Review Article

Human papillomavirus infection in adolescents

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final Approval of manuscript: All authors.

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Abstract: The human papillomavirus (HPV) is a family of viruses with several strains or types. Each type is associated with several conditions ranging from benign (such as common warts) to more severe conditions such as genital warts, vulvar intraepithelial neoplasia and invasive carcinoma of cervical epithelial cells. Cervical cancer is one of the leading causes of cancer deaths in women worldwide. The virus invades epithelial cells enabling its evasion of the host immune systems due to certain characteristics. HPV is spread by intimate contact with an infected partner. HPV is one of the most common sexually-transmitted infections (STI) worldwide. There is now a vaccine that offers primary prevention against HPV infections. Effective and timely administration of this vaccine is crucial towards decreasing disease burden of HPV-induced genitourinary cancers. Unique approaches may need to be considered to increase uptake of the HPV vaccine.

Keywords: Adolescent vaccine; cervical cancer; human papillomavirus; warts

Received: 29 June 2019; Accepted: 19 July 2019; Published: 03 September 2019.
doi: 10.21037/pm.2019.08.01
View this article at: http://dx.doi.org/10.21037/pm.2019.08.01

Introduction

The human papillomavirus (HPV) is the most common sexually-transmitted infection (STI) in the United States and worldwide, affecting the reproductive tract, oropharynx, and anogenital region via skin-skin contact or exchange of bodily fluids. In adolescents and young adults, HPV is associated most commonly with genital warts and changes in epithelial cells that lead to genitourinary cancers in both men and women, and is associated with oral cancers. Transmission occurs through intimate contact and is highly prevalent worldwide. Due to its replication process, affected individuals may present years after initial infection with HPV. Screening for this virus is challenging and not recommended. Vaccination offers primary prevention against HPV infection.

Epidemiology

Prevalence of HPV infections and HPV-associated cancers are highest in non-industrialized countries and disproportionately affect more women than men (1). According to the World Health Organization report, the worldwide prevalence of HPV among women with normal cytological findings is 11.7% (1). The highest prevalence is reported in Sub-Saharan Africa, Latin America and Caribbean, Eastern Europe, and Southeastern Asia (1). *Figure 1* depicts affected individuals by race and ethnicity with HPV-associated cancers in the United States as reported by the Centers for Disease Control and Prevention (CDC) (2). Despite decrease in prevalence after the HPV vaccination was introduced, cervical cancer remains one of the leading causes of death in women. In 2012, at least

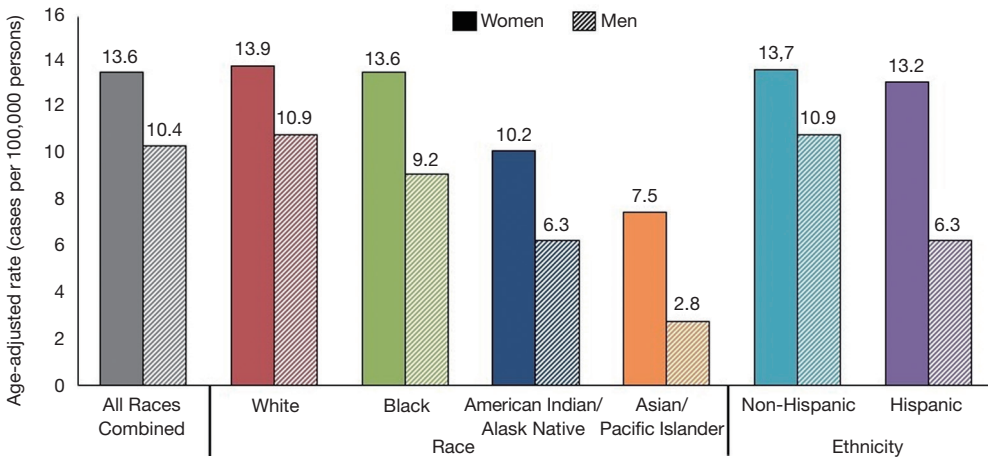

Figure 1 HPV-associated cancer rates per year by race and ethnicity, United States, 2011–2015. HPV, human papillomavirus. Accessed 9 June 2019. Available online: https://www.cdc.gov/cancer/hpv/statistics/race.htm

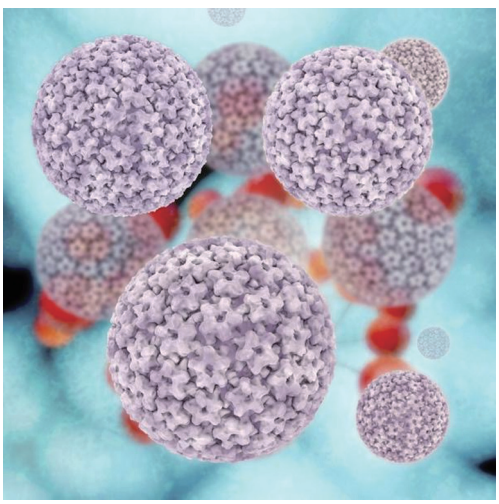

Figure 2 An illustration of HPV's spherical outer shell. Real HPV particles have DNA inside, while the vaccine uses artificially produced empty shells. HPV, human papillomavirus. Accessed 9 June 2019. Available online: https://twitter.com/CDCSTD/status/508692453835042817

half a million of new cases of cervical cancer was reported globally with higher burden in less non-industrialized countries (3). In the United States, the American Cancer Society (ACS) approximates around 13,000 new cases of invasive cervical cancer diagnosed each year, 30% of which will result in mortality (4). The economic burden of genital HPV has been reported to be about $4 billion yearly (5,6) with an estimated cost of about $4 million for non-cervical-related conditions (7).

The incidence of HPV infections is highest in women in the 3rd decade of life (1). If infections from high risk HPV types are not cleared, the risk of progression to pre-cancerous and cancerous lesions increases with age. There is no such age-associated risk in men. In sexually actives males, anal HPV infection is very common in men who have sex with men (MSM), especially HIV-positive MSM, the majority of whom also test positive for HPV. Men with ≥3 lifetime partners who have sex with women are also at an increased risk of HPV infection (1).

Human papillomavirus

The family Papillomaviridae is comprised of non-enveloped, double-stranded DNA viruses, that include HPV, and is highly-tissue specific (8,9). *Figure 2* illustrates the spherical outer shell and DNA within the HPV (10). Their genome consists of 8,000 base pairs that encode for proteins that promote cell growth (11). HPV primarily affects epithelial cells by invading basal layers of skin. Early genes are expressed that stimulate the host cell DNA polymerase to replicate viral DNA during human cellular division (12,13). As the virus travels through the basal layers of the epidermis, it assembles its structural proteins (12,13).

The HPV is able to evade immune detection and destruction in several ways. Since it does not invade the blood stream, there is no viremic phase and hence, does not induce an immune response (14). It grows very slowly and has low levels of gene expression. Fortunately, for immunocompetent individuals, the infection will clear

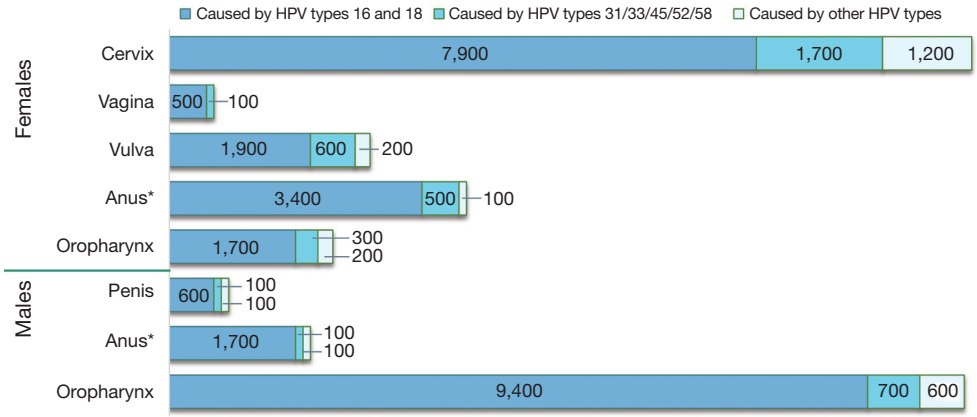

Figure 3 Estimated number of cancer cases attributable to HPV by sex, cancer type, and HPV type, United States. *, includes anal and rectal squamous cell carcinomas. HPV, human papillomavirus. Accessed 18 June 2019. Available online: https://www.cdc.gov/cancer/hpv/pdf/USCS-DataBrief-No4-August2018-508.pdf

spontaneously in 3–5 years (14). Those who do not clear HPV are at increased risk of developing cancer, particularly of the genitourinary tract. This is because HPV DNA is coded with oncogenes: *E6* and *E7*. *E6* binds and destroys p53 proteins. *E7* binds and inactivates retinoblastoma protein (14). Normally, p53 and retinoblastoma proteins act as tumor suppressors, hence their destruction or inactivation lead to unchecked growth of tumor cells (14). HPV DNA becomes integrated in to host DNA cells which increases expression of these oncogenes (14).

High- and low-risk types

The many different strains of HPV are typically characterized by the genomic makeup of the capsid protein, but can be classified further as "high-risk" or "low-risk" based on their ability to predispose cancer in those infected. *Figure 3* depicts currently available data by CDC on the estimated number of cancer cases in relation to HPV by sex, cancer type and HPV type (15).

High-risk strains are responsible for 71% of cervical cancers globally. HPV-16 is associated with 60.6% of cervical cancers, while 10.2% results from HPV-18 (1). Carcinomas of the anus (88%), vagina (78%), oropharynx (60%), penis (51%), and vulva (48%) are predominantly caused by type 16 (16-19). Other relatively common high-risk strains include types 31, 33, 35, 45, 52 and 58. Together, all high-risk strains are responsible for 90% of HPV-positive squamous cell carcinomas (1).

Low risk strains are far less associated with cancers, but manifest as benign skin lesions, commonly seen as genital warts (condyloma acuminatum) (1). Types 6 and 11 are the most common low risk strains accounting for up to 90% of anogenital warts (1). Although rare, these strains can become cancerous. Recurrent respiratory papillomatosis (RRP) is a potentially lethal condition in which warts form in the respiratory tract causing airway obstruction that may require surgical intervention (1,20-22).

Disease expression

Disease expression of HPV includes common warts (verruca vulgaris) which occur in about 20% of school-aged children with prevalence declining with age (23). Genital lesions from HPV are acquired from sexual contact, making it the most common STI worldwide. During the years 2013-2014, HPV was reported in nearly half (42.5%) of adults in the United States aged 18–59 years (24,25). Other clinical manifestations include genitourinary pre-cancerous lesions (such as low-grade squamous intraepithelial lesion and high-grade intraepithelial lesion) and cancers [such as vulvar intraepithelial neoplasia, vaginal intraepithelial neoplasia, and cervical intraepithelial neoplasia (CIN)]. The peak age for cervical cancer is from 35 to 44 years (3). Other associated conditions include pre-cancerous lesions and cancers in the rectum and penis, certain oropharyngeal cancers and RRP (26,27).

Health care providers and epidemiologists follow and track these diseases caused by HPV due to the associated risk of development of *in situ* and invasive squamous cell carcinomas, particularly of the cervix, but also of the vagina, vulva, penis, anus, and oropharynx. Yet, infections from

Table 1 CDC recommendations for treatment of external anogenital warts

Applied by patient	Administered by the provider
Imiquimod 3.75% or 5% cream	Cryotherapy with liquid nitrogen or cryoprobe
Podofilox 0.5% solution or gel	Surgical removal (tangential scissor excision, tangential shave excision, curettage, laser or electrosurgery)
Sinecatechins 15% ointment	Trichloroacetic acid or bichloroacetic acid 80–90% solution

CDC, Center for Disease Control and Prevention. Accessed 28 June 2019. Available online: https://www.cdc.gov/std/tg2015/warts.htm

high-risk strains most frequently remain asymptomatic without guaranteed progression to cancer. Approximately 70–90% of HPV-related infections spontaneously resolve within 1–2 years in most healthy immunocompetent individuals (1).

Papanicolau (Pap) smears are done in young adult women to detect early signs of cervical cancer. Persistent HPV lesions can progress towards various stages of precancerous lesions over subsequent months or years. Presence of infection or precancerous lesions should be noted at screening because these risk factors warrant follow-up to monitor for resolution. Lesions that persist require treatment to prevent disease progression to more advanced stages. (1).

Most of these lesions, called CIN will spontaneously resolve, but if found on routine screening, must be staged based on the quality and quantity of dysplasia displayed. From most mild to most severe dysplasia displayed, CIN stages are rated as CIN1, CIN2, and CIN3, including carcinoma in situ. This progression from HPV infection to CIN 3 and invasive carcinoma occurs over the course of many years (1).

Screening recommendations

Pap smear screening for cervical cancer is secondary prevention against cervical cancer (4). Recommendations for screening in the United States are based on guidelines from the ACS (28), American College of Obstetrics and Gynecology (ACOG) (29), and US Preventive Services Task Force (USPSTF) (30). Screening should begin at age 21, regardless of sexual activity, and repeated every 3 years. The recommendations regarding management of abnormal cervical cytology, high-risk HPV testing, or both, depend on age. Screening immunocompetent women younger than the age 21 years and older than 65 years (with prior adequate screening) have lower risk of cervical cancer, hence not recommended. Immunocompromised women (HIV-positive or women on immunosuppressant therapy), require more frequent screening. Thus far, HPV immunization status does not change screening recommendations (31).

Treatment

In healthy immunocompetent adults, most HPV infections resolve spontaneously. For individuals affected by non-cancerous HPV types 6 and 11, majority of cases result in external anogenital warts. The CDC treatment recommendations for these lesions are shown in *Table 1* (32). It is imperative to recognize that affected persons with external anogenital warts can have internal lesions as well.

In individuals affected by more than one high-risk type that leads to persistent infections resulting in life threatening conditions, treatment is dependent on the stage of disease. For pre-invasive cervical lesions, curative ablative methods, such as thermal coagulation and freezing, can be successful (33). High risk lesions, such as CIN 2–3 may be removed via cryotherapy, or surgical techniques such as loop electrosurgical excision procedure (LEEP), or cone biopsy for larger/recurrent lesions (33). However, with the availability of an effective vaccine against HPV, prevention is key.

HPV vaccination

HPV vaccination is primary prevention against HPV infection and genitourinary cancers. Currently, there is a United States Food and Drug Administration approved vaccine that protects against nine HPV types: 6, 11, 16, 18, 31, 33, 45, 52 and 58 (34). The 9-valent HPV vaccine is approved for use in males and females, and can be given as early as age 9 (especially for victims of sexual abuse). It is recommended for routine use in children between the ages of 11 and 12 with catch-up recommendations up to age 45 (34).

Due to a better immune response, two doses are recommended when the vaccine series is initiated before age 15. After age 15, three doses are required to ensure protection against HPV. The vaccine is not recommended for pregnant adolescents and adults. It should not be given to anyone who is allergic to any components of the vaccine.

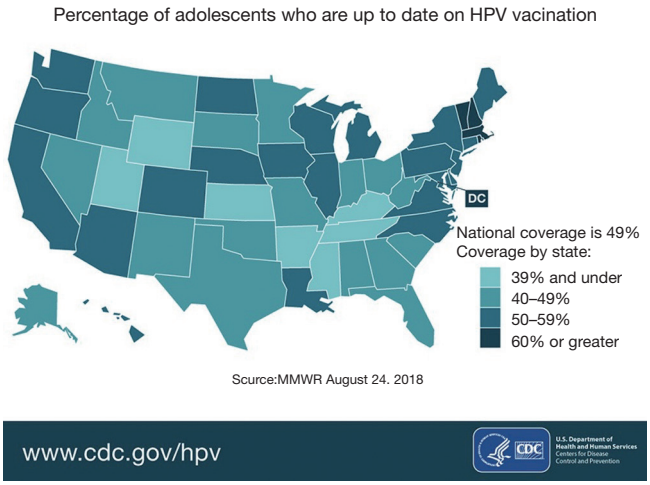

Figure 4 Percentage of adolescents who are current with their HPV vaccinations by state. HPV, human papillomavirus. Accessed 9 June 2019. Available online: https://www.cdc.gov/hpv/infographics/vacc-coverage.jpg

Side effects of vaccine administration are generally well tolerated and include injection site reaction (pain, swelling and redness), syncope, lightheadedness, nausea, headache and mild fever (26,34).

Since the introduction of HPV vaccines, there has been a decline in cervical precancerous lesions (35). This indicates that with time, this vaccine - if administered widely—will drastically reduce cervical cancer rates and HPV-associated cancer rates. When compared to similar age-appropriate vaccines in the United States, the rate of completed HPV vaccination series is much lower. For example, rates of vaccination for the Tetanus-diphtheria and acellular Pertussis vaccine and the A/C/Y/W-135 meningococcal vaccine (MCV4/MSPV4) approach 100%, while completed vaccine rates for HPV vaccines is barely 50% for females and even lower for males (36). *Figure 4* shows the percentage of adolescents who are current with their HPV vaccinations by state in the United States (37).

Barriers to HPV vaccination

Some perceived general barriers to immunizing adolescents include: fewer preventive visits overall (annual visits as opposed to every few months for the infant schedule); time constraints; reimbursement concerns; consent; tracking immunization records; and lack of education about the HPV vaccine, such as vaccine safety. Parents are influenced by provider recommendations, news media, other family members and school requirements with respect to likelihood of immunizing their child (38,39).

Hence, health care providers should not underestimate their influence and importance when recommending vaccines. Vaccine messaging from providers should emphasize the safety and efficacy of the HPV vaccine. Specifics regarding HPV acquisition can be tailored based on the age and developmental stage of the adolescent. HPV vaccines should be strongly recommended (26).

A unique aspect of the HPV vaccine is its ability to offer primary prevention against a highly prevalent STI with deleterious outcomes and high economic burden. There have been proposals to allow adolescents to consent for this specific vaccine on their own (as it is designed to prevent an STI and in the United States, many adolescents can consent to STI treatment though they are still considered minors under the law). This consideration would require support from policy makers and health care providers (including public health officials) (40).

Improving HPV vaccination

The conversation should start early which allows timely preparation and understanding from the child and his/her caregivers. Even if the vaccine can be given as old as 45 years, the younger the child initiates the series, the greater the response. The role of the medical practitioner is important when discussing HPV vaccination during clinic visits. One study found providers who make recommendations about the vaccine assuming parents' readiness to vaccinate had improved initiation of the vaccine among young adolescents (41). The highly effective HPV vaccine can be given as part of the other scheduled adolescent vaccines.

Rand *et al.* conducted a learning collaborative quality improvement (QI) model in different primary care practices to improve HPV vaccination rates by reducing missed opportunities at all visit types (42). The interventions targeted changes within the office systems, such as identifying a clinic champion, strong recommendations from provider, flagging charts for patients due for vaccines, assessing those in need to be vaccinated during any type of visits (wellness, nurse, acute, chronic, and other visits), and updating office policy on vaccinations. Utilization of the QI model resulted in less missed opportunities to vaccinate, increased overall initiation and completion of series (42).

In a systematic review of interventions done in unvaccinated college students found that increased uptake

of the HPV vaccine correlated with encouragement from both peers and medical practitioners (43). Hence, finding creative ways to engage adolescents and families, and to debunk myths about the infection and vaccine, is essential. The recommendations for the HPV vaccination are evolving. It is imperative to emphasize to families that getting immunized prior to exposure is the best way to prevent HPV associated infections.

Conclusions

The HPV is a highly contagious and prevalent infection. Disease burden is high in otherwise healthy young men and women leading to significant consequences. HPV infections also create significant economic burden to society. Although the disease and economic burden of HPV infections is greater in women, men can also be affected by HPV. The available vaccine against HPV is a safe and effective means of primary prevention. Immunogenicity is achieved at better rates when the vaccine is administered to younger adolescents, though the vaccine has been recently approved for use up to age 45 years. Challenges have occurred with administration of this vaccine however, leading to slower uptake when compared to other adolescent specific vaccines. Creative strategies to improve uptake include: utilizing vaccine-only visits and offering immunizations in school-based settings. Given the nature of acquisition of HPV, allowing adolescents to consent to their own immunization is another approach towards slowly but surely eliminating this infection.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Pediatric Medicine* for the series "Adolescent Gynecology". The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm.2019.08.01/coif). The series "Adolescent Gynecology" was commissioned by the editorial office without any funding or sponsorship. MDC served as the unpaid Guest Editor of the series. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/pm.2019.08.01
Cite this article as: Holder N, Ahmed N, Cabral MD. Human papillomavirus infection in adolescents. Pediatr Med 2019;2:46.