100%/23–73% (shunt CIN3+ from LSIL)	better predict the risk of disease	expensive
HPV carcinogenic protein detection	HPV anti-E6/E7 oncoproteins	-	-	-	better predict the risk of disease low cost	limitations of virus types detected

HC-2, second-generation hybridization capture technology; PCR, polymerase chain reaction; HPV, human papilloma viruses; HR-HPV, high-risk human papilloma viruses; CIN, cervical intraepithelial neoplasia; LSIL, low-grade squamous intraepithial lesion.

Table 2. Current status of clinical trials of HPV therapeutic vaccines (Phase II/III clinical trial).

NCT number	Type of vaccine	Antigen information	Applicable population (number)	Fase
3721978	Nucleic acid vaccine	Two plasmids encoding E6 and E7 protein of HPV 16/18	CIN or HSIL HPV16/18+ (198)	III
3185013			HSIL with HPV16/18+ (201)	III
2853604	Live vector vaccines	prfA-defective Listeria monocytogenes strain transformed with plasmid encoding HPV16 E7 antigen fused to a fragment of non hemolytic listeriolysin O (LLO)	local advanced cervical cancer (450)	III
2576561	Protein and polypeptide vaccines	TVGV-1(Pseudomonas exotoxin HPV16 E7 protein vaccine ± GPI-0100)	HPV (+) HSIL (10)	II
3946358		UCPVax Peptide vaccine + Atirizumab	Advanced/metastatic malignant tumor with HPV+ (47)	II
2139267	Nucleic acid vaccine	HPV16/18 E6/E7 DNA vaccine	CIN with HPV16/18+ (72)	II
3911076		PVX-2 DNA vaccine (detox)/HSP70 (HPV16 E7 DNA vaccine)	ASC-US, ASC-H, LSIL (122)	II
3946358	Protein vaccines	HPV 16 E6/E7/L2 protein vaccines	HPV(+) advanced/metastatic cervical cancer (47)	II
4180215	Live vector vaccine	HB-201, HB202 (Encoding HPV16 E6/E7 virus vaccine)	HPV associated squamous cell tumor (140)	I/II
2128126	Protein and polypeptide vaccines	ISA101/ISA101b (12 synthetic long peptides derived from the E6 and E7 proteins of HPV16) + Utomilumab/cemiplimab/Nivolumab	Advanced, metastatic, recurrent cervical cancer with HPV 16 (+) (93)	I/II

HPV, human papilloma viruses; ASC-US, atypical squamous cell of undeternined; ASC-H, atypical squamous cells-cannot exclude HIS; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion.

2.3 Enzymatic Digestion Signal Amplification Technology (Invader Assay)

Compared with HC-2, the advantage of enzyme digestion signal amplification technology is that it can qualitatively detect specific nucleic acid sequences of 14 HR-HPV types and require half the sample volume of the HC2 test. Cervista HPV HR test is approved by FDA for testing HPV DNA. The A5/A6 group can be used to detect HPV51/56 and 66. The A7 group can detect HPV18/39/45/59 and 68. A9 group can detect HPV16/31/33/35/52 and 58. By comparing HC-2 and Cervista, the investigators have found that the agreement between the two assays was 91.7% (802 of 875; k = 0.743; 95% confidence interval, 0.688–0.798) in the diagnosis of CIN2+ [25]. The Cervista HPV test is applicable to cervical cancer screening for women over 30 years of age, which can improve the diagnostic rate of CIN and cervical cancer.

2.4 In Situ Hybridization for HPV

In situ hybridization (ISH) is the only molecular method that can reliably detect and characterize the topographic relationship between HPV and its pathological lesions. It is able to detect HPV infection specifically, and studies have found that for HPV infection, ISH has a specificity of 100% and a sensitivity of 83% [26]. Most commercially available assays contain a mixture of probes for multiple types of HPV, but if the subtype is clinically relevant, the test can be performed using probes for a single type, such as HPV type 16. Currently, experts believe that the ISH test is too laborious and clinically insensitive to be used for routine screening.

2.5 HPV RNA Detection

HPV DNA positivity represents HPV infection, while the high expression of HPV E6 and E7 mRNA indicates that HPV is actively replicating. Therefore, compared with HPV DNA detection, detection of E6 and E7 mRNA can better predict the risk for disease progression. Compared with HC-2, HPV E6 and E7 mRNA can be used as a sensitive monitoring tool for cervical cancer screening, but the detection cost is expensive [27]. Currently, the kits approved by the FDA in the United States include Aptima HPV (AHPV) and Aptima HPV 16/18/45 Genotype (AHPV GT). Aptima HPV can detect 14 types of high-risk HPV infections, but it can only report an infection and not distinguish the specific type of HPV. AHPV GT can detect HPV type 16 and 18/45. For type 18/45, it can only report whether an infection is present and cannot distinguish specific types. Research showed that [28,29] Aptima HPV detection has higher specificity for cervical CIN2+, with its sensitivity remaining stable. Aptima HPV test can also be used to triage patients with abnormal cytological test results, determine the risk of disease progression, and determine which patients need further examination [30].

3. HPV Carcinogenic Protein Detection

Ewaisha *et al*. [31] found antibodies and early HPV proteins in sera of 20–46% patients who presented with cervical precancerous lesions or cervical cancer. A majority of the studies have focused on E6 and E7 antibodies of HPV 16/18. Being positive for E6/E7 protein of HPV 16/18 indicates that HPV DNA is being highly expressed. Compared with the detection of mRNA, the cost of screening for HPV oncogenic protein is relatively low, and it is being widely used in pathological examination [19].

4. HPV and Cervical Cancer

Cervical cancer is a chronic and complex disease caused by genetic factors and external environmental influences. Current studies have confirmed that high-risk HPV infection is closely related to cervical cancer. Integrating HPV genome into host chromosome is a key genetic step in cervical carcinogenesis [32]. During the process of tumor development, virus integration into the host genome usually results in the loss of E2, E4, E5, L1 and L2 expression, and the expression of E6 and E7 oncogenes is a necessary condition for cancer cell development. As previously described, E6 can bind and degrade p53 to allow viral DNA replication [8]. E7 inhibits tumor suppressor retinoblastoma 1 (RB1) and releases E2F transcription factors. It stimulates cyclin-dependent kinase 2 (CDK2)/cyclin A 58 as well as CDK2/cyclin E complex 59, thus abrogating cell cycle arrest and stimulating proliferation [10,33,34]. Previously, researchers detected a single copy of HPV16 in the intergenic region between KLF5 and KLF12 on chromosome 13q22 of SiHa cell line [35]. This is the first time that investigators have found that HPV is integrated into the human genome.

In addition to the integration of HPV into the host genome, somatic mutation in the host genome induced by HPV is also an important aspect in the study of cervical carcinogenesis. Ojesina *et al*. [36] have found that the common mutations in squamous cell carcinomas(SCC) were *EP300* (16%), *FBXW7* (15%), *PIK3CA* (14%), *HLA-B* (9%), and *p53* (9%) while *PIK3CA* (16%), *ELF3* (13%), *KRAS* (8%), and *CBFB* (8%) were in adenocarcinomas [36]. In addition, they found new mutations in *HLA-B*, *EP300* and *FBXW7* in cervical cancer, which had not been previously found. The discovery of these mutations can be used as potential biomarkers for early screening of cervical cancer, such as oncogene *EGFR*, *PIK3CA*, and the gene suppressors *TP53* and *PTCH1* [37–39]. The researchers also found that patients with mutations in the tumor suppressor gene *CADM1* had the worst prognosis, indicating that gene mutations can affect the outcome of cervical cancer [40]. The 3-year relapse free survival rate of patients with *PIK3CA* mutation was significantly improved, but the patients with *KRAS* mutation experienced a low rate of the relapse free survival time [41,42].

It has been found that DNA methylation is also involved in HPV induced carcinogenesis. By using a pyrosequencing method, researchers found that cervical cancer was associated with methylation of L1, L2 and E2/E4 regions in HPV16 genome [43]. In another study, researchers found that the level of DNA methylation in E2, L1 and L2 regions of HPV18, HPV31 and HPV45 was significantly increased in cervical intraepithelial neoplasia grade 3 (CIN3+) [44]. The study found that the methylation level was positively correlated with CIN and the presence of cervical cancer. The positive detection rate of gene methylation in CIN3 was 63.3%, 100% in cervical cancer, and only 5.5% in normal tissues [45]. The study found that CADM1/MAL methylation had a high sensitivity of 60.5%–100% for CIN3 and cervical cancer patients, and the correlation was as high as 78% compared with biopsy results [46,47].

5. HPV Vaccine

Persistently high-risk HPV infection rates are the main cause of cervical cancer, but there is no effective drug to eliminate persistent HPV infection. HPV vaccine is an important tool to reduce the incidence rates of HPV infection and HPV related cervical cancer. Evidence has shown that HPV vaccines reduce the incidence of HPV infection, cervical lesions, genital warts, and other lesions. A recent meta-analysis [48] showed a 70% reduction in HPV 16/18 infection after 5–8 years of HPV vaccination, a 54% reduction in HPV 31/33/45 infection in women aged 13–19 years, and a 51% reduction in CIN2+ in women aged 15–19 years. In women aged 20–24 years after 5–9 years of HPV vaccination, a national study in Sweden in 2020 showed that a 63% reduction in the risk of cervical cancer in women who had received the HPV vaccine [49]. HPV vaccines are divided into preventive vaccines and therapeutic vaccines.

5.1 Preventive HPV Vaccine

Many countries have launched national immunization programs for girls aged 9–25 years before the onset of sexual behavior. The goal of the 2030 Healthy People is that 90% of girls will complete the process of HPV vaccination before the age of 15. However, a study in the United States shows that the coverage rate of three doses of HPV vaccine for adolescents is only 58.6% [50]. The preventive vaccines approved by the FDA include the bivalent vaccine Cervarix for HR-HPV16/18, which is responsible for 70% of cervical cancer, the tetravalent vaccine Gardasil for preventing HPV6/11/16/18 infections and the 9-valent vaccine Gardasil 9 for 16/18 and five other types (31, 33, 45, 52 and 58) of infection. Recently, some scholars have suggested that HPV screening should be postponed for women who have received the HPV vaccine. An Italian study proposed that women receiving an HPV vaccination should take part in HPV screening from the age of 30, with the re-screening interval for HPV negative results being longer [51]. At present, the biggest problem faced by the marketed HPV preventive vaccine is that the protection type is limited and the cross type protection effect is poor. Therefore, in order to obtain the protective effect on more HPV types, it is necessary to increase the types of antigens. However, increasing the type of antigen means a higher immune dose, which potentially increases adverse reactions.

5.2 Therapeutic HPV Vaccine

The principle of human papillomavirus (HPV) therapeutic vaccine is that the antigen can stimulate the body to generate immune response to eliminate infected cells. E6 and E7 proteins are important targets of a therapeutic vaccine for cervical cancer. At present, therapeutic HPV vaccines are still in clinical trials, mostly in Phase I and Phase II. Only three vaccines have entered Phase III clinical trials, as shown in Table 2. According to the type of vaccine, HPV therapeutic vaccines can be divided into the following four categories: protein and polypeptide vaccines; recombinant vector vaccines; nucleic acid vaccines; and dendritic cell vaccines. Nucleic acid vaccines are mainly used, and are predominately DNA vaccines. The principle of a protein/peptide vaccine is to inject purified protein or peptide into the body to stimulate cytotoxic T cell activity. The protein vaccine may contain multiple HLA restricted cytotoxic T lymphocyte phenotypes applicable to the general population, while the peptide vaccine is only applicable to individuals with certain HLA haplotypes, which limits its widespread use. Given the limitations of peptide vaccines, studies have found that long peptide vaccines containing whole antigens may expand their use [52]. Protein/peptide vaccines are safe, stable and easy to mass produce, and are expected to be widely used in the treatment of HPV infection-associated cervical cancer. Nucleic acid vaccine is safe, but its immunogenicity is low. It needs to be enhanced by adjuvant, combination therapy, multiple vaccine inoculation or other methods. Nucleic acid vaccines mainly include DNA vaccine and RNA vaccine. DNA vaccines contain DNA fragments that can encode protein antigens. The main principle is to activate the immune response *in vivo* through antigen expression. RNA vaccines are mostly derived from RNA viruses, and their immunogenicity is stronger than other forms of nucleic acid vaccines. A phase III clinical trial showed that after 18 months of VGX-300 vaccination, 91% of patients turned negative for HPV DNA [53]. VGX-300 vaccine is a DNA vaccine designed for E6 and E7 of HPV16/18. The principle of a live vector vaccine is to splice the coding gene of tumor specific antigen into the attenuated virus or bacterial vector, synthesize proteins with tumor antigen characteristics in the body and activate the cellular immune response of the body. A phase III clinical trial showed that ADXS11-001 had a specific effect on recurrent or persistent cervical cancer [54]. The principle of dendritic vaccine is to use viral polypeptides, DNA, RNA to sensitize dendritic cells of patients *in vitro*, so that the

dendritic cells can load corresponding tumor antigens. It is then transfused back into the body to activate T cells and induce anti-tumor immune response. Testing has shown that HPV16/18 E7 was loaded onto dendritic cells and when injected subcutaneously into patients, demonstrated good safety and tolerance, and stimulated HPV specific humoral and CD4+ T cell immune responses, although these results have not been replicated and require further research.

6. Discussion

In this review, we comprehensively summarize and compare the methods of HPV detection and the research progress of HPV vaccines including prevention vaccines and therapeutic vaccines for the first time. It provides a reference for selecting HPV testing methods and new ideas for the future development of HPV vaccines. The role of HPV infection, especially HR-HPV infection in reproductive tract diseases has been confirmed. The main burden of HPV infection is the oncogenic effect of high-risk HPV. There are numerous clinical testing methods for HPV, each with its own advantages and disadvantages. Although HPV vaccination is currently included in the immunization plan in many countries, there are still significant disparities in different countries and regions. In China, the HPV vaccine was marketed late, with some research progress being made. However, the acceptance of HPV vaccine is still low due to the traditional perception of the current promotion of the HPV vaccine, insufficient vaccine supply, and the vaccine not being included in the national immunization plan. Reducing prices, expanding availability, raising awareness, and integrating the vaccine into immunization programs are the main challenges in China. The currently used prevention HPV vaccines are effective in preventing infection but not in treating current HPV infection, making the emergence of therapeutic vaccines critical. In the future, it is expected that clinical development of therapeutic vaccines to achieve treatment of existing HPV infections will occur.

7. Conclusions

HR-HPV infection is a major cause of cervical cancer. HPV vaccination and cervical cancer screening are primary and secondary prevention strategies for cervical cancer. With continued development of assay technology, assays with low cost, high versatility, operability, and improved sensitivity and specificity will be needed. The HPV vaccine, as a primary prevention measure for cervical cancer, has achieved significant results in preventing infection and reducing the incidence of cervical and reproductive tract diseases. It is hoped that a major breakthrough in the treatment of HPV infections will occur in the near future.

Author Contributions

LS and HP did the literature searching and screening. LS drafted the manuscript. HP and XH reviewed and revised the draft. All authors approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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