This book contains information to be used by AHEC representatives in the planning, implementation and evaluation of activities to increase HPV vaccination rates locally.

# HPV Vaccination Resource Book

## For Area Health Education Centers

May 2015

AHEC Stands for Jobs
NATIONAL AHEC ORGANIZATION

GW Cancer Institute
THE GEORGE WASHINGTON UNIVERSITY

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## A NOTE TO AREA HEALTH EDUCATION CENTERS

The HPV Vaccination Resource Book is a primer on human papillomaviruses (HPV) to help prepare you to facilitate professional education and provider outreach to help increase HPV vaccination rates in your area as part of a Centers for Disease Control and Prevention (CDC) funded cooperative agreement awarded to the National AHEC Organization. This is a 5-year project with the goal of increasing HPV vaccination rates among 11 and 12-year old boys and girls as well as administering "catch-up" vaccinations to older adolescents and young adults.

This book provides a basic introduction to HPV and HPV-associated cancers with data on the number of cases, death rates and cost of care nationally. The book also provides a basic overview of risk factors that increase the chance of an individual becoming infected with HPV. It describes the safety and effectiveness of available HPV vaccines in the United States, provides data on HPV vaccination rates nationally as well as factors, including policies, that influence whether a child receives the HPV vaccine. This book will be updated in January and June each year of the project. Please send questions and update requests to info@ntc.nationalahec.org.

NAO HPV Regional Coordinators will be responsible for gathering additional regional data, including assessing the local policy landscape, identifying local vaccination providers and clinician networks, and determining other potential partners who are working on HPV issues in the area.

Please contact the Project Manager with questions, concerns, or comments about your role or activities related to this project:

**Gretchen Forsell MPH, RD, LMNT**
HPV Project Manager
National AHEC Organization (NAO)
7044 S. 13th Street
Oak Creek, WI 53154 (402) 644-7256
gforsell@nnahec.org

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If you have questions about the book, please contact:
**Aubrey Van Kirk Villalobos, MPH, MEd**, NAO HPV Resource Book Team Lead
Director, Comprehensive Cancer Control, GW Cancer Institute
(202) 994-2680 or avillalobos@gwu.edu

GW Cancer Institute
THE GEORGE WASHINGTON UNIVERSITY

# LIST OF ACRONYMS AND KEY TERMS

| | |
|---|---|
| AAP | American Academy of Pediatrics |
| ACA | Patient Protection and Affordable Care Act |
| ACIP | The Advisory Committee on Immunization Practices (ACIP) is a group of medical and public health experts that develop recommendations on how to use vaccines to control diseases in the United States. Learn more. |
| ACS | American Cancer Society |
| AFIX | Assessment, Feedback, Incentives, and eXchange. AFIX is a quality improvement program used by CDC awardees to raise immunization coverage levels, reduce missed opportunities to vaccinate, and improve standards of practices at the provider level. Learn more. |
| APA | Academic Pediatric Association |
| CDC | Centers for Disease Control and Prevention |
| CEU/CME | Continuing Education Unit / Continuing Medical Education |
| CMS | Centers for Medicare and Medicaid Services |
| Completion | HPV vaccination completion rate is the proportion of those who get one shot who then finish the series. |
| Coverage | Coverage is the percentage of the indicated population who get a certain number of shots (1-shot coverage, 2-shot coverage, 3-shot coverage); Full HPV coverage requires 3 shots. |
| DCPC | CDC's Division of Cancer Prevention and Control |
| EHR/EMR | Electronic Health Record / Electronic Medical Record |
| FDA | Food and Drug Administration |
| HEDIS | The Healthcare Effectiveness Data and Information Set (HEDIS) is a tool used by more than 90 percent of America's health plans to measure performance on important dimensions of care and service. Learn more. |
| HIPAA | The Health Insurance Portability and Accountability Act (HIPAA) is a federal law enacted in 1996 requiring certain reforms to the healthcare industry in an attempt to reduce administrative costs, simplify administrative processes and burdens, help patients maintain continuity of coverage, and improve the privacy and security of patients' information. Learn more. |
| HPV | Human Papillomavirus |
| HPV-*associated* cancer | A cancer that is diagnosed in a part of the body where HPV is often found. These parts of the body include the cervix, anus, penis, vagina, vulva, and oropharynx (back of the throat, including the base of the tongue and tonsils). Learn more. |
| HPV-*attributable* cancer | A cancer that is probably caused by HPV. CDC studies use population-based data from cancer tissue to estimate the percentage of cancers that are probably caused by HPV. Learn more. |

| | |
|---|---|
| Initiation | Starting the HPV vaccine series; Coverage with 1-shot |
| IIS | Immunization information systems (IIS) are confidential, population-based, computerized databases that record all immunization doses administered by participating providers to persons residing within a given geopolitical area. Learn more. |
| Incidence | A cancer incidence rate is the number of new cancers of a specific site/type occurring in a specified population during a year, usually expressed as the number of cancers per 100,000 population at risk. Learn more. |
| MOC | Maintenance of Certification (for board certified clinicians) |
| NACCHO | National Association of County and City Health Officials |
| NCI | National Cancer Institute |
| NCIRD | CDC's National Center for Immunization and Respiratory Diseases |
| NIS-Teen | National Immunization Survey-Teen |
| NVAC | The National Vaccine Advisory Committee recommends ways to achieve optimal prevention of human infectious diseases through vaccine development, and provides direction to prevent adverse reactions to vaccines. Learn more. |
| SEER | The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute works to provide information on cancer statistics in an effort to reduce the burden of cancer among the U.S. population. Learn more. |
| PCP | Primary Care Provider (sometimes Primary Care Physician) |
| PHI | Protected Health Information |
| "Big P" Policies | "Big P" policies are formal laws, rules, and regulations enacted by elected officials and official bodies. |
| "Little p" policies | "Little p" policies are less formal policies, usually related to administration or implementation, such as resolutions adopted by an organization or decisions about local implementation of a formal policy. Watch this YouTube video to learn more. |
| PPHF | Prevention and Public Health Fund |
| Prevalence | Prevalence is defined as the number or percent of people alive on a certain date in a population who previously had a diagnosis of the disease. Learn more. |
| VAERS | The Vaccine Adverse Event Reporting System is a post-marketing safety surveillance program, collecting information about adverse events (possible side effects) that occur after the administration of vaccines licensed for use in the United States. Learn more. |
| Vax | Abbreviation for "vaccination" |
| VFC | Vaccines for Children (VFC) is a federally-funded program that provides vaccines at no cost to children who might not otherwise be vaccinated because of inability to pay. Learn more. |
| YRBSS | The Youth Risk Behavior Surveillance System monitors six types of health-risk behaviors that contribute to the leading causes of death and disability among youth and adults. Learn more. |

# INTRODUCTION TO HUMAN PAPILLOMAVIRUS (HPV)

## Background on HPV

Human papillomaviruses (HPV) are a class of more than 150 viruses that infect epithelial tissue, primarily in the genital and mouth/throat regions.[1] At least 40 of the virus subtypes/strains are easily passed between individuals through skin-to-skin contact during vaginal, anal and oral sex.[2] There is no treatment for HPV infection; however in the case of most healthy adults, HPV infection goes away on its own within 1-2 years without causing any health problems.[2] Individuals who have weak immune systems, unprotected sex, and sex with multiple partners are at greater risk for getting HPV. [3]

For most men and women there are typically no signs or symptoms of HPV infection.[2] HPV types 6 and 11 cause 90% of all anal/genital warts.[2] HPV types 6 and 11 can also cause a condition known as respiratory papillomatosis, when small tumors grow in the air passages from the lungs to the nose and mouth.[4] Genital warts and respiratory papillomatosis can be treated with prescription medication, excisional surgery, cryosurgery and laser surgery, but currently there is no treatment for the HPV infection itself.[1]

Persistent infections with high-risk or oncogenic (cancer-causing) HPV subtypes can cause damage to cells that may lead to anogenital (cervical, anal, vaginal, vulvar, penile) or oropharyngeal (mouth and throat) cancers.[1,2] The medical community generally diagnoses a persistent HPV infection when a woman tests positive for HPV in two consecutive visits at least 4-6 months apart;[5] however the FDA has not approved any tests to detect HPV in men.[1] The most common high-risk, cancer-causing subtypes include 16, 18, 31, 33, 45, 52 and 58.[6] Persistent infection with HPV 16 and 18 is the most important risk factor for development of cervical, anal, mouth, throat, vaginal, vulvar, and penile cancers. It is estimated that effectively all cases of cervical cancer, the most common HPV-associated cancer, are caused by persistent HPV infection; 7 of 10 cases can be directly linked to HPV subtypes 16 & 18.[1] HPV vaccination is a safe, effective cancer prevention method, that is best accomplished before an individual becomes sexually active and risk of HPV infection increases.[1-4]

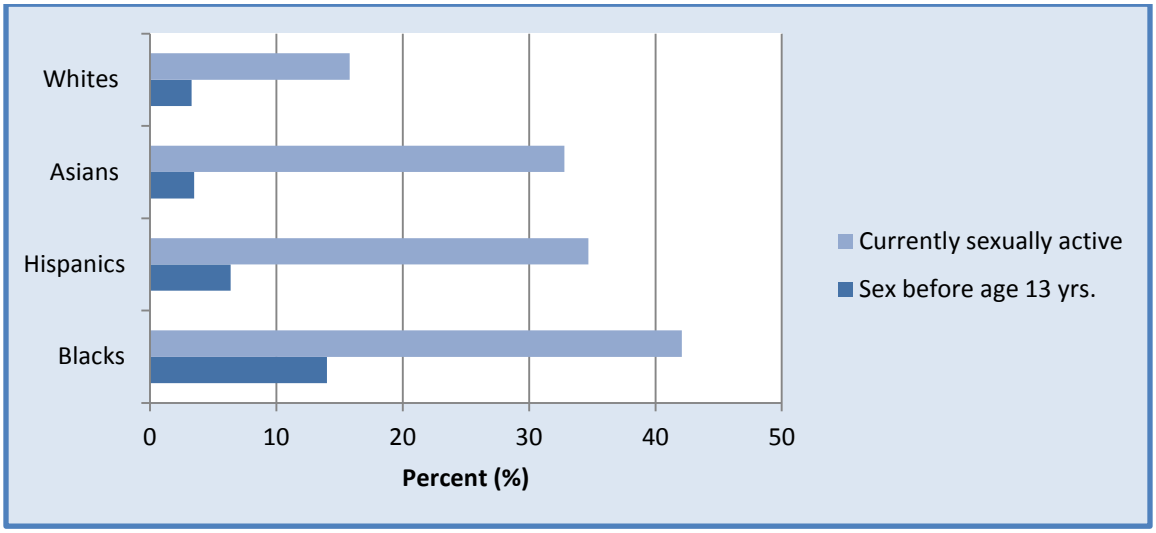
## Epidemiology of HPV Infection and Risk Behaviors

HPV is the most common sexually transmitted infection in the U.S.;[1] almost every sexually active person will acquire it at some point in their life.[7] In fact, HPV prevalence has nearly quadrupled since the year 2000, increasing from 20 to 79 million in 2008 and the incidence rate has more than doubled from 6.2 to 14 million people each year.[8] Adolescents and young adults have the highest HPV prevalence and incidence rates compared to other individuals.[8] Approximately, 75% of new HPV infections occur among those who are between the ages of 15-24 years, and as many as 64% of adolescent girls already have HPV.[8] Because of the high infection rates among adolescents it is suggested that young age (less than 25 years) is a risk factor for HPV infection.[8]

Age is not the single determining factor for an individual's risk for acquiring HPV. Sexual behavior including: sexual activity status, number of sex partners, unprotected sex, partners' sexual history, and age at sexual initiation are also well-documented risk factors for HPV.[8] The 2013 United States (U.S.) High School Youth Risk Behavior Survey (YRBS) provides the most recent data highlighting some of the populations that are at greatest risk for acquiring the HPV infection. Survey data indicate blacks and Hispanics have the highest rates for two of the most significant HPV risk factors: having sexual intercourse at an early age and being currently sexually active.[9] It was found that 14.0% blacks and 6.4% of Hispanics had had sexual intercourse before the age of 13 compared to 3.5% of Asians and 3.3% of whites (Figure 1).[9] Additionally, results indicate 42.1% of high-school aged blacks and 34.7% of Hispanics reported being sexually active compared to 32.8% of whites and 15.8% of Asians (Figure 1).[9] Furthermore, it was found that the likelihood of being currently sexually active was found to increase with age.[9] The responses to the 2013 YRBS indicate that 49.3% of 12th graders, 40.2% of 11th graders, 29.4% of 10th graders and 19.6% of 9th graders reported being currently sexually active.[9]

Survey data indicate blacks and Hispanics have the highest rates for two of the most significant HPV risk factors.[9]

**Figure 1. Sexual Activity Risk Factors for HPV by Race/Ethnicity (High School YRBS 2013)[9]**




**TAKE NOTE!**

*This resource book includes information on sexual activity and HPV infection as background information for AHECs only.* ***The CDC has found that discussing this type of data with parents or clinicians is counterproductive.*** *Unfortunately, if clinicians explain the link between sexual activity and HPV while recommending a child be immunized, parents are actually less likely to vaccinate the child. In outreach and continuing education for physicians, the CDC recommends emphasizing that adolescents in the targeted age range of 11-12 years have the most robust immune response when vaccinated and that the HPV vaccine is cancer prevention. The effects of physician recommendations on HPV vaccination*

*acceptability among parents and the surrounding influential factors are described in greater detail on pages 11-12.*

# PUBLIC HEALTH PROBLEM & SIGNIFICANCE

## Background on HPV-Associated Cancers

The role of HPV infection in the development of certain cancers has been well established. Persistent infection with HPV is associated with cervical, anal, oropharyngeal (mouth and throat), vaginal, penile, and vulvar cancers.[10] According to data collected by National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) and CDC'S National Program of Cancer Registries, from 2006 to 2010, 91% of all cervical and anal cancers can be attributed to persistent HPV infection.[10] Data also indicate 63-75% of all oropharyngeal, vaginal, penile, and vulvar cancers can be attributed to persistent HPV infections (Table 1).[10]

**Table 1. Estimated Percentages of Specific Cancers Attributed to Persistent HPV Infections (%)[10]**

| Cancer Site | Attributed to HPV |
|---|---|
| **Anus** | 91% |
| **Cervix Uteri** | 91% |
| **Vagina** | 75% |
| **Oropharynx /Oral Cavity** | 72% |
| **Vulva** | 69% |
| **Penis** | 63% |

## Impact of HPV-Associated Cancers

### Prevalence and Incidence

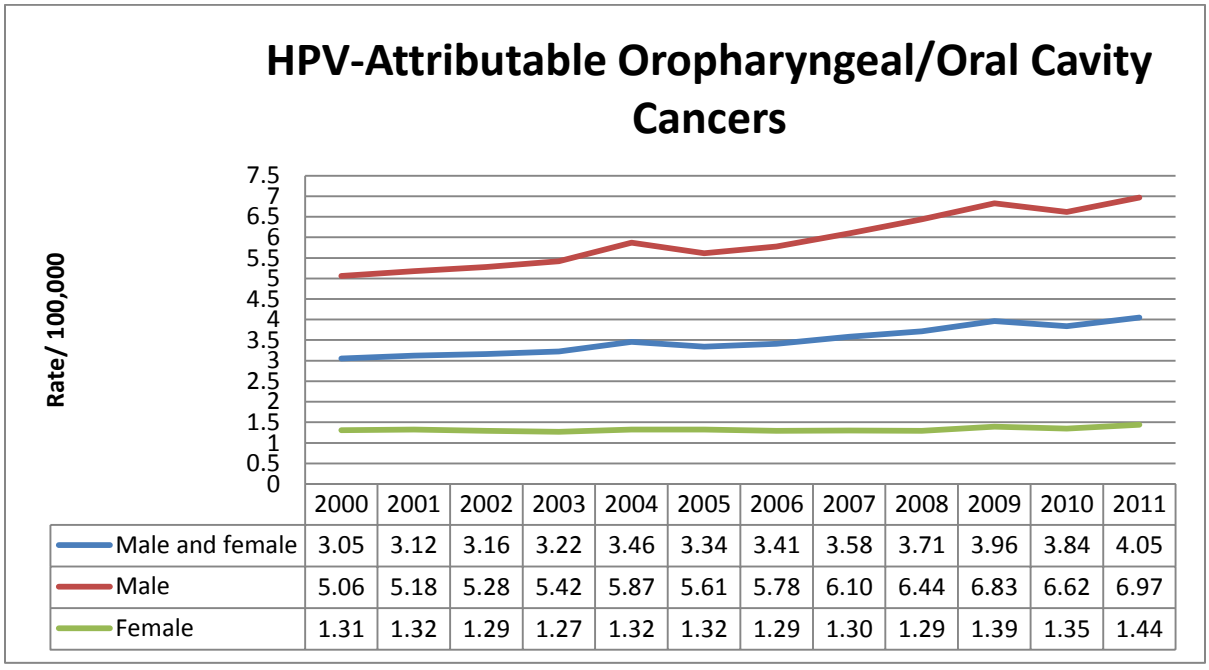
As of January 1, 2011, the most prevalent HPV-associated cancer among women in the U.S. was cervical cancer; oropharyngeal/oral cavity cancers were the most common among men.[11] Almost 13% of women, more than 200,000 nationwide as shown in table 2, were currently living with cervical cancer that could be directly attributed to HPV infection.[11] Almost 4% of men, more than 60,000, had oropharyngeal/oral cavity cancer.[11] Data on incidence, or new cases, from 2007 to2011 showed approximately 34,000 HPV-attributable cancers were reported in the U.S. each year; about 21,000 among females and more than 13,000 among males.[12] Cervical cancer has the highest rate of new cases (incidence) among women (7.6/100,000), and oropharyngeal/oral cavity cancer has the highest incidence rates among men (6.6/100,000).[12]

**Table 2. HPV-Attributable Cancer Prevalence and Annual Incidence in the United States[11,12,13]**

| Site | Sex | Prevalence Count | Population | Prevalence (%) | Incidence Count | Annual Incidence (per 100,000) |
|---|---|---|---|---|---|---|
| **Oropharynx /Oral Cavity** | **Females** | 13,253 | 157,779,629 | 0.84 | 2,209 | 1.4 |
| | **Males** | 60,719 | 152,674,800 | 3.977 | 10,077 | 6.6 |
| **Anus, Anal Canal, and Anorectum** | **Females** | 21,411 | 157,779,629 | 1.357 | 3,156 | 2.0 |
| | **Males** | 12,016 | 152,674,800 | 0.787 | 1,985 | 1.3 |
| **Cervix Uteri** | | 200,932 | 157,779,629 | 12.735 | 11,991 | 7.6 |
| **Vagina** | | 3,992 | 157,779,629 | 0.253 | 789 | 0.5 |
| **Vulva** | | 24,693 | 157,779,629 | 1.565 | 2,840 | 1.8 |
| **Penis** | | 7,389 | 152,674,800 | 0.484 | 1,221 | 0.8 |
| **TOTAL** | | **344,405** | | | **34,268** | |

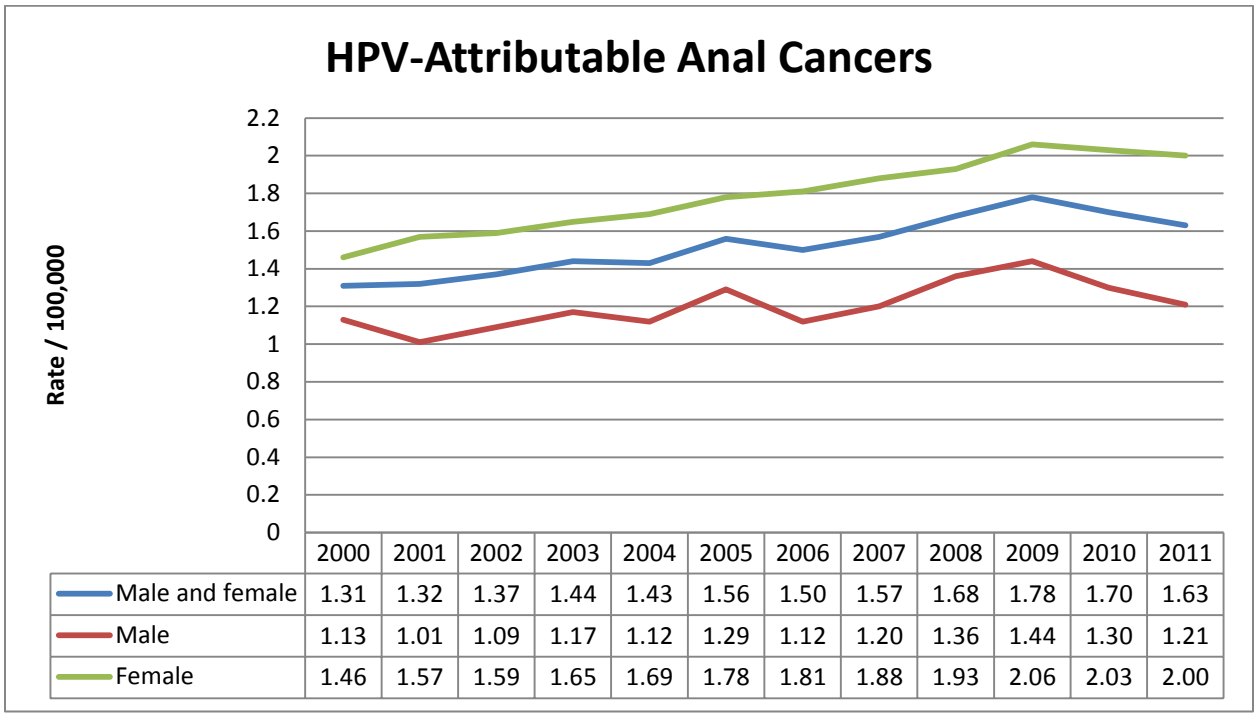
Although cervical cancer is the most common among the HPV-associated cancers, new cases of other HPV-associated cancers are rising in some populations. Based on data from 2000 to 2011, the rates of newly reported cancers of the oropharynx/oral cavity have been increasing for men and anal cancers have been increasing for women.[14,15] The rate of newly reported cervical cancer has continued to decrease since 1975, due primarily to preventive screening for pre-cancerous lesions with Pap tests, while the rates of vaginal, vulvar, and penile cancers have stayed relatively constant (Figures 2 to 4).[16,17,18] Appendix I includes a detailed description of data analysis methodology for information presented in Tables 2 and 3 as well as Figures 2 to 4.

**Figure 2. HPV-Attributable Oropharyngeal/Oral Cavity Cancers[12]**



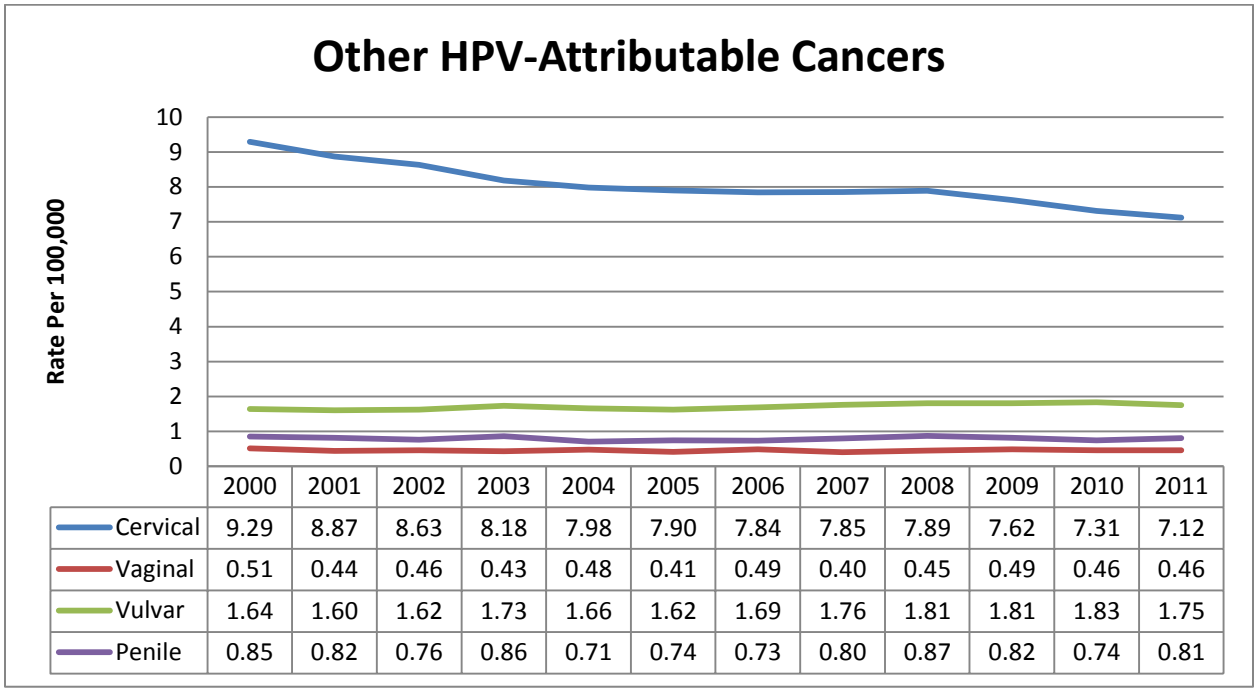

| | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Male and female | 3.05 | 3.12 | 3.16 | 3.22 | 3.46 | 3.34 | 3.41 | 3.58 | 3.71 | 3.96 | 3.84 | 4.05 |
| Male | 5.06 | 5.18 | 5.28 | 5.42 | 5.87 | 5.61 | 5.78 | 6.10 | 6.44 | 6.83 | 6.62 | 6.97 |
| Female | 1.31 | 1.32 | 1.29 | 1.27 | 1.32 | 1.32 | 1.29 | 1.30 | 1.29 | 1.39 | 1.35 | 1.44 |

**Figure 3. HPV-Attributable Anal Cancers[12]**




| | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Male and female | 1.31 | 1.32 | 1.37 | 1.44 | 1.43 | 1.56 | 1.50 | 1.57 | 1.68 | 1.78 | 1.70 | 1.63 |
| Male | 1.13 | 1.01 | 1.09 | 1.17 | 1.12 | 1.29 | 1.12 | 1.20 | 1.36 | 1.44 | 1.30 | 1.21 |
| Female | 1.46 | 1.57 | 1.59 | 1.65 | 1.69 | 1.78 | 1.81 | 1.88 | 1.93 | 2.06 | 2.03 | 2.00 |

**Figure 4. Other HPV-Attributable Cancers[12]**




| | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cervical | 9.29 | 8.87 | 8.63 | 8.18 | 7.98 | 7.90 | 7.84 | 7.85 | 7.89 | 7.62 | 7.31 | 7.12 |
| Vaginal | 0.51 | 0.44 | 0.46 | 0.43 | 0.48 | 0.41 | 0.49 | 0.40 | 0.45 | 0.49 | 0.46 | 0.46 |
| Vulvar | 1.64 | 1.60 | 1.62 | 1.73 | 1.66 | 1.62 | 1.69 | 1.76 | 1.81 | 1.81 | 1.83 | 1.75 |
| Penile | 0.85 | 0.82 | 0.76 | 0.86 | 0.71 | 0.74 | 0.73 | 0.80 | 0.87 | 0.82 | 0.74 | 0.81 |

In the U.S. there are significant disparities with respect to HPV-associated cancer incidence. While cervical cancer incidence rates are much higher among racial and ethnic minority groups, oropharyngeal cancer incidence rates are higher among whites.[19] Most recent data indicates cervical cancer incidence per 100,000 population was 10.6 for Hispanics, 10.2 for African Americans and 9.1 for Alaska Natives compared to 6.4 for Pacific Islanders and 7.1 for whites.[19] Oropharyngeal cancer incidence per 100,000 population was 4.4 for whites, 3.1 for African Americans, 2.8 for Alaska Natives, 2.0 for Pacific Islanders and 2.4 for Hispanics.[19]

> Cervical cancer incidence rates are much higher among racial and ethnic minority groups.[19]

## Mortality and Survival

Mortality and survival among adults diagnosed with HPV-associated cancers varies by cancer site and sex. During the period 2004 to 2010, the 5-year relative survival rate for cervical cancer was 67.8% (Table 3).[20] This means that almost 68 of every 100 women diagnosed with cervical cancer were alive 5 years after diagnosis.[20] This also means that 32 of every 100 women diagnosed with cancer were not alive 5 years later.[20] For the most common HPV-associated cancer in men, oropharyngeal/oral cavity, the survival rate was between 37.5-62.9%. [20]

Although the 5-year survival rates for some HPV-associated cancers are relatively high, there are still a substantial number of deaths. Most recent reports from 2007 to 2011 showed that oropharyngeal cancers cause the most deaths for men (0.35-0.9/100,000) while for women, cervical cancer death rates were highest (2.33/100,000), as shown in Table 3.[21]

**Table 3 - Annual U.S. Mortality Rates & 5-Year Relative Survival[20,21]**

| | Mortality Rate/100,000 (2007-2011 base) | | 5-year Relative Survival (%) (2004-2010 base)* | |
|---|---|---|---|---|
| **Site** | **Males** | **Females** | **Males** | **Females** |
| **Oropharynx** | 0.35 | 0.12 | 42.9 | 37.0 |
| **Tongue** | 0.90 | 0.36 | 62.9 | 62.1 |
| **Other Oral cavity & pharynx** | 0.80 | 0.20 | 37.5 | 30.5 |
| **Anus, Anal Canal, and Anorectum** | 0.20 | 0.25 | 60.8 | 68.5 |
| **Cervix Uteri** | | 2.33 | | 67.8 |
| **Vagina** | | 0.22 | | 51.7 |
| **Vulva** | | 0.49 | | 70.5 |
| **Penis** | 0.17 | | 68.0 | |

* Actuarial method. Ederer II method used for cumulative expected.

### Cost of Care

In addition to their impact on health, HPV-associated cancers also carry a huge financial burden to cancer patients, their caregivers, and society.[22] HPV prevention and treatment cost the U.S. health system nearly $8 billion dollars per year in direct medical costs, which makes HPV the second most expensive sexually transmitted infection (STI) after the human immunodeficiency virus (HIV).[23] Of the total cost, approximately $6.6 billion was for routine cervical cancer screening and follow-up, while $1 billion was for cancer treatment (including $0.4 billion for cervical cancer and $0.3 billion for oropharyngeal cancer).[23] Genital warts alone cost $0.3 billion and treatment of HPV-associated respiratory conditions cost $0.2 billion.[23] In addition, losses in time and productivity due to cervical cancer deaths in the U.S. were valued at $1.8 billion in 2005.[24] A more recent 2012 study projected that the general cost of all cancer care at the state-level will increase between 34 and 115%, with the cost to states ranging from $347 million to $28.3 billion in the year 2020.[24] Unfortunately, all cancer related direct medical expenditures and productivity costs are expected to increase as the quality of treatment advances, as the population ages, and with improved survival following diagnosis.[25] Reducing the financial burden on both the patient/family and society is an important goal and benefit of HPV-associated cancer prevention efforts, including HPV vaccination.

All cancer related direct medical expenditures and productivity costs are expected to increase as the quality of treatment advances, as the population ages, and with improved survival following diagnosis.[25]

## THE SOLUTION

### Background on HPV Vaccines

Currently, there are three vaccines on the market in the U.S. that prevent HPV infection. Gardasil, produced by Merck and Co., was first licensed in 2006 for use among girls and women aged 9-26 years (Table 4).[26,27] In 2009, the U.S. Food and Drug Administration (FDA) approved a second HPV vaccine called Cervarix, produced by GlaxoSmithKline, for use among females aged 10-25 years.[26,27] Both vaccines were licensed to be administered on a three-dose schedule (0, 1, and 6 months for Cervarix and 0, 2, and 6 months for Gardasil).[27] On December 10, 2014 the FDA announced approval of a third HPV vaccine, Gardasil 9 (HPV9),[ϒ] for women aged 9 to 26 and men aged 9 to 15.[28,29]

[ϒ] ACIP recommendation does not mean that HPV9 will be available immediately to patients. After addition to the ACIP recommended schedule of vaccinations, private insurers are required to cover the vaccine with no cost-sharing within one year of the recommendation, a result of the ACA. The HPV9 vaccine may also take additional time to be available from vaccine providers as they decide when and what quantities to order from the manufacturer.

**Table 4. Summary of Human Papillomavirus (HPV) Vaccines Licensed in the U.S.**

| Vaccine Name | Manufacturer | HPV Strains | Target Population (Sex, Ages) | FDA Approval Year | Doses Required | Approximate Cost per Dose |
|---|---|---|---|---|---|---|
| **Cervarix® (HPV2)** | GlaxoSmithKline | 16 & 18 | Females 10-25 years | 2009 | 3 | $128.75[30] |
| **Gardasil® (HPV4)** | Merck and Co. | 6, 11, 16, 18 | Males & Females 9-26 years | 2006 | 3 | $145[31] |
| **Gardasil 9® (HPV9)** | Merck and Co. | 6, 11, 16, 18, 31, 33, 45, 52, 58 | Females 9-26 years & Males 9-15 years | 2014 | 3 | $158[31] |

Although licenses were obtained at different times, Cervarix and Gardasil share a similar biological makeup.[32] Cervarix (HPV2) is a bivalent vaccine that prevents infection by high-risk, cancer-causing HPV types 16 and 18.[33] Gardasil (HPV4) is a quadrivalent vaccine that prevents infection by HPV types 6, 11, 16, and 18, protecting against cancer, genital warts and papillomatosis.[33] Both Cervarix and Gardasil prevent infection with HPV types 16 and 18, which cause 7 in 10 cases of cervical cancers.[1] In addition to the four HPV strains included in the original Gardasil vaccine, HPV9 also prevents infections with additional cancer-causing HPV types 31, 33, 45, 52 and 58 with 98% effectiveness, adding protection against an additional 15% of cervical cancers not previously covered.[26,28,29] According to the National Cancer Institute, "widespread vaccination has the potential to reduce cervical cancer deaths around the world by as much as two-thirds."[1] Recent U.S. estimates also suggest 81% of new cases of cervical cancer could be prevented by HPV vaccination.[29]

"Widespread vaccination has the potential to reduce cervical cancer deaths around the world by as much as two-thirds." [1]

The CDC Advisory Committee on Immunization Practices (ACIP) is the official body that makes evidence-based vaccination schedule recommendations in the U.S. Table 5 details the current HPV recommendations. ACIP recommends routine administration of HPV4 or HPV9 for males and either HPV2, HPV4 or HPV9 for females by age 11-12.[26,34] The reasoning for early vaccination is that the vaccine is effective in preventing, but not treating HPV infections, that are sexually transmitted.[26,34] Vaccinating at ages 11-12 provides protection before the adolescent is likely to become sexually active and thus before the chance of HPV exposure.[26,35,36] Furthermore, ACIP recommends "catch-up" vaccinations for females ages 13-26 and males 13-21 years.[34]

**Table 5. Advisory Committee on Immunization Practices (ACIP) Recommendations for Human Papillomavirus (HPV) Vaccines[26,34]**

| Target Population | ACIP Recommendation Administration |
|---|---|
| **Females age 11-12** | Routine vaccination with HPV9, HPV4 or HPV2 (Can begin series as early as 9 years) |
| **Females age 13-26** | "Catch-up" vaccination for those who have not been vaccinated previously or who have not completed the 3-dose series |
| **Males age 11-12** | Routine vaccination with HPV9 or HPV4 (Can begin series as early as 9 years) |
| **Males age 13-21** | "Catch-up" vaccination for those who have not been vaccinated previously or who have not completed the 3-dose series (May vaccinate males aged 22-26 years) |
| **High-Risk Populations** | |
| **Immunocompromised Persons** | ACIP recommends routine vaccination at age 11 or 12 years with HPV2, HPV4 or HPV9 for females and with HPV4 or HPV9 for males. Vaccination is recommended through age 26 years for immunocompromised persons who have not been vaccinated previously or who have not completed the 3-dose series. |
| **Men Who Have Sex with Men (MSM)** | For MSM, ACIP recommends routine vaccination with HPV9 or HPV4, as for all males, and vaccination through age 26 years for those who have not been vaccinated previously or who have not completed the 3-dose series. |
| **History of Sexual Abuse or Assault** | ACIP recommends HPV vaccination beginning at age 9 years for children and youth with any history of sexual abuse or assault who have not initiated or completed the 3-dose series. Females and males who are victims of sexual abuse or assault should receive HPV vaccine through the recommended ages if they have not already been vaccinated. |

## Safety and Effectiveness

FDA licensure and ACIP recommendation of Cervarix and Gardasil were based on several large scale clinical trials that proved the safety and effectiveness of both vaccines in females and males.[27,28,37,38] The 3-shot series of HPV2, HPV4 and HPV9 cause the body to produce a strong immune response against the specified HPV types and have outstanding safety records.[34,37,38,39,40] More specifically, research indicates that the vaccine has an even stronger immune response in preteens.[7] Studies have shown that protection against HPV can last for 10 years or more without losing effectiveness.[28] Clinical trials are currently underway to determine the effectiveness of only receiving two shots.

Globally, the highly effective Gardasil and Cervarix vaccines have been distributed in approximately 125 and 41 million doses, respectively.[39] During 2006 to 2014, 67 million doses of the HPV vaccines were administered in the U.S. alone.[41] Safety reports from the Vaccine Adverse Event Reporting System (VAERS) indicate that of the 67 million who received HPV vaccines, approximately 25,000 (less than 1% ) experienced adverse effects, 92% of which were non-serious (e.g. redness or soreness at the site of the injection, headache, or fainting immediately following vaccination).[37,38,40,41]

Of the reported adverse events among girls and women, 8% have been serious; including 47 verified mortalities.[42] CDC investigations into the reported deaths found that these deaths could not be directly associated with the vaccine.[42] Furthermore, neither the non-serious adverse events nor more severe

effects (e.g. Guillain-Barre Syndrome, seizures, stroke, venous thromboembolism and appendicitis) were any more common after HPV vaccination than among other adolescent vaccinations.[42,43] Specifically, VAERS shows that there have been 39 deaths following Meningococcal vaccination and 67 following pertussis, tetanus and diphtheria (Tdap).[44]

## HPV Vaccine Uptake

Despite proven safety and effectiveness, HPV vaccine uptake rates remain far below the Healthy People 2020 goal of 80% and below those of other vaccines recommended for adolescents.[27,45] Data from 2013 indicates vaccine coverage among adolescents aged 13-15 years was highest for Tdap (88%), followed by meningococcal (78%), and lowest for HPV (33%).[46] According to data from a 2014 CDC report, only 38% of girls and 14% of boys age 12-17 years old, were fully vaccinated for HPV.[46,47] Moreover, when comparing HPV vaccine uptake, many studies indicate a person's gender, race, ethnicity and socioeconomic status (SES) influenced vaccine completion[Φ] rates.[48,49] Another 2014 CDC report indicated adolescent boys had significantly lower vaccination completion rates compared to adolescent girls at 34.6% vs. 57.3%, respectively.[50] In regards to race/ethnicity, black females were more likely to start the HPV vaccine series compared to whites; however completion rates were much lower at 60.8% vs. 74.8% for whites.[51] Similarly, lower rates of vaccination completion were found among Hispanic females (69.4%) compared with whites (74.8%).[51] Moreover, the 2011 National Immunization Survey-Teen (NIS-Teen) study reported higher levels of vaccine initiation among females below the poverty line when compared to higher SES girls (62.1% vs. 50.1%), but completion rates for poor teens were lower than those for teens above poverty line at only 66.4% compared to 72.6%.[51]

According to data from 2014, only 38% of girls and 14% of boys age 12-17 years old, were fully vaccinated for HPV.[46,47]

Achieving the highest possible HPV vaccination coverage rates not only has the potential to decrease HPV incidence and associated cancer mortality rates but it also has the potential to establish herd immunity. Herd immunity is "the resistance to a disease that develops in an entire community when a sufficient number of individuals are vaccinated."[52 (p 801)] This form of immunity can provide a measure of protection for those who are unable to receive the vaccine.[52] The greater the number of individuals in a community who are immune to HPV, the smaller the odds are for individuals who aren't immune to get or come in contact with HPV. Though the uptake is currently lower for boys than girls, and male HPV vaccination is still controversial in some circles, a recent landmark study suggests that an increased effort to vaccinate boys is likely to protect more people from HPV-associated diseases for the same price.[53]

[Φ] The HPV vaccination "completion" rate is the proportion of those who get one shot who then finish the series; completion is not the same as coverage. "Full coverage" is the percentage of the population who get three shots (e.g. 2013 data from NIS-Teen shows that nationally 37.6% of female adolescents had received the recommended 3 doses, 57.3% of females had at least one shot and the completion rate was 70.4% for girls who had started the series, but there are many girls who start the series and do not complete it).[50]

## Factors Impacting HPV vaccination uptake

### *Parental Barriers and Facilitators of HPV Vaccination*

As summarized in Table 6, several factors have been identified that may explain the low HPV vaccination rates. Because administering the vaccine to adolescents most commonly requires parental consent, some of the greatest challenges to HPV vaccine acceptance are parental knowledge, attitudes and beliefs.[54,55] Many parents do not understand the urgency to target pre-pubertal girls, but this is the most effective time to vaccinate females.[55] Research has found that most parents feel their child is too young and would not initiate sexual activity for many years to come.[36,55,56] Furthermore, some parents feel vaccinating their child(ren) against an STI, sends a message to them that it is okay or expected that they become sexually active.[36]

**Table 6. Summary of Barriers and Facilitators of HPV Vaccine Uptake among Adolescents**

| | Barriers to Vaccination of Child(ren) | Facilitators of Vaccination of Child(ren) |
|---|---|---|
| **Parent** | • Knowledge, Attitudes, Beliefs & Perceptions<br>  ○ Lack of urgency<br>• Acceptability<br>  ○ Fear of condoning promiscuity or early sex<br>• Cost<br>• Safety<br>  ○ Fear side effects<br>  ○ Distrust "newness" | • Physician's strong recommendation |
| | **Barriers to HPV Vaccine Recommendation** | **Facilitators of HPV Vaccine Recommendation** |
| **Physician** | • Younger adolescent<br>• Anticipated parental disapproval<br>• Discomfort discussing sex with young patients<br>• Lack of time<br>• Fear of religious and cultural sensitivities<br>• Low perceived risk of sexual activity in patient<br>• Cost<br>  ○ To purchase, store<br>  ○ Low reimbursement<br>• Safety & Efficacy<br>  ○ Desire more information/data | • Younger doctor<br>• Female doctor<br>• Pediatrician |

### *Physician Barriers and Facilitators of HPV Vaccine Recommendation*

Parental perceptions' play a key role in the decision making process; however, physician recommendations have an even greater influence on HPV vaccine acceptability.[57] Health care providers making strong recommendations is the most effective method of encouraging HPV vaccination among adolescents.[58-61] According to the CDC a strong recommendation should be presented using a presumptive approach. [58-63] Presumptive recommendation includes verbal dominance and emphasis of vaccine effectiveness.[58-63] Personal belief in the importance of the vaccine can be highlighted by stressing cancer prevention and vaccine safety.[58-63] The presumptive approach calls for providers to

"announce" that it is time for the HPV shots, as opposed to "asking" if the patient wants to get the vaccine.[63] This helps to assure the patient of the providers' trust in the vaccine's safety and effectiveness. Visit the CDC's YOU ARE THE KEY website for tips to help vaccine providers with making strong recommendations. Quantitative data suggests physician discussions and a strong physician recommendation together is "associated with a 93-fold increase in the odds of initiating the HPV vaccine series among a sample of women aged 19-26 years."[58(p 621)] Moreover, the CDC and ACIP have suggested that physicians bundle (co-administer) HPV vaccination recommendations and delivery with other routine vaccinations for adolescents such as the meningococcal and pertussis, tetanus and diphtheria (Tdap) booster to achieve greater acceptability.[28,64,65,66] Co-administration also offers convenience to both patients and providers, which can increase the likelihood of on-schedule vaccine uptake among adolescents.[24,67,68] Providers should be trained to use a combination of the above approaches to ultimately convey to parents that the HPV vaccine is normal and should become a routine part of their child's vaccination schedule.

Although encouraging the use of strong provider recommendations has been proven effective in increasing HPV uptake, some physicians have expressed reservations and have been reluctant to recommend the vaccine to the intended population. In fact, previous research has found that nearly two-thirds (64%) of vaccine-eligible girls ages 11-12 remained unvaccinated for HPV after their routine preventive care visit, representing significant missed opportunities.[69] A recent study assessing barriers to physician recommendations found that physicians were least likely to recommend the HPV vaccination to early adolescents (34.6%) compared to middle adolescents (52.7%) and late adolescents (50.2%), which further demonstrates non-adherence with ACIP recommendations.[61] Evidence suggests that anticipated parental disapproval, discomfort discussing sexual matters with young people, insufficient time to discuss HPV vaccination with a parent, and fear of religious and cultural sensitivities are all known barriers impacting a physician's decision to recommend the vaccine.[36,55,60,70] Furthermore, perceived risk of expediting initiation of sexual activity has also been identified as a major factor impacting a physician's decision to recommend the HPV vaccine. In recent reports several providers described using an un-validated profiling method to assess their patients for perceived risk of sexual activity and in turn deciding when to recommend HPV vaccination.[55,71]

Nearly two-thirds (64%) of vaccine-eligible girls ages 11-12 remained unvaccinated for HPV after their routine preventive care visit, representing significant missed opportunities.[69]

Physician recommendations vary by physician characteristics, including gender, specialty, and age. Studies indicate younger physicians are more likely to recommend the vaccine, compared to older physicians, "who are not as receptive to adopting new practice."[60 (p 81)] Research also shows that of the three physician specialist types that typically provide preventive care for females ages 9-26, pediatricians have greater odds of recommending the HPV vaccine compared to family practitioners and

obstetrician/gynecologists.[61,72] Also, patients of female primary care providers (PCPs) are more likely to start the HPV vaccine series compared to male PCPs.[73]

### *Cost*

While parents and physicians have different motivations for vaccine hesitancy, both recognize cost and affordability as important barriers to provision and uptake. Costs for the complete HPV vaccine series can total to roughly $129-158 per dose plus administrative fees (Table 4).[33] Furthermore, although there are federally funded vaccine programs like the Vaccines for Children (VFC) program, which provides vaccines to Medicaid-eligible and uninsured children for low or no cost, "females 19 and older have limited access to vaccine-specific funding and they are also less likely to be insured."[73(p 520)] Research participants often report that HPV vaccines are too expensive without insurance coverage; especially for low income families.[74] Several studies have also shown that cost is often the most influential barrier to vaccine access.[72] For providers, the amount of reimbursement received for a vaccine plays a large role in whether a physician administers the vaccine.[70,75] It has been found that providers are 55% less likely to recommend the HPV vaccines due to inadequate insurance reimbursements.[55] Lastly, up-front costs of ordering and stocking the vaccine have also been identified as barriers to physician recommendations and administration of the vaccine.[76]

### *Misperceptions about Safety and Effectiveness*

In addition to financial burdens, several research studies have been published implicating safety concerns and lack of knowledge as barriers to HPV vaccine acceptance among parents and providers.[36,39,56,72,77] The literature suggests parents still fear the potential side effects and distrust the "newness" of the vaccine, despite 9 years of safety and effectiveness data accumulated since original FDA licensure.[39,54,78] In fact, in a qualitative study about parent perceptions, "24% of parents indicated the vaccine would have to be on the market for more than 5 years before they would feel comfortable providing it for their daughters."[73(p 522)] Furthermore, in recent studies and studies published in the initial years following vaccine availability, many parents and physicians reported information deficit as an additional barrier to HPV vaccine uptake. "It has been reported that many parents have expressed dissatisfaction with the information available to them and stressed the importance of receiving sufficient, clear and understandable information to enable them to make an informed decision."[36,56(p 5162)] Similarly, several studies published between 2008 and 2011 indicated that physicians want more information on safety and efficacy to feel comfortable administering the HPV vaccine.[50,50,64,79]

## Policies Impacting HPV Vaccination Uptake

Vaccine uptake is not only influenced by patients, parents and providers but several types of policies as well. Formal or "big P" policies that can impact HPV vaccination include laws, rules, and regulations enacted by elected officials and official bodies, such as US Preventive Services Task Force and ACIP recommendations, school entry vaccination requirements enacted at the state level, funding for public education campaigns to increase immunization rates, mandates on insurance coverage of vaccines, and required adherence to ACIP recommendations.[80,81] "Little p" policies that can impact HPV vaccination include less formal policies such as Medicaid funding decisions, lack of statewide coordination and planning, a fragmented health system, professional association endorsement of the ACIP

recommendations, provider-level decisions about administrative fees, and weak oversight of exemption from school mandates.

### *ACIP Recommendations*

As discussed previously, ACIP recommendations for HPV vaccines differ slightly by the target audience's age, sex, and risk status (Table 5).[26,82] All ACIP recommendations are based on several large scale clinical trials that proved the safety and effectiveness of both vaccines in females and males.[27,28,37,38] ACIP recommendations impact Medicaid policies, Vaccines for Children (VFC) programs, private insurance coverage, and state-level school vaccination policies.

### *Mandates for Insurance Coverage & Financing Issues*

With the 2010 enactment of the federal Patient Protection and Affordable Care Act (ACA), mandated insurance coverage for HPV vaccination was greatly expanded. ACA requires that the cost of the HPV vaccine be covered through both private and public insurers for the ages recommended by ACIP, with no cost-sharing (e.g. co-pay).[83] Table 7 shows specific information on coverage and cost by insurer type and assistance program. Unfortunately, vaccines are regarded as an optional benefit for adults by Medicaid and it is at a state's discretion whether to cover HPV vaccine.[84] Also, providers can charge an "administrative fee," even if the cost of the vaccine itself is fully covered. These rates are often negotiated between insurance companies and providers. The Centers for Medicare and Medicaid Services (CMS) sets maximum amounts for vaccine administration fees among participating providers, which vary by state; the 2014 range was between $19-$33.[83]

Of most salience to this project, the VFC program, run by the CDC, requires coverage of all ACIP recommended vaccines.[85] Those eligible for the VFC program include children under 19 years who are Medicaid-eligible, uninsured, underinsured, or American Indian or Alaska Native. According to the CDC,

> "underinsured means the child has health insurance, but it doesn't cover vaccines, doesn't cover certain vaccines, or covers vaccines but has a fixed dollar limit or cap for vaccines. Once that fixed dollar amount is reached, a child is then eligible. Underinsured children are eligible to receive vaccines only at Federally Qualified Health Centers or Rural Health Clinics."[85]

Additionally, CDC states that

> "there is no charge for any vaccines given by a VFC provider to eligible children. But there can be some other costs with a vaccination: Doctors can charge a set (or standard) fee to administer each shot. But if the family can't afford the fee per shot, the fee must be excused. A VFC-eligible child cannot be refused a vaccination due to the parent's or guardian's inability to pay for shot administration. There can be a fee for the office visit. There can be fees for non-vaccine services, like an eye exam or blood test."[85]

Through the VFC program, the CDC purchases discounted doses of vaccines from manufacturers and distributes directly to registered public and private health care providers.[85]

**Table 7. HPV Vaccine Coverage by Insurance Type**

| Insurance Type | Population Covered for HPV Vaccine | Coverage level |
|---|---|---|
| **Employer-sponsored and Private Insurance** | Covered as ACIP recommends | No cost-sharing (e.g. no co-pay, no co-insurance).<br>Providers may charge an administrative fee, which may be partially covered by the insurer. |
| **Medicaid** | 19-20 years, as ACIP recommends | No cost-sharing under Early Periodic Screening, Diagnosis, and Treatment (EPSDT) program.[86] |
| **Medicaid** | 21+, as ACIP recommends | Coverage depends on the state and whether or not they expanded Medicaid after ACA implementation.<br>In 2010, 9 states offered coverage with a co-pay and 28 offered coverage without a co-pay.[87]<br>Providers may charge an administrative fee, which may be partially covered by Medicaid – maximum varies by state (ranges from $19-$33).[88] |
| **Vaccines for Children (VFC)** | 9-18 years and<br>Medicaid-eligible<br>Uninsured<br>Underinsured<br>Native American or Alaska Native | No cost.<br>Those who are underinsured must receive immunizations through a Federally Qualified Health Center or Rural Health Clinic.<br>Providers may charge an administrative fee, which may be partially covered by Medicaid. |
| **State Children's Health Insurance Program (SCHIP)** | 9-18 years | No cost.<br>SCHIP programs that are separate from state Medicaid must cover ACIP vaccines because children enrolled are ineligible for VCF coverage. |
| **Section 317 of the Public Health Service Act (Immunization Grant Program)** | May include children not eligible for VFC or SCHIP or uninsured or underinsured adults (e.g. undocumented immigrant children) | Utilization of 317 funding varies by state.[89] |
| **Merck Vaccine Patient Assistance Program** | Adults 19-26 years old, not covered by any of the means above. | Gardasil® (HPV4) & Gardasil®9 (HPV9) at no cost http://www.merckhelps.com/VPAP/.[90] |
| **GSK Vaccines Access Program** | Adult women up to age 25, not covered by any of the means above. | Cervarix® (HPV2) at no cost http://www.gsk-vap.com/.[91] |

### *School Vaccination Requirements & Exemptions*

In the U.S., states have the authority and responsibility to regulate which vaccines, if any, are required for entry into public schools and daycare facilities. School vaccination requirements are typically

determined by the state legislature or a regulatory body such as the health department. Often, states follow CDC recommendations, but the requirements do differ by state.[92] If a state chooses to make a vaccine mandatory, it must consider and address financing issues such as coverage under Medicaid, SCHIP, VFC, coverage for children who may be uninsured, funding for public awareness and education campaigns, and historically, whether to require coverage by insurance providers.

The Immunization Action Coalition provides lists of required vaccinations by state. As of 2015, Virginia, Washington, D.C., and Rhode Island are the only three locations in the U.S. that have passed laws requiring the administration of the HPV vaccine for school entry, though the specifics differ. Virginia's law went into effect in October 2008 with the requirement being that girls entering 6th grade must have at least had the first dose of the 3-dose HPV series. Washington, D.C.'s law went into effect in January 2009 and also requires girls entering 6th grade to have started the series. Rhode Island's law will go into effect in August 2015 and requires girls and boys to have one dose by 7th grade, two doses by 8th grade and completed the series by 9th grade.[92] The CDC also has a detailed page with more information on state school vaccination laws and exemptions.

When thinking about school entry requirements, an additional policy to consider is the exemption process. As with other vaccines, parents are afforded the right to refuse to follow the requirement. Typically these exemptions are based on medical restrictions or religious beliefs, but increasingly parents are being allowed to opt out of vaccination requirements for philosophical reasons.[93] For example, Virginia's law states that upon reviewing educational materials from the Board of Health, the parent or guardian, may choose for the child not to receive the HPV vaccine.[94] Washington, D.C. parents wishing to opt out simply fill out a form available on the Department of Health website declaring that the parent or legal guardian has been informed of the HPV vaccination requirement and has elected not to participate.[95] Rhode Island's law only includes exemptions for religious or medical reasons.[96]

### *Parental and Minor Consent Laws*

Laws governing consent for delivery of health care services to minors also vary by state. As determined by various statutes and/or court decisions, parents or legal guardians are required to consent for most health care services provided to minors in every state.[97] It is generally understood that parental consent is required for each dose of a vaccine series; however, in every state a minor may consent for a vaccination on their own based on two types of exceptions.[97] The first exception allowing a minor to consent for health care services is based on status (e.g. emancipation, marriage, age and capacity, living apart from parents).[97] The second exception relates to the type of service (e.g. services for diagnosis and treatment of sexually transmitted and reportable diseases).[97] Again, varying by state, some laws not only allow minors to consent for diagnosis and treatment of STIs, but for prevention of STIs as well, and thus could include vaccinations for HPV.[97] NAO HPV Regional Coordinators will be conducting environmental scans of their geographic region to determine, in part, the HPV policy landscape.

## Conclusion

In conclusion, for nearly every challenge to HPV vaccine access, affordability, and acceptability, preventive strategies ranging from policies to educational interventions have been proposed and implemented. It has been proven effective for providers to engage in continuing education programs

that aim to increase knowledge, attitudes and beliefs regarding the HPV vaccine.[98] Similar educational programs targeting patients and their parents are equally impactful.[98] Furthermore, healthcare facilities adopting various procedural and operational methods, such as standing orders and immunization information systems (IIS), have also increased adolescent HPV vaccination rates.[98,99] In regards to IIS, recent studies found that managed care-based mail and telephone reminder/recall increased adolescent immunizations and preventive visits.[99,100] Both school entry requirements and health insurance reforms have also been proposed as strategies for increasing HPV vaccine coverage rates. Previous school entry immunization mandates have increased coverage rates among all children, decreased the incidence of infectious disease and reduced racial and ethnic disparities among school-age children.[50] **Finally, one of the most important interventions and key take home messages of this resource book is encouraging providers to decrease missed opportunities and deliver strong HPV recommendations.[58,59,69] The CDC recommends that physicians be trained to administer the HPV vaccine routinely with the other adolescent vaccines and to emphasize that the vaccine is normal, safe and has a more robust immune response in preteens.[7,57,64,68]**

**Figure 5. Social Ecological Model of Points of Potential HPV Vaccination Intervention**

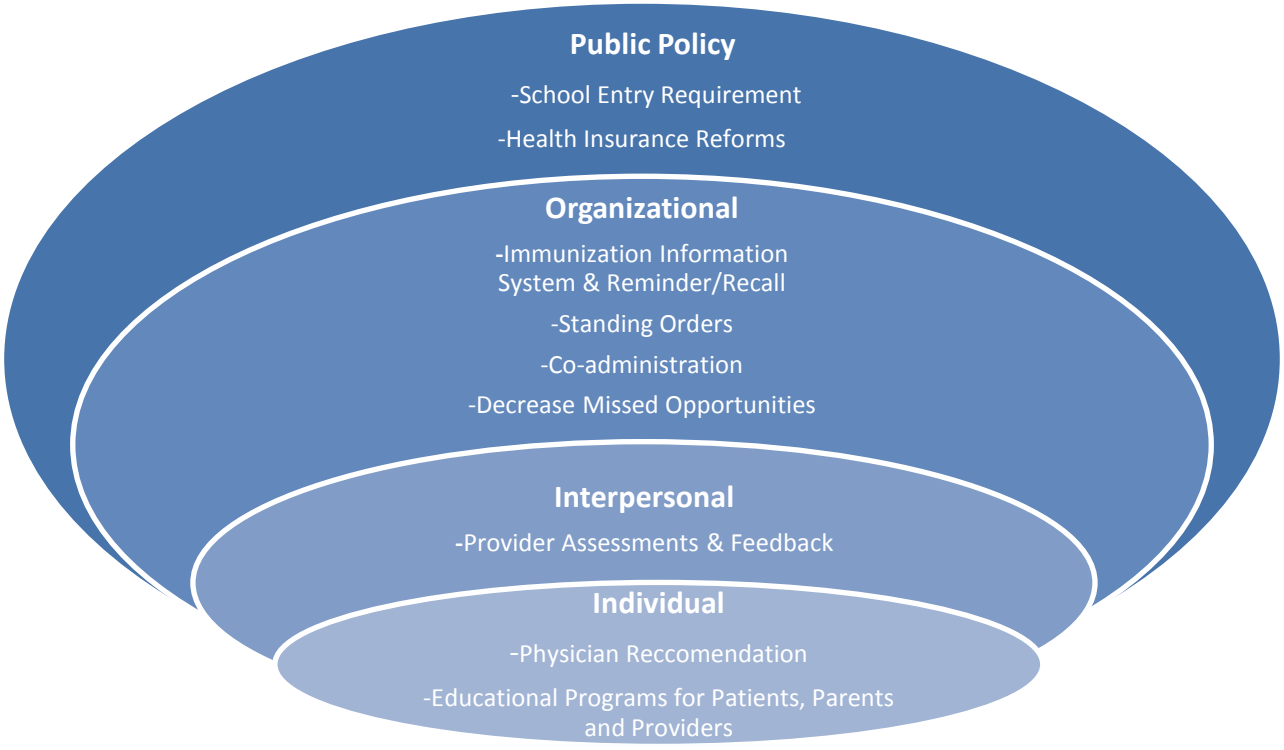



Figure 5 shows where each of these potential solutions falls in a social ecological model. It is important to consider the interrelationships among the various levels of impact when proposing prevention strategies.[101] Future intervention efforts should address both the population-level and individual-level determinants of vaccine uptake. Using an ecological approach to improve HPV vaccination rates will most likely be more effective and improve sustainability over time.[101]

## Opposition & Threats

Despite all of the evidence-based interventions and strategies, there is still a major barrier that stands in the way of HPV vaccinations. Opposition against vaccines dates as far back as 1869 and 1908 when the first anti-vaccination leagues were formed in the United Kingdom and the U.S., respectively.[102,103] The anti-vaccine movement was built on several claims including belief that vaccines cause illness, reduce immunity, that adverse events are underreported, and that policies are motivated by profit, among other claims.[104]Arguments against vaccination mandates include that they are an unacceptable infringement on personal liberty and violate the 1st and 14th Amendments to the U.S. Constitution, vaccines are inherently harmful, vaccine contradict religious beliefs, and vaccines are unnatural, among others.[103] Specifically regarding the HPV vaccine and potential school mandates, opponents have used similar arguments. Anti-vaccine activists believe the school requirement for HPV vaccine is a clear demonstration of inappropriate governmental intrusion of parental rights, is not sufficient for public health justification because HPV is not spread by casual contact, and promotes "sexual disinhibition" and thus it is inconsistent with family values and messages regarding abstinence.[50,92]

The efforts of the anti-vaccine movement have significantly threatened the effectiveness of the HPV and other vaccines. Over the past years, anti-vaccine advocacy has led to an increase in exemption policies, parental resistance, lower vaccination rates and delayed vaccination, effectively reducing herd immunity across the U.S.[105] Providers and parents may very well encounter webpages, social media, and popular press materials with anti-vaccine messaging. This carries serious implications for public health efforts to increase HPV vaccination rates. For further reading to help better understand the opposition, see the National Vaccine Information Center, Vaccination Liberation, and Natural News websites and read some of the many popular press articles on the subject over the last months and years. Also familiarize yourself with national and local groups that are potential allies such as Immunization Action Coalition, Every Child by Two and Voices for Vaccines.

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# Appendix I. Data Sources and Analysis Methodology

## Data Sources

U.S. prevalence estimates (36-Year Limited Duration Prevalence) were calculated from data extracted from the Incidence - SEER 9 Regs, Research Data, Nov 2013 Sub (1973-2011)<Katrina/Rita Population Adjustment>[11] and the Populations – Total U.S. (1969-2013) <Katrina/Rita adjustment>[13] databases in SEER*Stat (Table 2). The prevalence date was set to January 1, 2011 and the population was estimated based on the average of the U.S. population for years 2010 and 2011. SEER*Stat (version 8.1.5-March 31, 2014) and Projected Prevalence (ProjPrev) software (ProjPrev Version 1.0.4. April 2014; Data Modeling Branch, National Cancer Institute) were used to estimate the proportions.

U.S. incidence rates were estimated using the Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2013 Sub (2000-2011) <Katrina/Rita Population Adjustment>.[12] Rates are per 100,000 and age-adjusted to the 2000 US Standard Population (19 age groups - Census P25-1130). While SEER*Stat provides US age-adjusted rates, counts are limited to only cases in the registry (Table 2). Estimated incidence counts were calculated by multiplying the incidence rates by the average of the 2010 and 2011 US population per 100,000.

U.S. mortality rates were estimated using the Mortality - All COD, Aggregated With State, Total U.S. (1969-2011) <Katrina/Rita Population Adjustment> database and SEER*Stat (Table 3).[17] The 5-year survival percentages were estimated using the Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2013 Sub (1973-2011 varying) database and SEER*Stat.[16]

## Inclusion Criteria

Several criteria have been established to determine the burden of HPV-*associated* cancers.[10] The ICD-O-3 site codes, ICD-O-3 Histology Codes, and Diagnostic Verification in Table 8 below were identified and used to determine the percentage of HPV-*attributable* cancers in Tables 1 & 2 in the background section of this document.[10] These parameters were used to calculate HPV-*attributable* prevalence, incidence rates, and incidence trends (Figures 2-4). Although the Oropharynx is generally the cancer site stated in the literature, the base of the tongue and tonsils are also included in the ICD-O-3 Site Codes for inclusion in HPV-*attributable* cancer analyses. The ICD-O-3 recode groups that include the additional oral cavity site codes are the Tongue and Other Oral Cavity & Pharynx.

The parameters used for survival and mortality rates were limited to the ICD-O-3 site recode groups for ease of interpretation by the intended audience. Therefore, the survival percentages and mortality rates include all cancers for each recode site and not just the proportion attributed to HPV (Table 3).

**Table 8 – Inclusion Criteria[10]**

| ICD-O-3 Recode Site | ICD-O-3 Site Code | ICD-O-3 Histology Code | Diagnostic Verification |
|---|---|---|---|
| Oropharynx - including<br>Tongue<br>Other Oral cavity & Pharynx | C01.9, C02.4, C02.8, C09.0, C09.1, C09.8, C09.9, C10.2, C10.8, C10.9, C14.0, C14.8 | 8050-8084, 8120-8131 | Microscopically confirmed |
| Anus, Anal Canal, and Anorectum | C20.9, C21.0, C21.1, C21.2, C21.8 | 8050-8084, 8120-8131 | Microscopically confirmed |
| Penis | C60.0, C60.1, C60.2, C60.8, C60.9 | 8050-8084, 8120-8131 | Microscopically confirmed |
| Cervix Uteri | C53.0, C53.1, C53.8, C53.9 | 8010-8671, 8940-8941 | Microscopically confirmed |
| Vagina | C52.9 | 8050-8084, 8120-8131 | Microscopically confirmed |
| Vulva | C51.0, C51.1, C51.2, C51.8, C51.9 | | Microscopically confirmed |