

A Review of Factors that Influence Human Papillomavirus Vaccination Rates

by
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A THESIS

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This review aimed to identify the factors that influence human papillomavirus (HPV) immunization initiation and completion among adolescents and young adults. A review of literature pertaining to HPV vaccination was performed that used data published after 2012. It was found that the average HPV vaccination rate in the United States in 2017 was 49%. Barriers to obtaining and completing HPV immunization were determined to include physician recommendations, missed opportunities, knowledge of HPV and the HPV vaccine, perceived risk, place of residence (urban versus rural), and cost. This paper also evaluated two evidence-based programs designed to increase HPV vaccination rates, one targeting adolescents and another targeting young adults. The goal of this research was to elucidate factors that impact an individual's human papillomavirus immunization status and to suggest recommendations to healthcare providers and public health officials that may aid in increasing human papillomavirus immunization rates.

Key Words: Human Papillomavirus, Oncovirus, Vaccines, Vaccination Status

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I understand that my project will become part of the permanent collection of Oregon State University, Honors College. My signature below authorizes release of my project to any reader upon request.

Marina Aguiñaga, Author

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Introduction

At the age of 14, I received my first human papillomavirus (HPV) vaccine booster. I had no idea what HPV was at the time. I was simply frustrated by the fact that I was pulled out of school for the afternoon to go through the pain of yet another shot. It was not until five years later that I was informed of how widespread HPV is and of the potential threat that it poses to my health. HPV is something that far too few have a thorough understanding of, yet it is a virus that poses a risk to everyone.

Human Papillomavirus (HPV)

HPV encompasses a “family of small, non-enveloped, double-stranded DNA viruses.”¹ This family of viruses, designated as intraepithelial pathogens, is known to cause benign epithelial proliferations or warts, meaning that the virus can enter the outermost layer of cellular tissue of the body and negatively influence the cellular growth process.¹ These viruses are particularly potent given the manner in which they exploit their host’s cellular machinery and their potential to integrate into the host genome and remain dormant. These viruses have the ability to override the host’s cell cycle checkpoints and stimulate replication of the viral DNA even in non-cycling cells.¹ When a cell proceeds through cell cycle checkpoints before it is ready to do so, the host cell’s growth control becomes deregulated and can result in the development of cancer.¹

Broadly speaking, HPV can inhibit apoptosis, or programmed cell death, and bypass a host cell’s regulatory mechanisms. HPV also has the ability to compromise the immune system defenses that would otherwise attack and mitigate viral infection. Specifically, the E6 oncoprotein seen in high-risk HPV strains, such as HPV-16 and -18, stimulates the degradation of p53, a tumor suppressor protein, altering the cell’s control of its growth

cycle.^{2,3} Similarly, the E7 oncoprotein, also seen in high-risk HPV strains, binds with high affinity to the ‘pocket domains’ of the retinoblastoma protein (pRb), another tumor suppressor protein, ultimately promoting replication and cell division.^{2,3} As a result, HPV is known as an oncovirus, meaning that HPV is a family of viruses that can cause the formation of cancerous cells.

Around 79 million Americans were determined to have HPV infections as of 2019.⁴ For a majority of these cases, the infection clears on its own. However, cancer and other serious symptoms may arise. It is widely understood that “HPV is associated with cervical, vulvar, and vaginal cancer in females, penile cancer in males, and anal cancer and oropharyngeal cancer in both females and males”, as well as anogenital warts in both females and males.⁵ Oregon Health Authority published data indicating that in 2016 the HPV-related new cancer diagnosis rate was 12.0% for both males and females.⁶ Further, the high-risk HPV strains, HPV-16 and -18, were found to be attributable to “approximately 64% of invasive HPV-associated cancers (65% for females; 63% for males; approximately 21,300 cases annually).”⁵ However, there are steps that can be taken to protect against contracting HPV.

HPV Vaccine

The first HPV vaccine was approved for use in 2006. The HPV vaccine consists of virus-like particles that are assembled to mirror HPV strains’ major coat proteins. This vaccine is noninfectious given its use of virus-like particles and lack of HPV genetic material. Gardasil-9, a nine-valent vaccine (9vHPV), is the only HPV vaccine available in the United States since 2016. Gardasil-9 protects against HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58 and is approved for use in females and males aged 9 to 45.^{6,7}

Methods

A review of the literature was performed to obtain data from studies that evaluated HPV immunization rates, HPV-related cancer rates, and barriers to obtaining the HPV vaccine. The studies evaluated in this paper were procured from literature published no later than 2012. This review utilized HPV-related studies and data from across the U.S. as well as data from the Centers for Disease Control and Prevention (CDC). Inclusion criteria encompassed content pertaining to HPV vaccination rates, attitudes toward the HPV vaccine, and knowledge of HPV and the HPV vaccine among adolescents and young adults, as well as physician beliefs and practices regarding the HPV vaccine. Search words included but were not limited to: “barriers to HPV vaccination”, “HPV vaccine knowledge”, and “HPV physician recommendations.” Evidence-based programs targeting adolescents and young adults to increase HPV vaccine initiation and completion rates were also included to provide insight into particular interventions and the efficacy of such efforts.

Current Status

HPV Vaccine Guidelines

As of August 15, 2019, the Centers for Disease Control and Prevention (CDC) recommends two doses of the HPV vaccine for all 11 to 12 year old children; however, the HPV vaccine can be administered as early as the age of 9.⁷ If the HPV vaccine series is initiated on or after a child's 15th birthday, they must obtain three doses of the vaccine over 6 months.⁷ This vaccine is most effective if administered before sexual debut and is recommended for all through the age of 45, if they have not already received the vaccine. However, given the likelihood that individuals above the age of 26 have already been exposed to HPV, vaccination against HPV potentially provides less benefit. In 2015, the CDC's Advisory Committee on Immunization Practices (ACIP) stated that "because the additional five types in 9vHPV account for a higher proportion of HPV-associated cancers in females compared with males and cause cervical precancers, the additional protection from 9vHPV will mostly benefit females."⁵ This does not suggest though that it is not medically necessary for males to obtain the HPV vaccine.

HPV Vaccination Rates

Several years after the approval of the first HPV vaccine, the CDC reported that among adolescents the average HPV vaccine completion rate in 2017 was 49%, and 66% of individuals between 13 and 17 years old had only received one dose of the series.⁸ Oregon Health Authority published data that provides a picture of local HPV immunization trends. As of May 1, 2018, for adolescents between the ages of 13 and 17 in the state of Oregon, the average rate of HPV immunization was 46.4%.⁹ Jefferson County was the Oregon county with the highest rate of HPV immunization at 57.4% and Curry County was the Oregon

county with the lowest rate of HPV immunization at 22.2%.⁹ Jefferson County is in Central Oregon and has a population size of about 24,658. Census Bureau data indicates a median household income of \$50,339, with a population that is 75.4% White, 20.2% Hispanic or Latino, 18.8% American Indian or Alaska Native, and 1.4% Black or African American.¹⁰ Curry County has a similar population size of about 22,925 but is a rural, coastal county in Southern Oregon. Curry County's median household income is \$46,396 and its population is 92.1% White, 7.3% Hispanic or Latino, 2.6% American Indian or Alaska Native, and 0.6% Black or African American.¹¹ With respect to variation in vaccination rates among different ethnicities, CDC data from 2018 found that among adults aged 18 to 26 in the U.S., "42.1% of non-Hispanic white, 36.7% of non-Hispanic black, and 36.1% of Hispanic adults had ever received one or more doses of the HPV vaccine."¹² Further, the CDC indicated that "for all race and Hispanic ethnicity groups, women were more likely than men to have ever received one or more doses of the HPV vaccine."¹² Considering the relatively low HPV vaccination rates across the U.S. allows for a larger discussion of the downstream consequences.

HPV and Cancer

Such consequences may manifest in the form of cancer. CDC data from 2019 indicates that "each year, about 44,000 new cases of cancer are found in parts of the body where human papillomavirus (HPV) is often found. HPV causes about 34,800 of these cancers."¹³ While this number may seem small compared to the total number of cases of cancer that are diagnosed each year, the CDC determined that the 9-valent HPV vaccine can prevent about 92% of cancers that are attributable to HPV.¹⁴

Table 1. CDC data detailing the number of cancers per year found in sites where HPV is often found and the percent of cancers probably caused by HPV.¹³

Cancer Site	Average number of cancers per year in sites where HPV is often found (HPV-associated cancers)	Percentage probably caused by any HPV type (%)
Cervix	12,015	91
Vagina	862	75
Vulva	4,009	69
Penis	1,303	63
Anus	6,810	91
Female	4,539	93
Male	2,270	89
Oropharynx	19,000	70
Female	3,460	63
Male	15,540	72
Total	43,999	79
Female	24,886	83
Male	19,113	74

Barriers to HPV Vaccination

The factors that contribute to one's likelihood to obtain the HPV vaccine are wide ranging. For some individuals, barriers to HPV vaccination may be financial or social. Institutional barriers to care also pose a risk to many people. More specifically, these factors include whether physician recommendations are provided, missed opportunities, knowledge of HPV and the HPV vaccine, perceived risk, place of residence (urban versus rural), and cost of the vaccine.

Physician Recommendations

One study published in 2012 surveyed family medicine physicians, pediatricians, and obstetricians/gynecologists from the United States to collect information regarding physician recommendation beliefs and practices with respect to HPV vaccination. Some physicians surveyed in this study voiced objections to the HPV vaccine. Such objections “included perceptions that the vaccine: (a) encourages girls to forego regular screenings, (b) is unnecessary for girls under the age of 13, and (c) promotes promiscuity.”¹⁵ However, another study published in 2018 that surveyed healthcare providers in Tennessee stated, “Many providers indicated they have no concerns about the vaccine's safety, and one nurse practitioner stated, ‘At this point, I have more reservations about not giving it to [patients.]’”¹⁶ Some of the surveyed physicians from the 2012 study also noted that governmental and institutional policies and procedures were a burden and create a barrier for providing the HPV vaccine to their patients.¹⁵ Further, “physicians who indicated that parents' receptiveness was a barrier to vaccination either said they were in favor of the vaccine or did not indicate any personal preference.”¹⁵ The 2018 study also indicated that “many providers reported having a difficult time explaining HPV and the vaccine to their

patients due to limited parent and patient health literacy, and because it is associated with sexual behavior.”¹⁶ Additionally, physicians from the 2012 study indicated “that many parents were in ‘denial’ about the sexual activity of their daughters and felt the HPV vaccine was an ‘authorization’ for this behavior.”¹⁵ Notably, the responses from participants in a 2017 study performed in Mississippi identified a healthcare provider recommendation as the “strongest predictor of vaccination.”¹⁷ These beliefs and practices were seen to relate to the physicians’ likelihood to recommend the HPV vaccine to their patients which likely influences overall HPV vaccination rates.

Missed Opportunities

With regard to the interplay of physician recommendations and patient likelihood to vaccinate, missed opportunities were identified as another potential culprit for low HPV immunization rates. A statewide analysis of missed opportunities for HPV vaccination among females 11 to 26 years old performed in Utah and published in 2016 suggested that “missed opportunities for HPV vaccination represent a serious barrier to HPV vaccine coverage and protection from HPV-associated illnesses.”¹⁸ Interestingly, this study determined that compared to non-Hispanic patients, Hispanic females 11 to 18 years of age were less likely to miss an opportunity to vaccinate against HPV.¹⁸ This paper suggested that potential reasons for fewer instances of missed opportunities within this demographic may include “the increased strength of Hispanic community organizations in Utah, the support that Hispanic communities demonstrate for childhood vaccinations, as well as a developing sensitivity of health institutions to the needs of the growing Hispanic population.”¹⁸ Further, pre-teen females (ages 11 and 12) were more likely to have missed an opportunity for HPV vaccination than teens (ages 13 to 18).¹⁸ This study also asserted that the rate of missed

opportunities for girls between the ages of 11 and 12 “may reflect provider or parental discomfort with vaccinating early adolescents against a sexually transmitted infection.”¹⁸ Among young adults, another study published in 2017 reported that rates of provider recommendations for the HPV vaccine differed between young adult males and females, “with 62.4% of females compared to 21.6% of males reporting that they had been offered the HPV vaccine by a doctor or nurse ($p < 0.001$).”¹⁷

Knowledge of HPV and the HPV Vaccine

This data raises further concerns about the knowledge of HPV and the vaccine that can prevent HPV. A study published in 2017 among young adults, specifically college students, determined that, of those surveyed, 92.4% of female students and 82.9% of male students from a public university in Mississippi had heard of HPV, and 75.8% of female students and 56.2% of male students were aware that an HPV vaccine existed.¹⁷ This study also identified the internet and school as males’ most common source of HPV-related information, whereas females most frequently reported health care providers and school as their sources of HPV-related information.¹⁷ Through further analysis, the mean knowledge score determined by this study indicated that despite students reporting awareness of HPV, “there are significant gaps in their knowledge about HPV, including risk and protective factors.”¹⁷ Ninety percent of males and 62.9% of females stated that “they had never seriously thought about getting the HPV vaccination.”¹⁷ Further, the unvaccinated participants were asked how likely they are to obtain the HPV vaccine within the following six months. The responses suggested that the participants’ intention to vaccinate was relatively low, “with 51.7% of females and 52.5% of males reporting that they were ‘very unlikely’ or ‘unlikely’ to get the vaccine within the next six months.”¹⁷ This study also

determined that “most male college students were not even aware that a vaccine was available and few had been offered the vaccine by health care providers.”¹⁷

Perceived Risk

While knowledge regarding HPV and the HPV vaccine is an important indicator of one’s likelihood to vaccinate, perceived risk has also been determined to play a prominent role among young adults. Despite college students noting concerns for the impact and implications of HPV, the 2017 Mississippi study discerned “relatively low perceptions of susceptibility to contract HPV,” and less than 25% of participants agreed “that they are at risk for HPV or likely to contract HPV in their lifetimes.”¹⁷ A study published in 2016 collected survey data from 192 female students 18 years of age and older from Oakland University in Michigan. This study found that “two thirds (67%) of the participants believed that, based on the general sexual practices in the US, female college students in Michigan have a high chance of contracting an HPV infection; however, about 50% of the participants did not believe that they themselves were at a risk of contracting HPV.”¹⁹ Further, the respondents from the Mississippi study “reported relatively low levels of perceived risk related to HPV” despite 63.4% of respondents reporting that they have engaged in sexual intercourse and 63.2% of respondents stating that they were currently in a relationship.¹⁷

Additionally, a study evaluating parental acceptance of HPV vaccination in 9 to 18 year old females indicated that “parents who believe that their daughter was more susceptible to HPV disease and held positive attitudes toward vaccines were more likely to vaccinate.”²⁰ This study also suggested that “it is plausible that parents who have no intent to vaccinate may underestimate risk because they cannot reconcile that their child may be engaging in sexual activity.”²⁰ Another study evaluated mothers’ decisions to vaccinate their 11 to 12

year old daughters. This study indicated that about half of the mothers surveyed “noted that a personal or family history of HPV, other STIs, or cancer (both cervical and other types) influenced her decision to vaccinate.”²¹ This study asserted that “these experiences influenced mothers’ decisions to vaccinate by increasing their awareness of the risk of HPV infection or the severity of HPV-related disease, or by increasing their sense that their daughters were vulnerable to HPV or cervical cancer.”²¹ This data suggests that an individual’s perceived risk with respect to HPV may influence their decision to receive the HPV vaccine.

Rural vs Urban

Rural and urban residency is another component relevant to HPV vaccination. As discussed previously, provider recommendations play a critical role in HPV vaccine uptake. However, whether an individual has access to healthcare and health providers varies across rural and urban demographics. A study published in 2020 examined differences in access to primary care among rural and urban individuals. Specifically, researchers evaluated rural-urban differences across accessibility, accommodation, and acceptability of care in order to develop a more thorough understanding of “the types of providers they have, the characteristics of providers and their practices, and perceptions of patient–provider communication.”²² This study’s findings suggested “that residents of nonmetro areas were more likely than residents of metro areas to have individual usual source of care (USC) providers”, which aligns with past research.²² However, this study also determined that “the providers of nonmetro residents were more likely to be facilities, rather than individuals, and less likely to be physicians.”²² Further, when researchers considered the effects of accessibility and accommodation of care, rural disadvantage became more apparent. The

study asserted that “longer travel times in rural areas mean that rural residents have greater need for providers who offer weekend and evening hours than urban residents, but they have less access to such providers.”²² The 2016 study on missed opportunities also determined that rural patients between the ages of 11 and 12 were more likely than their urban counterparts to have missed an opportunity for HPV vaccination, “which mirrors research detailing the differential and oftentimes lower access to cancer prevention and treatment services available to individuals living in rural areas.”¹⁸ When disparities exist between urban and rural communities with regard to access to healthcare, HPV vaccine uptake can also be affected.

Cost

Cost is the final barrier to HPV immunization discussed in this analysis. The Oakland University study noted that each dose of the HPV vaccine costs about \$140 with the total cost for all doses reaching about \$500.¹⁹ This study also discussed the concerns for individuals that are uninsured or underinsured. While the HPV vaccine is covered under most insurance plans, many individuals are uninsured. This study noted that “teenagers and children under the age of 19, who do not have insurance or are eligible for Medicaid, are covered under the Vaccines for Children (VFC) program.”¹⁹ However, concerns for cost arise when considering individuals between the ages of 19 and 26 because the Vaccines for Children Program does not provide coverage for this age cohort. Further, 19 to 26 year olds have “high rates of being uninsured and/or under-insured.”¹⁸ While the initial price of the HPV vaccine is relatively high, the long-term costs of mitigating HPV-related illness are massive: “screening for and treating cervical cancer, in total, costs up to 6 billion dollars annually in the United States. This makes HPV one of the most expensive sexually transmitted infections to care for, second only to HIV.”¹⁹

Evidence-Based Programs

To further investigate the barriers that affect HPV immunization among adolescents and young adults, two programs were identified that applied various interventions designed to increase HPV vaccine initiation and completion. The first program was applied to three middle schools in Texas. The interventions applied in this study included the provision of physician-led education regarding HPV at school and community events, as well as hosting on-site vaccination events at one of the schools. The second program was applied to two community-based obstetrics and gynecology clinics and targeted young adult women. This program expanded stocking and standing orders for the HPV vaccine, developed reminder call programs, identified an immunization “champion”, expanded the clinics’ payment assistance program, and educated the clinic staff on HPV and the HPV vaccine. Following the implementation of their respective interventions, these two programs reported significantly increased rates of HPV vaccine uptake.

Adolescents

A study performed in Rio Grande City Consolidated Independent School District (RGCCIDS) in Texas “implemented an onsite school-based vaccination program and physician-led education on HPV and HPV vaccines for parents/guardians, school nurses/staff, and pediatric/family providers in the surrounding community (15-mile radius of RGCCISD) at 1 middle school (“intervention school”), and education-only for the remaining 2 schools (“comparison schools”).”²³ For all three schools, one gynecologist and one oncologist led 30-minute presentations about the importance of HPV vaccination at various school and community events, and a pediatrician was available to answer questions and provide educational handouts from the CDC.²³ Parents could also request a private,

educational session with a member of the study's team. The study also utilized social media, local radio stations, and local newspapers to publicize the vaccination program and its efforts.²³ In addition to these education-based efforts, the "intervention school" disseminated consent forms for students to bring to their parents and held a series of events that provided on-site vaccinations.²³

Between August, 2016 and April, 2018, this study "conducted 411 educational events (262 professional and 149 public events). [They] educated 8558 professionals and 15,528 public individuals directly and distributed 38,307 educational materials."²³ HPV vaccine initiation rates increased from 28.97% to 41.56% in the "comparison schools" and from 20.00% to 53.67% in the "intervention school."²³ Further, HPV vaccine completion rates increased from 14.56% to 20.53% in the "comparison schools" and from 8.70% to 28.36% in the "intervention school."²³ Ultimately, this study determined that "students from the intervention school were over 3.6-times more likely to newly initiate/complete the HPV vaccinations than students from the comparison schools."²³

Young Adults

A study performed in two community-based obstetrics and gynecology clinics, which are a part of Denver Health and Hospitals, implemented a multimodal intervention aimed at increasing immunization rates of tetanus, diphtheria, and acellular pertussis (Tdap), HPV, and influenza. The cohort that addressed HPV immunization included 15 to 26 year old, nonpregnant women "lacking any of the 3 HPV vaccines in the series."²⁴ The following interventions were applied: "stocking of immunizations in clinics, revision and expansion of standing orders, creation of a reminder/recall program, identification of an immunization champion to give direct provider feedback, expansion of a payment assistance program, and

staff education.”²⁴ Specifically, this study expanded an assistance program available in one of the clinics to provide vaccines for uninsured patients, streamlined the documentation process for this program, and expanded the electronic standing order for vaccines to uninsured patients.²⁴ Further, the reminder/recall program that was implemented was designed to alert patients when their following doses were to be administered.²⁴ This involved noting the patient’s preferred mode of communication and contact information so that the “champion nurse” could inform the patients of when their subsequent doses were recommended to be completed. This study, performed over two years, found that “the overall rate of HPV vaccination with an eligible visit increased from 7.1% before to 23.7% after the intervention.”²⁴

Future Recommendations

Given the prevalence of HPV-associated cancers and the cost of screening for and treating HPV, the low immunization rates for HPV must be addressed. Extensive research suggests that the HPV vaccine is most effective if administered before sexual debut. This raises the following question: What steps can healthcare providers and public health officials and organizations take to increase the average rate of HPV immunization in the U.S.?

To provide a broader understanding of barriers to HPV immunization, the 2017 study from Mississippi included an analysis that identified factors corresponding to vaccination status: “being offered the vaccine by a health care provider, believing that people who care about you think you should get the vaccine, and belief that the vaccine is likely to cause health problems.”¹⁷ As this paper has discussed, there are a number of factors that influence one’s likelihood to obtain the HPV vaccine. These factors provide insight into how healthcare providers and public health organizations can improve HPV vaccine uptake.

Specific steps that healthcare providers can take include knowing their patients’ vaccination status, using every visit as an opportunity to vaccinate, utilizing reminder call strategies to maintain contact with patients, and scheduling appointments to receive the next dose before the patient leaves the office. Middle schools, high schools, and colleges and universities are recommended to take steps to ensure that their students have adequate and accurate knowledge regarding HPV and the HPV vaccine. Such steps may include organizing programs or activities that promote health education and health comprehension across their campus.¹⁷ These institutions also have the opportunity to establish protocols for providing students with ‘catch-up’ vaccination if they have not already received or completed their HPV immunizations. This may be supplemented through the implementation of on-site

vaccination programs. Public health organizations are recommended to provide the public with information that “correct(s) the misunderstanding that only sexually experienced women need the HPV vaccine. Additionally, educational initiatives should be tailored so that women [and men] can better understand why vaccination prior to sexual initiation is important as well as their lifetime risks of acquiring HPV.”²⁵

Integrating these recommendations into healthcare offices, colleges and universities, and public health organizations has the potential to increase the average rate of HPV vaccine initiation and completion. Given the costs and impact on lives that arise in response to HPV-related illnesses, the need for higher HPV immunization rates cannot be understated. Investment in HPV research is not simply a financial concern but a concern for societal livelihood.

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