Chapter 12

Preventive Strategies against Human Papillomaviruses

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Additional information is available at the end of the chapter

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Abstract

Human papillomavirus (HPV) infection is among the most common viral infections of the reproductive tract. Out of more than 100 different types of HPV identified so far, only a few (termed as "high-risk" subtypes) are associated with cervical cancer. On the other hand, "low-risk" subtypes are associated with genital warts and other benign changes in cervical and oral mucosa. Majority of the HPV infections usually clear up without any intervention within a few months. However, a fraction of HPV infections, such as those with types 16 and 18, can become persistent which may lead to the development of anogenital or cervical cancers. HPV subtypes 16 and 18 together are responsible for approximately 70% of all cervical cancer cases, the fourth major cause of cancer-related deaths in women. In the absence of any specific treatment options, preventive measures are considered as cornerstone of strategies aimed at curbing the burden of this disease. This chapter presents a comprehensive review of strategies that can be employed to prevent and eradicate HPV infection. Minimizing the exposure to HPV risk factors such as unprotected sex, multiple sex partners, early age sex, and not being circumcised, can reduce the chances of getting HPV infection to a significant level. Mass screening programs have also been effective in HPV eradication. Nevertheless, immunization against HPV has proven to be the most promising strategy in fight against HPV. Virus-like particles based on bivalent, quadrivalent, and nonavalent anti-HPV vaccines have been licensed and are available in market under the trade names of Cervarix®, Gardasil®, and Gardasil9®, respectively. Various clinical trials and population-based studies have demonstrated high levels of efficacy for all the three vaccines in preventing type-specific malignancies.

Keywords: human papillomavirus (HPV), prevention of HPV, immunization, HPV vaccines, cervical cancer

1. Introduction

Although genital warts, papillomatous, and verrucous lesions of skin have been known to human beings since ancient times [1, 2], it was not until the dawn of twentieth century that infectious nature of these warts could be demonstrated [3]. Toward the end of twentieth century, data started to emerge that hinted toward a link between papillomavirus infection and cervical cancer [4]. It is now well established that this heterogeneous family of epitheliotropic viruses is responsible for a spectrum of diseases that range from mild self-limiting anogenital warts and rare recurrent respiratory papillomatosis (RRP) to the penile, vaginal, vulvar, cervical, anal as well as pharyngeal carcinomas [5, 6].

Disease	Commonly associated HPV subtypes
Cutaneous lesions	
Verrucae vulgares, verrucae palmares et plantares	1, 2, 4
Bowen's disease	16
Butcher's warts	7
Verrucae planae	3, 10
EV-squamous cell carcinomas	5, 8
Epidermodysplasia verruciformis (EV)	3, 5, 8
Mucosal lesions	
Condylomataacuminata	6, 11
Laryngeal papillomatosis	6, 11
Buschke–Löwenstein tumor	6, 11
Bowenoidpapulosis, erythroplasia of Queyrat	16
Squamous intraepithelial neoplasias and invasive carcinomas of the anogenital tract	16
Heck's disease	13, 32

Table 1. Diseases caused by HPV Infection and associated subtypes.

More than a 100 types of Human papillomaviruses (HPV) have so far been identified and are classified into five genera; alpha beta, gamma, mu, and nu [7]. HPV genus alpha, also known as genital or mucosal HPV, comprises of about 40 different subtypes and is the most important genus from medical point of view. These genital or mucosal HPV types are further categorized as low-risk (non-oncogenic) and high-risk (oncogenic) types [8] and infect epithelial cells of skin as well as mucosa of anogenital and upper aerodigestive tracts. There are about 15 high-risk subtypes associated with various cancers of anogenital tract as well as head and neck cancer [7]. Notable high-risk HPV genotypes include subtypes 16 and 18 which together account for more than 90% of cervical cancer cases worldwide [9]. Low-risk subtypes, such as

subtypes 6 and 11, on the other hand, are responsible for benign changes in cervical tissue as well as genital warts [10]. The beta genus of HPV includes various cutaneous subtypes some of which might act as a cofactor in the development of non-melanoma skin cancer [11]. The genera gamma, mu, and nu also have cutaneous tropism and are rare [12]. **Table 1** summarizes the diseases caused by HPV infection and associated subtypes.

HPV is the most commonly occurring sexually transmitted infection [5] and around 300 million women worldwide are HPV carriers [13]. In USA, around 14 million people acquire HPV infection every year [14]. Young women are the most commonly affected with highest prevalence in <25 years age group [15, 16]. The incidence of HPV infection is directly correlated with the start of sexual activity as well as the number of sex partners. However, even the persons who remain monogamous for their whole lives are still at the risk of contracting this infection. The major route of HPV transmission is oro-genital and genital–genital contact, and it does not necessarily involve sexual intercourse [5]. More than 90% of HPV infections are cleared within 2 years without any major consequences on the health of patients [17]. A petite fraction of infections with certain types of HPV can persist and progress to cancer, however, this progression usually takes many years. Only persistent viral infection turns into tumors or cancer in the body [18].

Cervical cancer is the fourth major cause of cancer-related deaths in women, and more than 90% of cases are associated with high-risk HPV infection [19]. Infection with any of the 15 high-risk HPV types, particularly subtypes 16 and 18, is considered as necessary but not a sufficient cause of cervical cancer [20]. More than 500,000 new cases of cervical cancer are diagnosed every year out of which about 80% live in developing countries [10] and about 250,000 women die of this malignancy every year [15]. More than 90% of cervical cancer cases are curable with surgical and radiochemotherapeutic interventions if diagnosed at early stages.

Recent years have seen phenomenal success in fight against HPV infection and related cancers. However, the major focus of these efforts remained to be cancerous subtypes or at the best only a couple of warts causing subtypes like 6 and 11. Therefore, there is an urgent need to broaden the scope of preventive strategies to other clinically relevant subtypes as well. This chapter covers an expert commentary on various preventive as well as eradication strategies against HPV and methods being practiced routinely in developed and underdeveloped countries. Guidelines and bottlenecks established by WHO and other-related bodies in prevention and control of HPV will also be a part of this commentary in order to highlight strengths and shortcomings of prevention strategies currently in practice in various regions of the world. Since immunization has been proved the most promising method for HPV prevention, this chapter will focus mainly on the components of the immune system, passive and active immunity, mechanisms of vaccines for immune stimulation, and types of HPV vaccines available.

2. Preventive strategies for HPV

As no specific treatments are available against HPV yet, therefore, more emphasis is put on the prevention rather than treating the infection. Many developed countries including USA,

Australia, Canada, Brazil, Sweden, and United Kingdom have established national guidelines to defeat the HPV and associated cancers [21]. Notably, the established guidelines in mentioned countries altogether focus mainly on the HPV-related cervical cancer in women only. There is no recommendation to screen men particularly and women under the age of 30 years. Similarly, only a small portion of management guidelines refer to other HPV-associated infections/cancers in both genders.

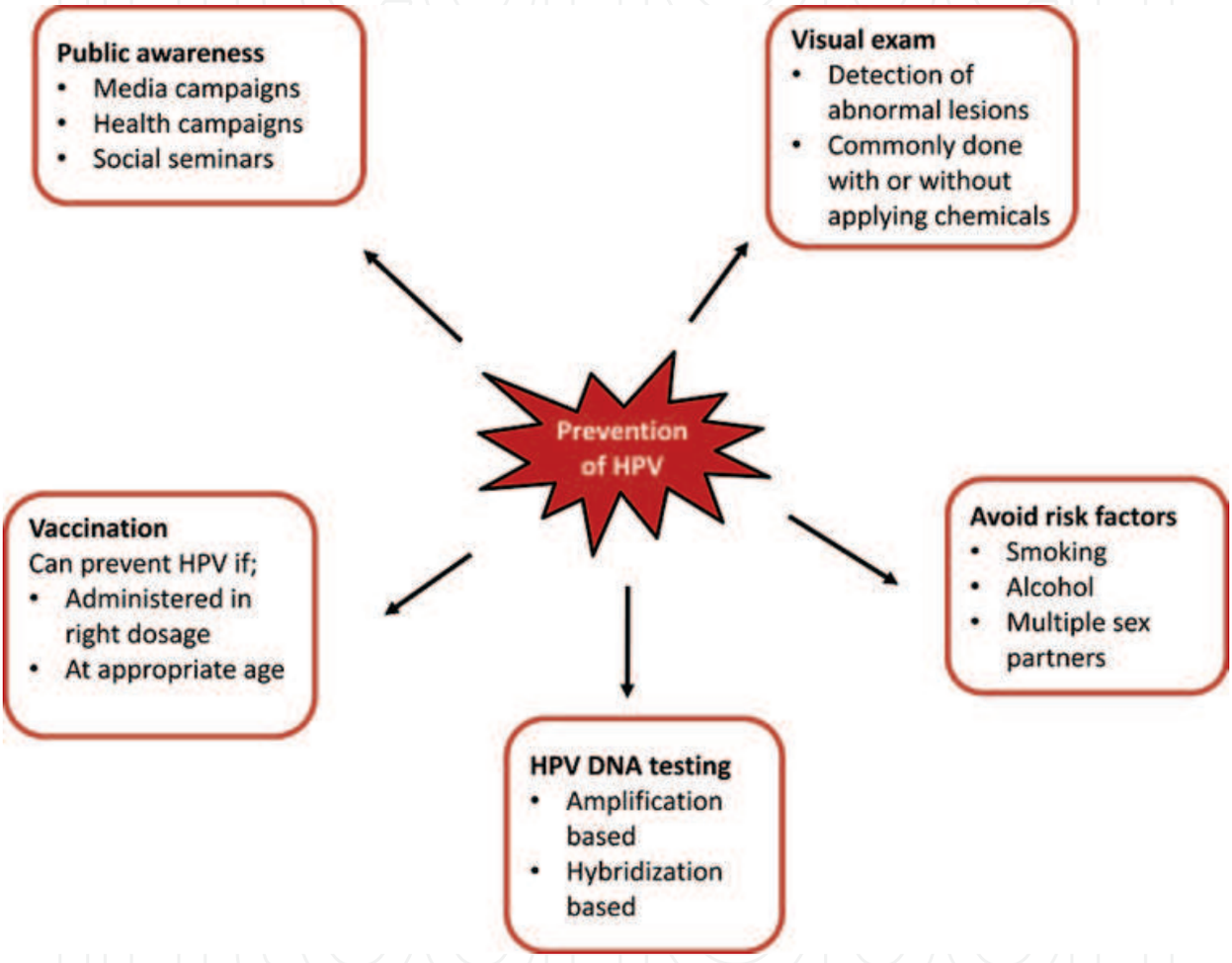

Figure 1. The possible ways for prevention and eradication of the HPV infections.

Despite millions of new HPV infections cases every year, only a few women infected even with hrHPV types manifest precancerous lesions and even fewer develop invasive cervical cancer. This difference in the ratio between HPV infections and HPV-related cancers clearly indicates the role of other risk factors that might be involved in the development of cervical cancer [22]. Current guidelines suggest that HPV infections can be avoided by minimizing the exposure to risk factors such as unprotected sex, multiple sex partners, early age sex, and not being circumcised. In addition to that, practice of mass screening in women aged 21–65 years has been declared a promising strategy to combat the burden of HPV [23].

Above all, vaccination against HPV in both men and women has proven to be the most critical way in preventing the HPV infection. The possible way forward in handling the HPV infections are depicted in **Figure 1**.

2.1. Reduction of exposure to the risk factors

Almost all HPV infections are transmitted from skin to skin and sexual contact [5]. To the best of our knowledge, HPV transmission through body fluids and secretions has never been reported. However, HPV can be transferred vertically from infected mother to child during birth such as in papillomatosis [18, 22]. Risk factors associated with HPV infection and development of its long-term sequelae, particularly cancers, can be broadly categorized into two categories: those associated with HPV infection of mucosal layers lining the oral cavity and lungs and the second category that is associated with warts and cancers of anogenital tract.

Factors, such as smoking, alcoholism, drugs, and direct skin contact with infected person, can play a supportive role for initiating HPV infection, and thus cancer, in the mucosal layers lining the oral cavity and lungs. These types of cancers already constitute a smaller fraction among HPV-associated cancers. Nonetheless, oropharynx cancer has exhibited increasing trend in USA and other parts of the world since the last decade. The cancer of mucosal layers can be prevented by avoiding direct skin contact with infected person. Further, decrease of tobacco and alcohol can also be helpful in reducing head, neck, and oropharyngeal cancer [22].

Genital infections and ultimately cancers are commonly transmitted through sexual contact. Indeed, HPV is the most commonly occurring sexually transmitted virus. Different studies revealed that the sexual behavior including early age sex, multiple sexual partners, oral contraceptives, and co-infection with other sexually transmitted diseases predispose the HPV infection [5]. Data show that risk of HPV infection among women of 18–25 years of age with three life time sexual partners is more than double as compared to women of same age group with one life time partner [24]. Therefore, genital HPV infections can be prevented by reducing the number of sexual partners. Likewise, HPV burden is also linked with certain risk factor in male; for instance, circumcised males are associated with a lower risk of penile HPV infection [25]. Various cohort studies carried out for cervical cancer prevention has demonstrated that the use of alcohol and smoking along with poor and unhealthy sexual practices lead to cervical cancer in early ages [24, 26]. Vulvar, vaginal anal, and penile cancers are also attributed to same risk factors. Altogether, safe and ethical practices can reduce the spread of disease among population.

2.2. Screening methodologies

Up till now, no precise guidelines have been put forward by medical organizations for the surveillance of all HPV types except for those associated with cancer. The available guidelines vary with the severity of pathogenesis and the level of gender involved. There is no requirement of HPV screening for anogenital warts or papillomatosis. However, cervical cancer and precancerous lesions are strongly recommended to be screened at regular intervals for suspicion of cancer. In this regard, the mass screening is helpful in order to detect the virus at

early stages before becoming drastic and uncontrollable. It is also helpful to diagnose the silent HPV infection where virus does not produce any disease symptoms. Common methods available for HPV screening are visual examination, cytology-based tests, and a few molecular assays. Although these methods are equally beneficial for detection of HPV in any part of the body, they are commonly practiced for the screening of cervical cancer only [27]. Researchers have also endorsed the implementation of these methods for the screening of HPV in anogenital warts and cancer, oropharyngeal cancer/infection, lung cancer, vaginal, and vulvar or penile cancer.

2.2.1. Cytology-based screening

Since the most commonly performed HPV screening involves the cervical cancer, therefore, most of the tests and data are available in this regard. The Papanicolaou test usually known as Pap test is the most common method of cervical screening. This test is applied to detect abnormal cervical cells, precancerous lesions, or early stage cancerous lesions among women between ages of 30 and 65 years. Moreover, it is practiced equally for both non-HPV and HPV-infected cervix. Due to accuracy and ease of performance, this test has become the cornerstone of cervical HPV screening strategies [28]. Unfortunately, no Pap-like test is available for the screening of HPV among men [29]. Similarly, histopathological examination is the only method carried out for anogenital, vulvar, vaginal, or oropharyngeal cancers to detect the involvement of HPV in these cases.

2.2.2. Visual examination

Regularly repeated Pap smears followed by appropriate treatment has saved the lives of millions of women in developed countries [27]. But HPV infections and associated cancers still pose a burden in less developed countries where poor socioeconomic conditions prevail. Therefore, in such low resource set ups such as Africa, Asia, South and Central America visual examination is recommended in screening programs [14]. This paradigm shift in screening programs has occurred due to the moderate sensitivity of cytology-based tests. Moreover, quality assurance and high possibility of false positives has led to the evaluation of alternative methods such as visual examination and HPV DNA testing. Visual inspection with 3–5% acetic acid or Lugol's iodine is performed to observe abnormal lesions in HPV associated cervical and penile cancers. However, the application of acetic acid has been most widely evaluated as compared to visual inspection with iodine as most of the cohort and field studies in the areas of Africa, India, Bangladesh, Thailand, China, and Philippines, report the utilization of acetic acid before visual examination. Altogether, these studies have suggested visual screening as an effective, acceptable, safe, accurate, and cost-effective method for the screening of cervical cancer [14].

However, visual inspection is not feasible for the detection of HPV in oropharyngeal or anogenital cancers. But genital warts or other HPV warts can be identified by their peculiar characteristics on visual examination [30]. In addition to all the merits of visual exam, one

needs to be sure for the HPV genotype involved in the infection. For this purpose, some tests with high accuracy and efficiency are required such as nucleic acid testing.

2.2.3. Molecular testing of HPV

Molecular tests offer more rapid and robust screening of HPV and its particular genotype involved in the infection. Based on the nucleic acid detection of virus in clinical specimen, these tests are helpful to detect the virus before the appearance of any cellular abnormalities [27]. Numerous molecular screening modalities have been developed for the detection of hrHPV and lrHPV types among the subjects showing abnormal Pap test. These tests include Hybrid Capture 2 assay, Cervista High Risk HPV assay, Cobas 4800 HPV test, Abbot real Time High Risk HPV test, Papillocheck HPV screening, APTIMA HPV assay, E6/E7 quantitative PCR, GP5+/6+ PCR, and Matrix-assisted laser desorption/ionization time-of-light (MALDI-TOF). Despite the availability of a large number of commercial assays, only Hybrid Capture 2 assay, GP5+/6+ PCR, Cobas 4800 HPV test and APTIMA HPV assay are commonly applied [9, 31]. These four tests were validated in various cohort studies and large randomized trials carried out for 8 years or more in different parts of the world. Moreover, FDA and WHO have recommended these tests to be used in first-line primary screening. They can be used both in adjunct to cytology assays or alone for screening purpose [32]. Other mentioned tests are in the process of validation on large and small cohorts but they still need approval from FDA and other relevant governing bodies.

Usually, HPV testing with above-mentioned assays is not practiced in mass screening of men where simple PCR is performed for the detection of HPV in penile and anal cancer. Most of the testing data constitutes the cross-sectional studies on patients with sexually transmitted diseases (STDs), men having HPV infected partner, military recruits, and few small-scale studies [5]. Similarly, no research or analytical data have been found in support of practicing nucleic acid based assays for the detection of HPV in other associated cancers. But there lies a great potential in these methods for the detection of HPV due to high sensitivity and specificity as compared to visual or cytological examination.

2.3. Immunization

2.3.1. Immunity and principles of vaccine development

A fair comprehension on the basic function of the immune system is absolutely necessary in order to understand the mechanism of vaccines preparation and the prescribed ways to use them. However, the detailed discussion is beyond the scope of this chapter. The immune system is a multifaceted system comprising of interacting cells, tissues, and organs whose prime purpose is to identify and protect the body from pathogens and other potentially damaging foreign objects known as antigens. It is generally divided into two categories: "Innate" and "Adaptive" Immune systems that interact with each other to provide an effective immune response. The Innate immune system is first line of defense against invading pathogens and is equipped with physical and chemical barriers and some non-specific immune cells

such as phagocytic leukocytes, dendritic cells, and natural killer cells which come into action immediately (within hours) after the manifestation of the antigens in the body [33]. Though non-specific but innate immunity plays a significant role in controlling infections until the initial adaptive response takes place [34], the adaptive immune response is composed of two arms: the humoral and cell-mediated response. The humoral response involves the production of antibodies by B-lymphocytes; whereas, cell-mediated response includes the specific cells known as T-lymphocytes which facilitate the elimination of foreign substances. The adaptive immune system provides a more versatile means of security as it manifests wonderful specificity for its target antigens and confers increased protection against subsequent re-infection with the same pathogen [30].

The active and passive ways are two basic mechanisms for acquiring the immunity. Active immunity emerges from the person's own immune response either as a result of exposure to a live pathogen or induced by the vaccine. It involves the production of antigen specific antibody or cellular response of T-lymphocytes. This kind of immunity is very long lasting, usually continues for life time in the form of immunologic memory mediated by memory B cells which survive in the blood after infection, and generate antibodies very quickly in case of re-exposure to the same antigen providing the rapid protection [35]. Some vaccines create the immune response analogous to natural infection without causing a disease signs and symptoms. Likewise, vaccine-mediated immune response also involve production of immunologic memory similar to the natural infection [36]. Unlike active immunity, passive immunity is a short-term immunization in which antibodies from another organism are transferred to the recipient. that is, antibodies are not generated by the immune cells of recipient. This type of immunity protects the host temporarily as the injected antibodies will be degraded over the short time span (weeks to months) leaving the host no more protected. Numerous host factors such as age, genetics, co infection of other disease, immune status, and nutritional factors may influence the response of passive immunization [37, 38].

2.3.2. Classification of vaccines

As a matter of fact, the immune response extremely diverges with antigenic variation. Therefore, a fundamental information of antigen properties; for instance, how it infect cells and what is the response of immune system to that antigen, must be considered for designing vaccines. The most efficient immune response is produced against live antigens. However, purified products from the microbes may also be used to formulate vaccines, though the immune response will not be much effective [39]. Likewise, recent developments in molecular biology enabled scientists to devise the alternative methods of vaccine production. Followings are different possibilities:

- Whole organism vaccines (Live attenuated and inactivated vaccines)
- Subunit vaccines (Subvirion, toxoid, and capsule polysaccharides vaccines)
- DNA vaccines
- Recombinant vaccines

Greater part of the vaccines being used today is based on the use of whole virus, whether, live attenuated or killed. Live attenuated vaccines contain the laboratory prepared version of the viruses which are usually attenuated by passaging in cultures. The attenuated virus retains the replication ability inside the host and induces immunity but lacks pathogenecity. In fact, the live-attenuated vaccines generate nearly identical immune response to that of natural infection [35]. Conversely, inactivated vaccines consist of pathogens that are usually inactivated by the effect of heat or chemicals. Inactivated strains lack replication ability within the host and cannot produce disease even in the immunocompromised individuals. Unlike, live-attenuated vaccines, inactive vaccines produce only humoral but not the cellular response. The protection in case of inactive vaccine is for limited time period because the antibody titer declines after some time [37].

Subunit vaccines include purified macromolecules (antigens) rather than the entire organism. More precisely, major antigenic sites of viral antigens that are recognized efficiently by antibodies or T cells are identified and subjected to purification. These purified molecules are often coupled to an immunogenic carrier protein or adjuvant, for instance, an aluminum salt in order to enhance their immunogenic potential. Immunologists obtain subunit vaccines either by breaking the microbes with chemicals in the laboratory or using recombinant DNA technology [40].

The development of DNA vaccines has ushered the immunization technology into a new exciting era. Precisely, DNA vaccines employ only the genes encoding the immunogenic antigen. Genes of interest are injected either alone (naked) or mixed with molecules that facilitate their entry into the cell, by taking up some cells which prepare the antigen under the instructions of foreign DNA. This way the host cells become vaccines making factories producing the antigens required to evoke the immune response [31]. The immune response to DNA vaccines is very strong and involves cellular and antibodies reaction. Some serious concerns are also linked with DNA vaccine, for instance, the integration of foreign DNA in host chromosome where it can manipulate the expression of onco- or tumor suppressor genes [41].

Only a handful of viral infections can be prevented using conventional live attenuated or killed vaccines. However, advances in recombinant DNA technology have opened up novel avenues for the development of vaccines against organisms for which development of conventional vaccines has so far proved unsuccessful. Virus-like particles (VLPs) are an efficient recombinant DNA technology-based tool which have been used as carriers of other organisms' genes. Immunogenic protein/s of a particular microorganism is introduced into harmless and weakened viruses which act as a vehicle to carry these proteins of interest to the desired site/organ inside the body. Similarly, attenuated bacteria are used as a vector where they display the antigens of other microbes on their surface and induce a strong immune response [42]. Recombinant vaccines mimic the natural infection in producing the immune response and stimulate both humoral and cellular immunity [15]. Five genetically engineered vaccines including Human papillomavirus (HPV) vaccine are being used in USA these days. The pros and cons of all above discussed vaccine types are summarized in the **Table 2**.

Type of vaccines	Features						
	Dose	Booster shots	Requirement of adjuvant	Virulence	Duration of efficacy	Potential advantages	Limitations
Live attenuated vaccines	Low	Single	No	Possible	More than 10 years	Produce immunity like natural infection	Instable, heat labile
Killed vaccines	High	Multiple	Yes	No	Temporary	Can be administered to immune-compromised patients	Can only activate humoral immune response
Subunit vaccines	High	Multiple	Yes	No	Short	Safe as compared to live attenuated vaccines	Sometimes may produce toxins, initiate hypersensitivity response
DNA vaccines	Low	Single	No	No	Long lasting	Safe, cost-effective, no side effects	May trigger the expression of onco-genes
Recombinant vaccines	Low	Single	No	Possible	Long lasting	Cost-effective, easy production	May cause contagious spread of virus

Table 2. General features of various vaccines used for immunization against HPV.

2.3.3. HPV vaccines

The HPV vaccines in use are based on recombinant DNA technology where the major capsid proteins L1 of HPV strains are synthesized and expressed in *in vitro* system. This protein is capable of self-assembling into HPV virus-like particles (VLPs) which display the morphological and antigenic properties similar to HPV virion but lack the viral DNA, therefore not capable of producing cancer. These HPV VLPs are used to synthesize HPV subunit vaccines [43]. All HPV vaccines being used today contain an adjuvant but not a preservative. The VLPs-based vaccines are highly immunogenic and generate even stronger response than the natural HPV infection [44]. All HPV vaccines available today and some other viral vaccines for instance Hepatitis B vaccine are VLP based.

2.3.4. Currently available HPV vaccines

An explosion of interest has been observed in vaccine production against HPV in recent years. Unfortunately, after many scientific endeavors, vaccines are not available against all strains of HPV; however, scientists are manufacturing newer vaccines including more strains of HPV.

Till now, three HPV vaccines have been licensed by Food and Drug Administration (FDA) and equally recommended by Advisory Committee on Immunization Practices (ACIP).

2.3.4.1. CervarixTM

The CervarixTM is a bivalent HPV vaccine marketed by GlaxoSmithKline Biologicals, Belgium, which protects the host from two most lethal types of HPV, 16 and 18, that are responsible for 70% cases of cervical cancer. These HPV types are also responsible for genital warts as well as head and neck cancer [21]. The CervarixTM contains L1 capsid proteins from HPV 16 and 18 in the form of VLPs and an adjuvant AS04 containing: 3-O-desacyl-4'-monophosphoryl lipid A. In fact, the L1 protein from HPV 16 and 18 strains are cloned in a baculovirus vector and expressed in Hi-5 Rix4446 cells that are derived from insect Trichoplusia. The VLPs for these strains are generated separately and then combined together. In addition to protection against HPV16 and 18, this vaccine has manifested cross reactivity with HPV 45 and 31. However, it does not provide protection in case the women have previously been exposed to one of the HPV strains. Clinical data in 2009 have shown that Cervarix TM was still affective after 7 years of vaccine administration showing that protection provided by this vaccine is long lasting [45].

2.3.4.2. Gardasil®

The quadrivalent HPV vaccine Gardasil® is being marketed by Merck & Co. Inc, against 4 HPV types: 16, 18, 6, and 11. The HPV strains 6 and 11 altogether are responsible for 90% of genital warts burden [46]. The VLPs from L1 capsid protein of each strain are produced using a recombinant Saccharomyces Pombe vector and mixed with alum adjuvant for better delivery. In addition to contributing protection against mentioned HPV types, this vaccine manifested a fractional protection against some other HPV types which are responsible for anal, vulvar, and vaginal cancer as well as genital warts [47].

2.3.4.3. Gardasil 9®

Very recently, in 2014, another HPV vaccine namely Gardsil9® was approved by US Food and Drug Administration. It is 9-valent recombinant vaccine which provides protection against wide range of HPV strains. It was recommend for the prevention of cervical, vulvar, anal, and vaginal cancers caused by HPV 16, 18, 31, 33, 45, 52, and 58, genital warts caused by HPV 6 and 11 and dysplastic lesions caused by HPV types: 16, 18, 31, 33, 45, 52, and 58 [12, 48]. Both Gardasil and Gardasil9 HPV vaccines are recommended for males also. In addition, both Gardasil and Gardasil 9 are recommended by FDA for males against the HPV-caused precancerous and cancerous lesions, and genital warts.

All three available HPV vaccines are administered into the body by a series of three intramuscular shots during a period of 6 months. The first shot is followed by second and third shots after 2 and 6 months, respectively.

3. Effective implementation of HPV vaccines

3.1. Age for HPV vaccination

The Centers for Disease Control and Prevention (CDC) recommends the routine administration of HPV vaccines in preteen boys and girls at the age of 11 or 12 before their first potential exposure to HPV [38]. Likewise, a more vigorous immune response is produced against vaccines at this age. However, if they are not fully vaccinated at this age, it is also recommended that women can get vaccinated at age 26 and boys and men at age 21. Recently, FDA has approved the Gardasil® and Gardsil®9 use in both male and female ages 9 through 26 [49]. Young homosexual men with weakened immune response may also get vaccine until they are 27. No vaccine is licensed yet in both male and female over the age of 27 years. However, the HPV vaccines can be given at the same age, similar to other age-specific vaccines for instance, tetanus toxoid, acellular pertussis vaccine, influenza vaccine, and hepatitis B vaccine. The HPV vaccine-targeted population is further enlisted in **Table 3**.

Persons who can receive HPV vaccine	Persons who cannot receive HPV vaccine
Patients with HPV positive test	Patients with history of hypersensitivity
Females with abnormal Pap test	Patients with acute illness
Lactating mothers	Pregnant woman
Patients suffering from any mild disease/immunocompromised	Persons who may develop allergies to yeast, latex or any vaccine component

Table 3. List of possible candidates who may or may not be safely administered with HPV vaccines.

3.2. HPV vaccine efficacy

The available HPV vaccines target the HPV types that most commonly cause cervical cancer and genital warts. Several studies have been conducted for bivalent and quadrivalent HPV vaccines to check their efficacy in young women of age between 15 and 25 years. These studies demonstrated that antibody response against the included types of HPV is generated approximately 1 month after the 3 shots of HPV vaccines in 99% of studied female population [38]. Clinical trials have demonstrated that the bivalent vaccine is 93% efficient in preventing cervical cancers caused by HPV 16 and 18 in women who had not been previously exposed to those strains [50]. The quadrivalent HPV vaccines have demonstrated more promising results as they were found 100% efficient in women for preventing cervical, vulvar, vaginal cancers along with genital warts due to HPV types 16, 18, 6, and 11 [48, 51]. The quadrivalent vaccine was equally effective in controlling genital warts and anal precancerous lesions of male. Besides that HPV vaccines have no therapeutic effects on HPV caused diseases and do not confer protection to the host already infected with those HPV types [52].

3.3. HPV vaccines safety

Large-scale clinical trials have confirmed the safety of vaccine [53]. However, common minor side effects such as pain, redness, fever, dizziness, and nausea could be observed. The medical procedure of injecting HPV vaccines may cause syncope (to faint) in teens or preteens such as other medical procedures. Being safe to use, 46 million doses of HPV vaccine have been distributed in United States as of June 2012 [54].

3.4. Impact of HPV vaccination

In general, vaccines are considered the most victorious medical intervention because they have provided protections against various diseases axf nd saved the death of millions of people [55]. In fact, HPV vaccines have been proved to be an important strategy for a notable decrease in the global burden of cervical cancer and genital warts. According to an estimate, the common use of vaccine during last decade has reduced cervical cancer deaths by 50% [56]. In addition, some additional long-term benefits are also associated with HPV vaccination such as it shows marked reduction in the prevalence of high-grade lesions CIN grade 2 and 3 [57]. The reduction in percentage of cervical associated deaths are further anticipated to rise up to 70% by next few decades when more vaccines would be available against a wide range of HPV strains.

4. Public awareness

Biomedical scientists have succeeded to develop reasonable approaches to cope with the obnoxious HPV infection. However, the success of these methods relies largely in creating awareness among general public about HPV infection and cervical cancer particularly in countries where inadequate attention is paid to the health problems. At first, the knowledge about HPV infection and its relation to anogenital as well as cervical cancer must be tailored in a very comprehensive and easily understandable way for general public in the form of booklets and brochures. The cultural and religious aspects should also be considered while devising an HPV prevention strategy. The dissemination of information should be ensured as much as possible through medical practitioners, teachers, and other sectors of the society. Likewise, the parents should be convinced and encouraged to get their child vaccinated at preteen ages. Both paper and electronic media should play a constructive role in spreading the information about HPV.

5. Conclusions

HPV is the main sexually transmitted viral infection which is associated with the cancers of oral cavity and reproductive tract of both male and female. In the absence of particular treatment for obnoxious HPV infection, the prevention strategies have been centered upon. The prevention paradigm against HPV infection must be multipronged. Briefly, to fend off HPV infection systematically the armamentarium should include avoiding risk factors which support the establishment of HPV infection such as multiple sex partners, early age sex, and unprotected sex, regular screening for cervical cancer, and administration of HPV vaccines.

Indeed, during last few years, it has been revealed that early and specific diagnosis in combination with effective therapeutic intervention could be the pragmatic and preeminent choice to overcome HPV-related diseases. In addition to that, several molecular therapeutic strategies can prove to be the indispensable allies in this quest against HPV infection. However, vaccination at the age of 10–12 in both genders is even a better choice since it provides immunity even before the first exposure to HPV lethal strains. The bivalent, quadrivalent, and nanovalent HPV vaccines have been successfully used in developed countries during last decade and proved to be highly efficient and safe to use. Theses vaccines not only provided a significant protection against highly virulent HPV strains against which they were designed, but also showed considerable seroconversion rate and lowered the occurring of other HPV-related abnormalities such as CIN and genital warts.

6. Future perspectives

Currently, no specific therapies are available for HPV infected patients. Therefore, there is an urgent need to invest our efforts in developing novel drugs against HPV. Moreover, the costs associated with HPV prevention and therapy is so far among the major hurdles in eradication of this problem. Considering the fact that more than 80% of HPV positive cases reside in low- and middle-income countries, accessibility and cost-effectiveness of any new drugs should also be kept in consideration. Any future HPV strategies must also take into account the cultural and religious stigma attached to vaccination in general and HPV in particular. Necessary measures should be devised and implemented in order to do away with these stigmas. There is also a need to devise and implement global anti-HPV vaccination campaigns for women of developing countries.

Development of new, sensitive, and cost-effective diagnostic tests is also one of the areas which demands high attention. To overcome this issue in developing countries, a sufficient advancement in diagnostics is mandatory. Although, screening and vaccination are being applied successfully in different parts of the world, HPV is still causing a significant number of deaths per year [58]. Likewise, quality control and assurance is another great hurdle towards the success of currently proposed modalities for elimination of HPV [20]. Keeping in view the given scenario, updated screening, and management guidelines are needed.

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