Chapter 15
Human Papillomavirus

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HPV Infection

Etiology

Human papillomavirus (HPV), of the *Papillomaviridae* family, is a small, non-enveloped double-stranded DNA virus whose genome encodes for early proteins (required for viral replications) and late structural proteins (L1 and L2) which form the icosahedral capsid. HPV infects and replicates in either the cutaneous or the mucosal epithelium. The HPV types which infect the cutaneous epithelium lead to plantar, flat, or filiform warts. Separately, the HPV types which infect the mucosal epithelium are stratified into low-risk or high-risk types based on their oncogenic potential. Low-risk HPV types, most commonly HPV-6 and HPV-11, cause low-grade cervical cell abnormalities, genital warts, and respiratory papillomatosis. High-risk HPV types, most commonly HPV-16 and HPV-18, lead to low-grade and/or high-grade (precancerous) cervical cell abnormalities, anogenital cancers, and oropharyngeal cancers.

The association of cervical cancer and sexual activity had been speculated long before the identification of HPV. Since it was well known that cancer was not contagious, it was theorized that this particular cancer must be caused by an infection. In the 1970s, Harald zur Hausen, a German virologist who had previously identified Epstein-Barr virus DNA from human tumors, started his work toward identifying the infectious etiology of cervical cancer. Although herpes simplex virus-2 (HSV) was initially thought to be the infecting pathogen, zur Hausen was unable to detect HSV-2 DNA from any of the cervical cancer samples. Upon further review of patient reports, he noted anecdotal data supporting the malignant transformation of

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genital warts. In 1976, he published his hypothesis that the papillomavirus that causes genital warts was potentially the same agent causing cervical cancer [3]. Just a few years later, his lab identified HPV-6 from genital warts and HPV-11 from respiratory papillomas, but, to his disappointment, these HPV types could not be identified in cervical cancer biopsies. Further investigation finally led to the discovery of HPV-16 and HPV-18 DNA in cervical cancer samples and in precancerous lesions. Subsequent international studies found that almost all cervical cancers contain HPV DNA [4, 5]. Today, we know that there are over 120 HPV types, and over 40 of these types infect the genital mucosa. In 2008, just 2 years after the first HPV vaccine was approved by the FDA for the prevention of cervical cancer, zur Hausen was awarded the Nobel Prize for Medicine or Physiology for his work leading to the development of this cancer prevention vaccine.

Pre-vaccine Epidemiology

HPV infection is the most common viral anogenital infection among men and women worldwide [6]. Globally, HPV is associated with 4.5% of all cancers [7]. Each year, over 600,000 and 300,000 new cases of HPV-attributable cancers and cancer deaths, respectively, are reported, 83% of which are cervical cancer [7]. Worldwide, cervical cancer is the third leading cause of cancer and cancer deaths among all females and the second leading cause of cancer and cancer deaths among females aged 15–44 years. In 2018, alone, 569,847 women around the world were newly diagnosed with cervical cancer, and 311,365 women died from this disease.

Similarly, HPV is the most common sexually transmitted infection in the United States, with almost all adults predicted to be infected with HPV at some point in their lifetime. It is estimated that 79 million people in the country are currently infected. Of the 14 million new infections each year, half occur in young adults between the ages of 15 and 24 years. Each year, in the United States, there are over 44,000 cases of HPV-attributable cancers, 25,000 among women and 19,000 among men. Cervical cancer alone accounts for 12,000 new cases and 4000 deaths annually. HPV is known to cause almost all of the anal and cervical cancers, 70% of oropharyngeal and vaginal/vulvar cancers, and more than 60% of penile cancers. Of note, HPV now causes more oropharyngeal cancers than alcohol and smoking combined.

Transmission

Transmission of cutaneous HPV infection occurs through casual contact, particularly if it is an area with minor skin trauma. Autoinoculation is common, leading to spread of lesions. Individuals with altered cell-mediated immunity have more severe disease and dissemination of skin lesions.

Genital HPV infection is transmitted through skin-to-skin contact, most often, though not always, through sexual intercourse. New acquisition of HPV occurs most commonly after sexual debut. Vertical transmission from mother to newborn during delivery can lead to juvenile-onset recurrent respiratory papillomatosis.

Clinical Presentation

Most HPV infections are subclinical, with 90% self-resolving within 2 years. Clinical presentation is dependent on HPV type and location of infection (Table 15.1).

Table 15.1 Clinical manifestations of HPV infection

HPV clinical manifestations	
Cutaneous infection	
Plantar warts	Warts on the feet, tend to be larger than other warts, can be painful with walking
Flat warts	Typically seen on the face and extremities, flat (not papillomatosis) in appearance, painless
Filiform warts	Seen on face and neck
Epidermodysplasia verruciformis	Rare genetic disorder, increased susceptibility to HPV infection, chronic cutaneous lesions of childhood with malignant transformation during adulthood
Mucosal infection	
Low-risk HPV types	
Juvenile-onset recurrent respiratory papillomatosis	Recurring papillomas in the upper respiratory tract, particularly the larynx, most common benign, laryngeal tumor of childhood, typically results from vertical transmission of HPV during delivery, manifestations may include hoarseness or stridor, may require intra-lesion injections or repeated debulking procedures to prevent respiratory tract obstruction
Anogenital warts	"Condyloma acuminata," skin-colored warts, cauliflower-like in appearance; painless but may be associated with itching, burning, or bleeding
Low-grade squamous intraepithelial lesions	In the cervix, these lesions are referred to as cervical intraepithelial neoplasia (CIN1)
High-risk HPV types	
Low-grade squamous intraepithelial lesions	In the cervix, these lesions are referred to as cervical intraepithelial neoplasia (CIN1)
High-grade squamous intraepithelial lesions	In the cervix, these lesions are referred to as CIN2 or CIN3
Anogenital cancers	Cervical cancer is most common HPV cancer in women
Oropharyngeal cancers	Most common HPV cancer in men

Management

There is no antiviral therapy indicated for the treatment of HPV infection. Supportive management, however, varies by the type of HPV infection.

Cutaneous Warts

One-third of cutaneous HPV warts resolve within 6 months. Those that do not resolve, cause significant pain, or are socially distressing may be managed with lesion-targeted therapy. These treatments, including cryotherapy, salicylic acid, immunomodulating agents, or laser or surgical removal, are not curative and recurrence of the lesions is common.

Respiratory Papillomatosis

Although a benign process, life-threatening complications may occur as papillomas grow in the airway. Consultation with an experienced otolaryngologist is necessary as intra-lesion therapy or surgical debulking may be required to prevent airway obstruction.

Anogenital Warts

Treatment goals of anogenital warts include wart removal, symptom improvement, and reduction of psychosocial distress. Treatment should be guided by the size, number, and anatomic site of warts, patient preference, cost, and provider experience [8]. Available treatment can be either patient-applied (imiquimod, podofilox, sinecatechins) or clinician-applied (cryotherapy, surgical removal, trichloroacetic acid, bichloroacetic acid).

Abnormal Cervical Cytology

Women with abnormal cervical cytology may require colposcopy, biopsy, excision (loop electrosurgical excisional procedure [LEEP]), or ablative treatment [9].

Prevention

HPV infection and associated complications can be prevented through (1) reducing the risk of exposure, (2) HPV screening, and (3) routine immunization. New HPV acquisition typically occurs shortly after sexual debut, with increased risk of infection with increasing number of sexual partners. Behaviors that will reduce the likelihood of being exposed to HPV include abstaining from sexual activity, correct and consistent use of physical barriers (i.e., condoms) during sex, delaying onset of sexual activity, and minimizing the number of lifetime sexual partners. Cervical cancer is the only HPV-associated cancer that can be prevented through routine screening (Table 15.2). Routine immunization against HPV among adolescents aims to prevent both HPV infection and associated complications, including cancer development.

HPV Vaccine

Vaccine Characteristics

HPV vaccines consist of L1 proteins, expressed by using recombinant DNA technology, self-assembled into noninfectious, non-oncogenic, virus-like particles that are highly immunogenic. There are three HPV vaccines used around the world (Table 15.3). The HPV types included in the nine-valent vaccine account for over 90% of all HPV-associated cancers worldwide. While the bivalent and quadrivalent HPV vaccines are still licensed for use, nine-valent HPV vaccine is the only one currently available in the United States.

Table 15.2 Cervical cancer screening recommendations as per the 2018 US Preventive Services Task Force guidline [10]

Healthy women with a cervix, no signs or symptoms of cervical cancer, and no history of high-grade precancerous cervical lesions	Cervical cancer screening recommendation
<21 years of age	No screening
21–29 years of age	Cervical cytology every 3 years
30–65 years of age	Cervical cytology every 3 years or High-risk HPV testing every 5 years or Combination of cervical cytology and high-risk HPV testing every 5 years
>65 years of age and appropriate prior screening	No screening

Table 15.3 HPV vaccines used worldwide

HPV vaccine	Manufacturer	HPV types included	FDA approval year
Bivalent	GlaxoSmithKline	16, 18	2009
Quadrivalent	Merck	6, 11, 16, 18	2006
Nine-valent	Merck	6, 11, 16, 18, 31, 33, 45, 52, 58	2014

Table 15.4 HPV vaccine recommendations

Cohort	HPV vaccine recommendations
Females and males of ages 9–12 years[a]	Routine vaccination with two-dose vaccine series[b]
Females and males of ages 13–14 years[a]	Catch-up vaccination with two-dose vaccine series[b]
Females and males of ages 15–26 years	Catch-up vaccination with a three-dose vaccine series[c]
Females and males of ages 27–45 years	Shared clinical decision-making regarding vaccination

[a]Healthy individuals without immunocompromising conditions
[b]Dose 2 given 6–12 months after dose 1 (minimum interval of 5 months)
[c]Dose 2 given 1–2 months after dose 1 (minimum interval of 4 weeks), dose 3 given 6 months after dose 1 (minimum interval of 5 months after dose 1 and 12 weeks after dose 2)

Vaccine Storage, Preparation, and Administration

HPV vaccines should be stored at refrigerator temperatures (2–8 °C). Do not freeze vaccine. Administer as soon as possible after removal from refrigeration, as a 0.5 mL dose given intramuscularly, preferably in the deltoid muscle.

Vaccine Recommendations

HPV vaccines are not therapeutic and should not be used to treat infection. Vaccination is most effective in disease prevention when administered before exposure to infection. HPV vaccination may include either a two-dose or a three-dose series, depending on age at vaccine series initiation. The Advisory Committee on Immunization Practices recommends that routine administration of the HPV vaccine series begins at 11–12 years of age (Table 15.4). Vaccinating at this medical visit allows for bundling of the HPV vaccine with the other adolescent vaccines. Further support for immunizing at the 11–12-year visit is the robust immune response to vaccination allowing a two-dose series. If the HPV vaccine series is not started until on or after the 15th birthday, a three-dose series is required to achieve the same response.

HPV vaccine doses administered earlier than the required minimum interval should be readministered after the appropriate time interval passes. If the HPV vaccine series is interrupted, it does not need to be restarted. The nine-valent vaccine can be used to complete a series that was started with either the quadrivalent or bivalent vaccine. Individuals with a prior exposure to or history of HPV infection should still be vaccinated to protect against other HPV types.

Contraindications to HPV Vaccine

Mild illness is not a contraindication to HPV vaccine receipt. If moderate or severe illness is present, vaccination should be deferred until after clinical improvement. Contraindications to the HPV vaccine include a severe allergic reaction to a vaccine component or prior dose of HPV vaccine. An anaphylactic latex allergy is a contraindication for bivalent HPV vaccination, as the prefilled syringe is capped with natural rubber latex. Severe yeast allergy is a contraindication to the nine-valent HPV vaccine, which is made in yeast. While it is not recommended that HPV vaccine be administered during pregnancy, testing for pregnancy before vaccination is not needed. If a woman is found to be pregnant after starting the HPV vaccine series, completion of the vaccine series should be delayed until after pregnancy.

Adverse Events

The most common adverse effects of the HPV vaccine are local reactions at the site of injection (pain, redness, swelling) that occurs with increasing frequency after subsequent doses. As with other vaccines administered to adolescents, syncope following vaccination has been reported. It is recommended that individuals receiving HPV vaccine be observed for 15 minutes after vaccine administration. Over 90 million doses of HPV vaccine have been administered in the United States, with no serious adverse events reported.

Immunogenicity

More than 97% of individuals develop antibodies after receiving the three-dose HPV vaccine series. Two doses of HPV vaccine administered to 9- to 14-year-olds result in similar levels of protection as the three-dose series administered to 16- to 26-year-olds. Follow-up studies a decade after initial vaccination shows persistence of protection without waning.

Impact of Vaccine on Disease Burden

In 2005, 500,000 and 260,000 cervical cancer cases and deaths, respectively, were reported worldwide. In some regions of the world, the incidence of cervical cancer was as high as 50 per 100,000 females. While screening and management of abnormal cervical cells are effective in preventing 80% of cervical cancers, implementation of screening programs in low- and middle-income countries, where rates of

cervical cancer and deaths are the highest, has proven to be difficult. Since 2009, the World Health Organization has recommended that countries introduce the HPV vaccination into their national immunization programs, with a focus on immunizing females between the ages of 9 and 13 years [6, 11, 12]. By 2018, 79 (63%) countries had implemented a national HPV vaccination program, and 44 (22%) announced plans for or piloted the use of the vaccine in their country (Fig. 15.1).

Since the introduction of HPV vaccine, more than 15 countries have shown a reduction in vaccine-type HPV detection in vaccinated females, demonstrating vaccine effectiveness, and in unvaccinated females and males, suggesting herd immunity [13]. Countries with vaccination rates of at least 50% saw reduction in HPV-16 and HPV-18 infections by 68% and a decline in anogenital warts by 61% [14]. A review of the impact of HPV vaccination in real-world settings over a decade found maximal reductions of approximately 90% for quadrivalent-vaccine-type HPV infection [15].

In the United States, the quadrivalent HPV vaccine was first approved in 2006 for females aged 9 through 26 years of age. In 2009, this recommendation was expanded to include males, 9 through 21 years of age (and high-risk males through 26 years). In 2014, the nine-valent HPV vaccine was approved and essentially now has replaced the quadrivalent HPV vaccine in this country. In 2019, the catch-up vaccine recommendation was again expanded to include all individuals through 26 years of age, regardless of gender. Most recently, in 2020, the FDA added prevention of oropharyngeal cancers to the indication for use of HPV vaccine. Still, 12 years following initial recommendation, national vaccine series completion rates

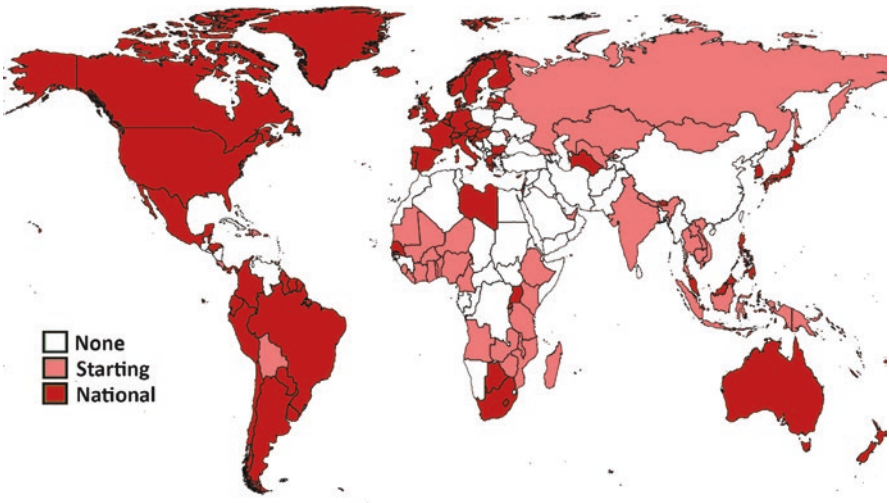

Fig. 15.1 HPV vaccine use among countries around the world, stratified by countries with no HPV vaccination program, countries that have started to implement an HPV vaccine program (announced plans, piloted, or have a partial program), and countries that have implemented a national HPV vaccination program

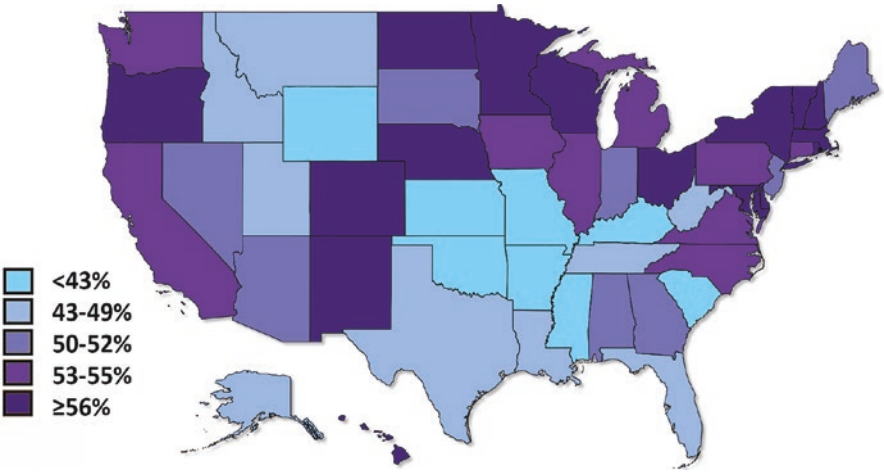

Fig. 15.2 US HPV vaccination rates by state, 2018

among 13- to 17-year-olds remain just over 50%, leaving half of US adolescents susceptible to HPV infection and HPV-associated cancer development (Fig. 15.2).

Over the course of 10 years following HPV vaccine introduction, there has been a decline in the detection of quadrivalent vaccine HPV type by 80% among vaccinated females and 40% among unvaccinated females [16, 17]. Population-based studies found significant reductions in all grades of CIN, particularly in women who were vaccinated under 20 years of age [18, 19]. In addition, Chaturvedi found that the prevalence of oral HPV-6/HPV-11/HPV-16/HPV-18 was significantly reduced among vaccinated individuals compared to the unvaccinated, with an estimated 88% reduction in prevalence of adjusting for demographics [20].

The HPV vaccine is safe and effective in the prevention of HPV infection and related complications, including oropharyngeal and genitourinary cancers. Low vaccine uptake is related to provider and parental vaccine hesitancy. Interventions geared toward emphasizing the HPV vaccine as cancer prevention are needed to improve adolescent vaccine uptake and prevent them from future development of HPV-associated cancers.

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