

Warts and All: HPV Vaccine Uptake

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Nursing)
in The University of Michigan
2011

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Chapter One

Introduction

The human papillomavirus (HPV) is the established cause of virtually all cervical cancers (Bosch, Lorincz, Munoz, Meijer, & Shah, 2002) and costs the United States health system five billion dollars a year in direct medical costs (Insinga, Dasbach, & Elbasha, 2005). In June 2006, the United States Food and Drug Administration (FDA) approved Gardasil® as the first vaccine available in the United States to help protect nine to 26 year old females from the significant health consequences of HPV (United States Food and Drug Administration, 2006). The vaccine was later approved in 2009 for males of the same age (United States Food and Drug Administration, 2009b). The vaccine protects against HPV-16 and HPV-18, which cause 70% of all cases of cervical cancer (Muñoz et al., 2003), and HPV-6 and HPV-11, which cause 90% of all cases of genital warts (Brown, Schroeder, Bryan, & Stoler, 1999; Greer et al., 1995; Lacey, Lowndes, & Shah, 2006). An additional vaccine, Cervarix®, was approved for 10 to 26 year old females in October 2009 and protects against HPV-16 and HPV-18 (United States Food and Drug Administration, 2009a).

Shortly after the FDA approved Gardasil® in 2006, the Center for Disease Control and Prevention Advisory Committee on Immunization Practices, or ACIP, voted to recommend the vaccine for all females starting at age 11 to 12 years old, with “catch-

up” vaccination for all females 13 to 26 years old (Centers for Disease Control and Prevention, 2007). The ACIP extended the same recommendation to Cervarix® (Centers for Disease Control and Prevention, 2010c) giving patients the option of routine HPV vaccination with either Cervarix® or Gardasil®. The ACIP has not extended routine recommendation of HPV vaccination to males (Centers for Disease Control and Prevention, 2010d).

Many professional organizations followed the lead of the ACIP in their own recommendations, including the American Medical Association, the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, the American Academy of Family Physicians, the Association of Women’s Health, Obstetric and Neonatal Nursing, the Society for Adolescent Medicine, the American College Health Association, as well as the American Cancer Society, supporting routine HPV vaccination for females. Despite widespread support for the vaccine and high acceptability (55-100%) among adolescents, young adults, and parents of adolescents for HPV vaccination (Brewer & Fazekas, 2007), by the end of 2010, only 49% of females ages 13 to 17 had initiated the series and only 32% had received the full three doses required for full immunization (Centers for Disease Control and Prevention, 2011). Even fewer young adult females ages 19 to 26 years old have started the series, with national estimates at 17% (Centers for Disease Control and Prevention, 2010a).

To improve vaccination, opportunities for vaccine administration outside of traditional primary care offices should be considered (Schaffer et al., 2008). Reproductive health organizations such as Planned Parenthood often face unique challenges in their attempts to implement vaccination services, aiming to protect

populations at high risk for HPV, but struggling with the limited financial resources needed to carry out interventions that could improve vaccine uptake for their mostly uninsured patients. Because of the significant influence of cost on HPV vaccine uptake, it may be necessary to identify areas to target resources that would improve vaccine uptake at the clinic encounter level. In this introduction, I will provide background on HPV and the HPV vaccine, as well as present a conceptual framework intended to help understand the complexity of influences involved in vaccinating individuals.

Background

Health Relevance of HPV

HPV infects more than six million people in the United States every year (National Cancer Institute, 2007). The high prevalence of HPV makes it the most common sexually transmitted infection in the world. In the United States, 25% of 14 to 19 year old females, 45% of 20 to 24 year old females, and 27% of 25 to 29 year old females are infected with HPV (Dunne et al., 2007). Despite its widespread prevalence, most individuals never realize they carry the virus. It is often asymptomatic and in most individuals with an intact immune system, the immune response activated by the virus is enough to render it undetectable and without clinical manifestations of disease (Stanley, 2006). However, the virus persists in some individuals for unknown reasons and about 10% of women experience its more serious health consequences, such as cervical cancer (Franco et al., 1999; Ho, Bierman, Beardsley, Chang, & Burk, 1998; Molano et al., 2003; Moscicki et al., 1998; Richardson et al., 2003).

More than 100 strains of HPV have been identified (Bernard et al., 2010). Of those, 15 to 18 are considered “high-risk” strains causing cancer, 12 are considered “low-

risk” strains causing genital warts, and the remaining strains have no identified health implications (Muñoz et al., 2003). HPV is the necessary cause of virtually all cervical cancers (Bosch et al., 2002). In addition, emerging data suggest that HPV is partially responsible for several other types of cancers, including vulvar and vaginal cancers in females, penile cancers in males, and anal, head and neck cancers in males and females (Centers for Disease Control and Prevention, 2009). HPV also causes genital warts in males and females and rarely, recurrent respiratory papillomatosis (Centers for Disease Control and Prevention, 2009). Females are disproportionately affected by HPV, as it causes more female specific cancers (cervix, vulva, vagina) than male specific cancers (penile). Females in the United States experienced an estimated 3,900 vulvar cancers and 2,300 vaginal cancers in 2010 (Jemal, Siegel, Xu, & Ward, 2010). Despite the widespread availability of cervical cancer screening using the Papanicolaou test, which detects precancerous cervical lesions caused by HPV and can result in early treatment and prevention of cervical cancer, an estimated 12,200 females developed cervical cancer in 2010, and 4,210 females died from it (Jemal et al., 2010). This figure is more than ten times the estimated number of deaths (350) from testicular cancer in 2010 (Jemal et al., 2010).

A total of 5.6% of 18 to 59 year olds have experienced an outbreak of genital warts (Dinh, Sternberg, Dunne & Markowitz, 2008). While genital warts do not have the potential to result in death the way cancer does, the visible genital lesions are difficult to treat, often requiring multiple treatment visits and costing an average of \$291.36 per outbreak (Fine et al., 2007). Without treatment, the warts can last for years, increasing the risk of transmission to others as well as potentially contributing to prolonged time

periods of emotional suffering. The psychological distress from the shame and stigma of genital warts can lead to a decreased quality of life for many individuals (Ireland, Reid, Powell, & Petrie, 2005; Jeynes, Chung, & Challenor, 2009; Mortensen & Larsen, 2010; Woodhall et al., 2008)

The health consequences of HPV are costly. The United States spends an estimated five billion dollars in direct medical costs annually on the prevention and treatment of HPV related disease, not including vaccination (Insinga et al., 2005).

Widespread use of the HPV vaccine specifically is generally considered cost-effective at the population level if greater than 80% of females are vaccinated, according to a review of 12 cost-effectiveness modeling studies (Brisson, Van de Velde, & Boily, 2009). With lower population levels of vaccination, the benefit of herd immunity diminishes, leaving the benefits of individual immunity only.

Vaccine Background

The first HPV vaccine developed, Gardasil®, is manufactured using recombinant DNA technology. The vaccine is formulated by extracting a piece of the L1 structural protein of HPV -6, -11, -16 and -18 to function as the antigen, which stimulates the production of antibodies by the host, and combining it with amorphous aluminum hydroxyphosphate sulfate as the adjuvant to boost the immune response. The first dose provides immune protection greater than natural HPV infection, and the second and third doses help sustain the immune response over time (Villa et al., 2005). At the time of FDA approval of Gardasil® in 2006, clinical trials demonstrated efficacy extending through five years post-vaccination (Villa et al., 2006). Studies are ongoing to determine how long the protection will last beyond five years. In 2006, the ACIP recommended

(Centers for Disease Control and Prevention, 2007) and continues to recommend (Centers for Disease Control and Prevention, 2010c), initiation of the vaccine in 11 to 12 year olds, an age young enough to increase the likelihood that the recipient is not yet sexually active and therefore HPV-naïve when the vaccine is most effective, but an age old enough to increase the likelihood that immunity will persist after the onset of sexual activity, when the recipient is most at risk. The ACIP also recommends “catch-up” vaccination for all females through age 26 who did not receive the vaccine at age 11 to 12 (Centers for Disease Control and Prevention, 2010c). “Catch-up” vaccination was recommended because the vaccine was still found to be effective among individuals with previous exposure to HPV, as most (74%) of females were infected with only one HPV strain included in the vaccine, thereby remaining susceptible to protection from other strains of HPV included in the vaccine (Centers for Disease Control and Prevention, 2007).

According to the CDC Vaccine Price List, Gardasil® costs \$130 per dose, plus vaccine administration costs, making it the most expensive vaccine of all routinely recommended pediatric and adult vaccines (Centers for Disease Control and Prevention, 2010b).

The evidence supporting Gardasil’s® safety profile is well documented through FDA pre-licensure clinical trials and post-licensure safety surveillance. Because there are no live viruses used in the production of Gardasil®, it is not possible for the vaccine to cause infection in recipients. According to the prescribing information (<http://www.gardasil.com>), possible side effects include syncope, headache, fever, nausea, dizziness, injection-site pain, swelling, erythema, pruritis and bruising. Post-

licensure safety surveillance through the Vaccine Adverse Event Reporting System (VAERS) continues to monitor adverse events following immunization (AEFIs) in the general public and has found most of Gardasil's® reports of adverse events to be no greater than other vaccines (Slade et al., 2009). With 23 million doses dispensed, VAERS did find an increase in reports of syncope (8.2 per 100,000), however it was later concluded that this effect was not specific to Gardasil®, but rather a common occurrence when vaccinating adolescents. There are reports of venous thromboembolic events (e.g. deep vein thrombosis) (0.2 per 100,000 doses) in individuals receiving Gardasil®, although 90% of the 31 recipients with venous thromboembolic events had other known risk factors (Slade et al., 2009). Of the 32 deaths reported, only four were unexplained by other causes (Slade et al., 2009).

In October 2009, the FDA approved a second HPV vaccine, Cervarix®, which provides cervical cancer protection from HPV-16 and HPV-18 in females 10 to 25 years old (United States Food and Drug Administration, 2009a). Cervarix® is similarly priced at \$128 (Centers for Disease Control and Prevention, 2010b) and similarly effective, although does not provide the additional protection against genital warts that Gardasil® provides. Also in October 2009, the FDA approved Gardasil® for use in males (United States Food and Drug Administration, 2009b), although the ACIP issued a permissive use recommendation (stating that Gardasil® may be given to males) but not recommending routine vaccination (in which all males would be vaccinated) at that time due to cost-effectiveness concerns (Centers for Disease Control and Prevention, 2010d). The difference in ACIP recommendations between males and females may have financial ramifications for individuals, as many insurance companies only provide cost coverage

for vaccines recommended by the ACIP. Due to its earlier approval and availability, a majority of the research on HPV vaccine uptake in the United States at this time is limited to Gardasil® use in females, although the uptake of Cervarix® in females and Gardasil® in males will likely expand in the coming years.

HPV Vaccine Uptake

The 2010 National Immunization Survey-Teen provides a recent measurement of adolescent HPV vaccine uptake in the United States (Centers for Disease Control and Prevention, 2011). In 2010, an average of 49% of adolescent females ages 13 to 17 years old had started the series and only 32% had completed it, an increase of 5% from 2009. Rhode Island boasts the highest vaccination rate in the country where 73% of adolescent females have begun the series, in sharp contrast to Idaho where only 29% of adolescent females have started the series. In Michigan, the rates fall at the national average, where 49% of adolescent females have received the first dose and 25% have completed the series.

The 2009 National Health Interview Survey found that HPV vaccine initiation for 18 to 26 year old females is significantly lower, at 17% (Centers for Disease Control and Prevention, 2010a). This survey, as well as most other studies, focus on series initiation rather than series completion, due to the logistical burdens of longitudinal research.

National Priorities

Healthy People 2020 (<http://www.healthypeople.gov>) continues to identify HPV reduction as a national priority. In the objectives, Healthy People 2020 includes the goal to, “Reduce the proportion of females with human papillomavirus (HPV) infection.” To achieve the goal, it targets vaccinating 80% of adolescent females against HPV.

Conceptual Framework: Ecological Model of HPV Vaccine Uptake

The research literature provides support for using an ecological model as a conceptual framework for understanding and researching HPV vaccine uptake. First described by psychologist Urie Bronfenbrenner in 1979 and modified over the past 30 years for use in many other disciplines and various populations, the ecological model recognizes that there are many levels of influence on an individual's behavior (Bronfenbrenner, 1979). Bronfenbrenner described his model as one of concentric circles, each circle, or level, influencing the circles, or levels, within. The individual exists at the center of the circles. Individual behavior is conceptualized as being influenced by the circles surrounding him or her. One can easily adapt Bronfenbrenner's model to the various levels of influence on HPV vaccine uptake, as described below (see Figure 1.1). This dissertation uses the ecological framework to critically examine factors affecting HPV vaccine uptake at different levels.

Public Policy

As described in Chapter Two, public policy at both the federal and state levels, including federal funding and school immunization requirements, influence an individual's vaccination status. At the federal level, researchers in Australia were able to measure both the individual and population level effects after the country rapidly achieved 70% vaccination coverage in females in 2007 resulting from a national HPV vaccination policy (R. Lester and G. Whiteside, personal communication in Fairley et al., 2009). After years of increasing incidence of genital warts, the proportion of females with genital warts declined by 25% each quarter in 2008, and even unvaccinated, heterosexual males experienced a 5% reduction in genital warts during the same time

period, consistent with the concept that herd immunity in populations with large numbers of individuals vaccinated will provide secondary protection to unvaccinated individuals (Fairley et al., 2009).

Similar results could be found in the United States. Historically in the United States, national campaigns with financial commitments and school requirements at the state level have demonstrated effectiveness in reaching high vaccination rates against other infections, such as hepatitis B (Averhoff et al., 2004; Jacobs & Meyerhoff, 2004; Orenstein & Hinman, 1999; Wilson, Fishbein, Ellis, & Edlavitch, 2005). In the case of HPV vaccination, despite a national recommendation by the ACIP for routine female vaccination and federal vaccine funding for underserved individuals, no states, except Virginia and Washington, DC, have enacted legislation to include HPV vaccination in their school entry requirements (see Chapter Two for further discussion on this topic). Absent widespread state mandated school entry requirements, the responsibility for vaccinating individuals has been passed to health care organizations.

Health Care Organization

As discussed in Chapter Three, there are many specific influences in health care organizations that can present as barriers or facilitators for individual vaccination. These influences can range from insurance coverage to cost charged by the organization to the patient, to provider recommendation, as well as educational information provided by the health care organization regarding HPV risk or vaccine safety concerns. Every individual is unique, often making it difficult for researchers to study the multi-level complex interactions that determine vaccine uptake, but understanding the broader system of

influences in HPV vaccine uptake should illuminate the search for solutions to determine which interventions would have the greatest impact.

Statement of Overall Problem Addressed in the Research

The health and economic consequences of HPV are severe and prevention through HPV vaccination can significantly reduce them. However, uptake of this potentially lifesaving vaccine remains low. Examining influences at the public policy level (Chapter Two) and the health care organization level (Chapter Three) supports at this time exploration into possible vaccine interventions for health care organizations. In organizations with high-risk patients but limited financial resources, targeting vaccination (Chapter Four) to reduce cost may be one possibility to improve uptake.

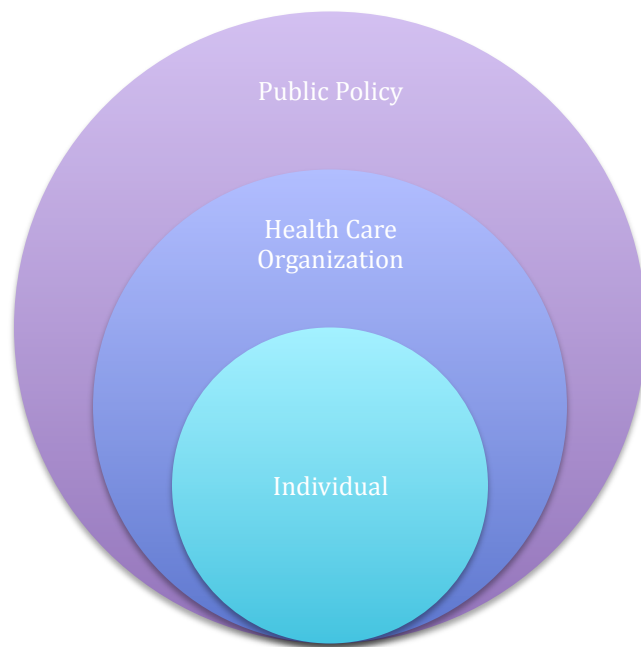


Figure 1.1. Ecological model of HPV vaccine uptake.

References

- Averhoff, F., Linton, L., Peddecord, K. M., Edwards, C., Wang, W., & Fishbein, D. (2004). A middle school immunization law rapidly and substantially increases immunization coverage among adolescents. *American Journal of Public Health, 94*(6), 978-984.
- Bernard, H. U., Burk, R. D., Chen, Z., van Doorslaerck, K., Hausen, K., & de Villiers, E. M. (2010). Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. *Virology, 401*(1), 70-79.
- Bosch, F., X., Lorincz, A., Muñoz, M., Meijer, C., J., Shah, K. V. (2002). The causal relation between human papillomavirus and cervical cancer. *Journal of Clinical Pathology, 55*(4), 244-65.
- Brewer, N. T., & Fazekas, K. I. (2007). Predictors of HPV vaccine acceptability: A theory-informed, systematic review. *Preventive Medicine, 45*, 107-114.
doi:10.1016/j.ypmed.2007.05.013
- Brisson, M., Van de Velde, N., & Boily, M. C. (2009). Economic evaluation of human papillomavirus vaccination in developed countries. *Public Health Genomics, 12*(5-6), 343-351. doi:10.1159/000214924
- Bronfenbrenner, U. (1979). *The ecology of human development: Experiments by nature and design*. Cambridge, MA: Harvard University Press.
- Brown, D. R., Schroeder, J. M., Bryan, J. T., & Stoler, M. H. (1999). Detection of multiple human papillomavirus types in condyloma acuminata lesions from otherwise healthy and immunosuppressed patients. *Journal of Clinical Microbiology, 37*(10), 3316-3322.

- Centers for Disease Control and Prevention. (2007). Quadrivalent human papillomavirus vaccine; Recommendations of the advisory committee on immunization practices (ACIP). *Morbidity and Mortality Weekly Report*, 56ER(March 12, 2007), 1-24.
- Centers for Disease Control and Prevention. (2009). Genital HPV infection: CDC fact sheet. Retrieved from <http://www.cdc.gov/std/HPV/STDFact-HPV.htm>
- Centers for Disease Control and Prevention. (2010a). Adult vaccination coverage reported via NHIS. Retrieved from www.cdc.gov/vaccines/stats-surv/nhis/default.htm
- Centers for Disease Control and Prevention. (2010b). CDC vaccine price list. Retrieved from www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm
- Centers for Disease Control and Prevention. (2010c). FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report*, 59(20), 626-629.
- Centers for Disease Control and Prevention. (2010d). FDA licensure of quadrivalent human papillomavirus vaccine (HPV4, Gardasil) for use in males and guidance from the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report*, 59(20), 630-632.
- Centers for Disease Control and Prevention. (2011). National and state vaccination coverage among adolescents aged 13 through 17 years-United States, 2010. *Morbidity and Mortality Weekly Report*, 60(33), 1117-1123.
- Dinh, T. H., Sternberg, M., Dunne, E. F., & Markowitz, L. E. (2008). Genital warts among 18- to 59- year- olds in the United States, national health and nutrition

examination survey, 1999-2004. *Sexually Transmitted Diseases*, 35(4), 357-360.
doi:10.1097/OLQ0b013e3181632d61

Dunne, E. F., Unger, E. R., Sternberg, M., McQuillan, G., Swan, D. C., Patel, S. S., & Markowitz, L. E. (2007). Prevalence of HPV infection among females in the United States. *The Journal of the American Medical Association*, 297(8), 813-819. doi:10.1001/jama.297.8.813

Fairley, C. K., Hocking, J. S., Gurrin, L. C., Chen, M. Y., Donovan, B., & Bradshaw, C. S. (2009). Rapid decline in presentations of genital warts after the implementation of a national quadrivalent human papillomavirus vaccination programme for young women. *Sexually Transmitted Infections*, 85(7), 499-502.
doi:10.1136/sti.2009.037788

Fine, P., Ball, C., Pelta, M., McIntyre, C., Momtaz, M., Morfesis, J.,...Rash, R. M. (2007). Treatment of external genital warts at Planned Parenthood Federation of America centers. *The Journal of Reproductive Medicine*, 52(12), 1090-1096.

Franco, E. L., Villa, L. L., Sobrinho, J.P., Prado, J.M., Rousseau, M.C., Desy, M., & Rohan, T. E. (1999). Epidemiology of acquisition and clearance of cervical human papillomavirus infection in women from a high-risk area for cervical cancer. *Journal of Infectious Diseases*, 180(5), 1415-1423.

Greer, C. E., Wheeler, C. M., Ladner, M. B., Beutner, K., Coyne, M. Y., Liang, H.,...Ralston, R. (1995). Human Papillomavirus (HPV) type distribution and serological response to HPV type 6 virus-like particles in patients with genital warts. *Journal of Clinical Microbiology*, 33(8), 2058-63.

- Ho, G. Y., Bierman, R., Beardsley, L., Chang, C. J., & Burk, R. D. (1998). Natural history of cervicovaginal papillomavirus infection in young women. *New England Journal of Medicine*, *338*(7), 423-428.
- Insinga, R. P., Dasbach, E. J., & Elbasha, E. H. (2005). Assessing the annual economic burden of preventing and treating anogenital human papillomavirus-related disease in the US: Analytic framework and review of the literature. *Pharmacoeconomics*, *23*(11), 1107-1122.
- Ireland, J. A., Reid, M., Powell, R., & Petrie, K. J. (2005). The role of illness perceptions: psychological distress and treatment-seeking delay in patients with genital warts. *International Journal of STD & AIDS*, *16*, 667-670.
- Jacobs, R. J., & Meyerhoff, A. S. (2004). Effect of middle school entry requirements on hepatitis B vaccination coverage. *Journal of Adolescent Health*, *34*(5), 420-423. doi:10.1016/j.jadohealth.2003.08.014
- Jemal, A., Siegel, R., Xu, J., & Ward, E. (2010). Cancer statistics, 2010. *CA: A Cancer Journal for Clinicians*, *60*(5), 1-24. doi:10.1002/caac.20073
- Jeynes, C., Chung, M. C., & Challenor, R. (2009). 'Shame on you' - the psychosocial impact of genital warts. *International Journal of STD & AIDS*, *20*, 557-560. doi:10.1258/ijsa.2008.008412
- Lacey, C. J. N., Lowndes, C. M., & Shah, K. V. (2006). Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. *Vaccine*, *24*, S35-S41.
- Molano, M., Van den Brule, A., Plummer, M., Weiderpass, E., Posso, H., Arslan, A.,...Franceschi, S. (2003). Determinants of clearance of human papillomavirus infections in Colombian women with normal cytology: A population-based, 5-

- year follow-up study. *American Journal of Epidemiology*, 158(5), 486-494.
- Mortensen, G. L., & Larsen, H. K. (2010). The quality of life of patients with genital warts: A qualitative study. *BMC Public Health*, 10, 113-120. doi:10.1186/1471-2458-10-113
- Moscicki, A. B., Shiboski, S., Broering, J., Powell, K., Clayton, L., Jay, N.,... & Palefsky, J. (1998). The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. *The Journal of Pediatrics*, 132(2), 277-284.
- Muñoz, N., Bosch, F. X., de Sanjosé, S., Herrero, R., Castellsangüé, X., Shah, K. V.,... Meijer, C. J. L. M. (2003). Epidemiologic classification of human papillomavirus types associated with cervical cancer. *New England Journal of Medicine*, 438(6), 518-27.
- National Cancer Institute. (2007). Human papillomavirus (HPV) vaccines: Questions and answers. Retrieved from <http://www.cancer.gov/cancertopics/factsheet/risk/HPV-vaccine>
- Orenstein, W. A., & Hinman, A. R. (1999). The immunization system in the United States - the role of school immunization laws. *Vaccine*, 17(Suppl 3), S19-24.
- Richardson, H., Kelsall, G., Tellier, P., Voyer, H., Abrahamowicz, M., Ferenczy, A.,...Franco, E. L. (2003). The natural history of type-specific human papillomavirus infections in female university students. *Cancer Epidemiology, Biomarkers and Prevention*, 12(6), 485-490.
- Schaffer, S. J., Fontanesi, J., Rickert, D., Grabenstein, J. D., Rothholz, M. C., Wang, S. A., & Fishbein, D. (2008). How effectively can health care settings beyond he

traditional medical home provide vaccines to adolescents? *Pediatrics*, 121, Supplement 1, S35-S45.

Slade, B. A., Leidel, L., Vellozzi, C., Woo, E. J., Hua, W., Sutherland, A.,...Iskander, J. (2009). Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *The Journal of the American Medical Association*, 302(7), 750-757. doi:10.1001/jama.2009.1201

Stanley, M. (2006). Immune responses to human papillomavirus. *Vaccine*, 24(1), S16-S22.

United States Food and Drug Administration. (2006). June 8, 2006 approval letter – human papillomavirus quadrivalent (Types 6, 11, 16, 18) vaccine, recombinant. Retrieved from <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm11283.htm>

United States Food and Drug Administration. (2009a). October 16, 2009 approval letter- Cervarix. Retrieved from <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm186959.htm>

United States Food and Drug Administration. (2009b). October 16, 2009 approval letter- Gardasil. Retrieved from <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm186991.htm>

Villa, L. L., Costa, R. L. R., Petta, C. A., Andrade, R. P., Ault, K. A., Giuliano, A. R.,...Barr, E. (2005). Prophylactic quadrivalent human papillomavirus (types 6,

11, 16, and 18) L1 virus-like particle vaccine in young women: A randomized double-blind placebo-controlled multicentre phase II efficacy trial. *The Lancet Oncology*, 6, 271-278. doi:10.1016/S1470-2045(05)70101-7

Villa, L. L., Costa, R. L., Petta, C. A, Andrade, R. P., Paavonen, J., Iversen, O. E.,...Barr, E. (2006). High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow up. *British Journal of Cancer*, 95(11), 1459-1466.

Wilson, T. R., Fishbein, D. B., Ellis, P. A., & Edlavitch, S. A. (2005). The impact of a school entry law on adolescent immunization rates. *Journal of Adolescent Health*, 37(2005), 511-516.

Woodhall, S., Ramsey, T., Cai, C., Crouch, S., Jit, M., Birks, Y.,...Lacey, C. J. N. (2008). Estimation of the impact of genital warts on health-related quality of life. *Sexually Transmitted Infections*, 84, 161-166. doi:10.1136/sti.2007.029512.

Chapter Two

How Gardasil's® Policy History Influences A Patient's Vaccination Status

HPV causes a variety of serious health problems, including cervical, vulvar, vaginal, anal, penile, and head and neck cancers, as well as genital warts, and recurrent respiratory papillomatosis (Centers for Disease Control and Prevention, 2009c). Passed through sexual contact, HPV infects 45% of all 20 to 24 year old females (Dunne et al., 2007) and an estimated 80% of all individuals will contract HPV in their lifetime (Myers, McCrory, Nanda, Bastian, & Matchar, 2000). In June 2006, the United States Food and Drug Administration (FDA) approved Gardasil®, the first vaccine to help protect against cervical cancer and genital warts caused by HPV (United States Food and Drug Administration, 2006). However, in the United States only 49% of adolescent females ages 13 to 17 years old have started the recommended three dose series and only 32% have completed the series (Centers for Disease Control and Prevention, 2011).

This chapter will provide an illustrative exploration into Gardasil's® policy history at the federal, state, and health care organization level. Policy history at the federal level includes the FDA approval of Gardasil®, the Advisory Committee on Immunization Practices' (ACIP) HPV vaccine recommendation, and the Vaccines for Children (VFC) funding of the HPV vaccine. Because federal public policy defers to states for implementation and management of vaccine programs, this chapter will next

describe state attempts at legislating vaccination policies to include Gardasil® in school entry requirements, using the examples of the unsuccessful attempt in Texas and the successful legislation in Virginia and Washington, DC. Because most states have not passed legislation to include HPV vaccines in school entry requirements, health care organizations have been left to improve vaccination rates of individual patients. Therefore, the chapter next presents an example of one organization's struggle to vaccinate its patients to illuminate the influence of the federal and state policies on health care organizations and ultimately, individuals. Finally, this paper will look toward the future at the potential influence of the Affordable Care Act on HPV vaccine uptake.

Federal Policy: Approval, Recommendation, and Funding

Approval: FDA

In June 2006 after an expedited review of data presented by Merck & Co. of clinical trials involving 29,000 participants, the FDA approved Gardasil® for the prevention of cervical cancer and genital warts in females ages nine to 26 years old (United States Food and Drug Administration, 2006). With the emergence of new data, the FDA expanded the indication of Gardasil® in September 2008 to include the prevention of vulvar and vaginal cancers (United States Food and Drug Administration, 2008) and in October 2009, the FDA approved Gardasil® for the prevention of genital warts in males ages nine to 26 years old (United States Food and Drug Administration, 2009b).

Gardasil® protects against four of the most common strains of HPV, which cause 90% of all cases of genital warts (Brown, Schroeder, Bryan, & Stoler, 1999; Greer et al., 1995; Lacey, Lowndes, & Shah, 2006) and 70% of all cases of cervical cancer (Muñoz et

al., 2003). Gardasil® requires three shots given over six months at a cost of \$360 per person, not including vaccine administration fees (Centers for Disease Control and Prevention, 2009b). By May 2010, Merck & Co. had distributed 29.5 million doses of Gardasil® in the United States, making Gardasil® a highly profitable product in addition to a highly effective vaccine (Centers for Disease Control and Prevention, 2010).

Until recently, Gardasil® was the only HPV vaccine available in the United States. A second HPV vaccine, Cervarix®, was approved by the FDA in October 2009 for use in females ages 10 to 25 (United States Food and Drug Administration, 2009a). Cervarix® protects against the two common strains of HPV causing cervical cancer, and has been approved for the prevention of cervical cancer. Because of its recent availability and limited market share, Cervarix® has not yet substantially influenced HPV vaccination policy in the United States as it has in other countries, such as the United Kingdom.

Recommendation: Advisory Committee on Immunization Practices

Once the FDA approves a vaccine based on safety and efficacy, the Advisory Committee on Immunization Practices (ACIP) is charged with the task of establishing vaccine recommendations. Consisting of 15 immunization experts appointed by the Secretary of the U.S. Department of Health and Human Services, the overall goal of the ACIP is to “provide advice that will lead to a reduction in the incidence of vaccine preventable diseases in the United States, and an increase in the safe use of vaccines and related biological products” (Centers for Disease Control and Prevention, 2009a). The group meets three times each year to evaluate available evidence and update immunization recommendations.

At the ACIP meeting in Atlanta in June 2006, the group finalized their recommendation for Gardasil®, which had been approved by the FDA earlier in the month. The committee evaluated extensive clinical trial safety and efficacy data, plans for post marketing surveillance, and studies modeling cost-effectiveness. After a public comment session at which not a single individual or group offered opposition, the group voted 13 to 0 (with two abstentions due to conflicts of interest) in favor of routine recommendation for all females ages nine to 26 years old (Advisory Committee on Immunization Practices, 2006). A few years later, in October 2009, it voted 12 to one in favor of a permissive recommendation for Gardasil® for males, stating that the “Quadrivalent HPV vaccine may be given to males...to reduce their likelihood of acquiring genital warts” (Advisory Committee on Immunization Practices, 2009, p. 53). The ACIP was unable to support for males the routine recommendation it provided to females due to cost-effectiveness concerns.

While the ACIP recommendations emerged as straightforward and scientifically supported, the ACIP could not escape the appearance of a possible conservative Christian influence not found in other vaccines. Interesting to note in the ACIP group was the inclusion of Reginald Finger, MD who concluded his term as a member of the ACIP at the meeting in which the ACIP established the recommendation for Gardasil®. Dr. Finger’s appointment to the ACIP by the Bush administration concerned many HPV vaccine supporters who feared his work as a medical issues analyst for the conservative Christian organization Focus on the Family, would compel him to put faith ahead of scientific objectivity. In fact, his own website acknowledges that “In everything I do, I seek to put Jesus Christ and His kingdom first” (Finger, 2011a). Dr. Finger’s

appointment was seen as part of a larger political strategy to support a conservative Christian agenda. According to James A. Monroe, Jr., a political science professor at Brown University, “What the Bush administration has done has taken this coterie of people and put them into very influential positions in Washington. And it’s having an effect in debates like this” (Stein, 2005).

Dr. Finger did give vaccine supporters reason to be concerned. He told *The Washington Post*, “There are people who sense that it [Gardasil®] could cause people to feel like sexual behaviors are safer if they are vaccinated and may lead to more sexual behavior because they feel safe” (Stein, 2005), raising concerns in the minds of the public about adolescent female sexual disinhibition. The comments may have been taken out of context, as he made the comments fully realizing and subsequently acknowledging that the concerns were unfounded.

I and others pointed out on several occasions that the issue of "disinhibition" - the impact on sexual behavior that can result when a sexually transmitted disease becomes preventable or more easily treatable - should be considered and thought through with regard to HPV. Experts at CDC have studied the issue and have concluded that disinhibition is not a significant factor with HPV and should not be a reason to avoid the vaccine. *I have consistently agreed with this conclusion* (Finger, 2011b).

Focus on the Family and other conservative Christian organizations, initially uncomfortable with the idea of a vaccine protecting against a sexually transmitted infection that can only be acquired outside of their abstinence doctrine, also quickly recognized the importance of supporting a vaccine that prevents cancer for the sake of public relations (Gold, 2007). However, the groups continued to provide conflicting messages in which they implied that HPV was a punishment for ignoring their abstinence only message despite their support for the vaccine. Focus on the Family’s Linda

Klepacki was quoted in a *New York Times* article stating, “You can’t catch the virus. You have to go out and get it with sexual behavior. We can prevent it by having the best public health method, and that’s not having sex before marriage” (Harris, 2006).

Merck & Co. recognized the potentially devastating effects that comments by Dr. Finger and conservative Christian organizations could have on public support for the vaccine, and the possible threat that Dr. Finger’s religious affiliation could have on his vote in the ACIP. Merck & Co. began lobbying Focus on the Family and Dr. Finger directly. Whether Merck & Co.’s lobbying efforts determined the organization’s position, or if public opinion or scientific evidence was more influential, is unclear. Ultimately, the mission of Focus on the Family, “To cooperate with the Holy Spirit in sharing the Gospel of Jesus Christ with as many people as possible” (Focus on the Family, 2009) proved to be compatible with preventing the sharing of HPV. The Vice President for Policy at the Family Research Council, another conservative Christian organization, in an editorial in the *Washington Post* at the time of the ACIP recommendation, clarified the reconciliation of his organization’s abstinence-only message with its pro-vaccine position by writing,

Behavioral self-restraint and vaccination are not mutually exclusive, since even someone who practices abstinence and fidelity could be exposed to HPV through sexual assault or marriage to an infected partner. But, as with other public health issues such as smoking, we should not limit ourselves to risk-reduction strategies when risk elimination is the ultimate goal (Sprigg, 2006).

In the end, Focus on the Family and other conservative Christian organizations publicly supported the HPV vaccine and Dr. Finger voted with the rest of the ACIP in its recommendations.

Many professional organizations followed the lead of the ACIP in their own recommendations, including the American Medical Association, the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, the Association of Women's Health, Obstetric and Neonatal Nurses, the American Academy of Family Physicians, the Society for Adolescent Medicine, and the American College Health Association, supporting routine HPV vaccination for females. The agreement of professional organizations with the ACIP's recommendations strengthened the likelihood of HPV vaccine uptake in the population, as a provider's professional organization recommendation is strongly associated with a provider's willingness to recommend the vaccine to patients (Raley, Followwill, Zimet, & Ault, 2004; Riedesel et al., 2005) and a provider's recommendation of the HPV vaccine is significantly associated with a patient receiving the vaccine (Dempsey, Abraham, Dalton, & Ruffin, 2009; Jain et al., 2009; Reiter, Brewer, Gottlieb, McRee, & Smith, 2009).

Funding: Vaccines For Children

After the FDA approved Gardasil®, and the ACIP established the recommendations for Gardasil®, the final federal policy contribution included funding Gardasil® through the Vaccines for Children (VFC) program, a federal program that pays for nearly half of all childhood vaccines provided in the United States. While the ACIP's recommendation clearly had a strong influence in establishing guidelines for HPV vaccination and winning the healthcare community's support for the HPV vaccine, it also had an important impact on making Gardasil® financially feasible for many individuals by voting to include Gardasil®, as it has with all other recommended vaccines, in the VFC program.

The VFC program has been funding vaccines for specific populations in the United States since the 1990s. On October 1, 1994, the Omnibus Budget Reconciliation Act of 1993 established the VFC program with the purpose of providing free vaccines to children through age 18 who may otherwise be unable to afford them. Initially proposed as the Childhood Immunization Initiative, the program was a sweeping solution to the resurgence of measles due to low vaccination rates (Centers for Disease Control and Prevention, 1994). Caught up in the short-lived enthusiasm for universal health care under the Clinton Administration, the Childhood Immunization Initiative would have provided recommended vaccines to all children regardless of income, streamlining the delivery of vaccines for all providers and eliminating cost concerns for all recipients. Had the Childhood Immunization Initiative succeeded, providers today may have enjoyed a single source of free vaccines for all patients rather than having to manage multiple sources of vaccines and the multiple ordering, storage, eligibility and billing requirements that accompany a fragmented delivery system.

Instead of the universal vaccination program envisioned under the Childhood Immunization Initiative, the more restrictive VFC program was passed as an entitlement program under Medicaid. The VFC program is limited to specific populations, including children who are Medicaid eligible, American Indian, Alaska Native, uninsured, or underinsured. The reasoning was sound- have private insurance companies pay for vaccines for their own enrollees to reduce the cost to the federal government and the federal government would pay for vaccines for those children not covered by private insurance. Unfortunately, the intended effect of universal vaccination was diminished by the unintended complexity of implementation.

The federal government funds the VFC program and requires that certain children, including those with Medicaid, be eligible for participation, but leaves administration of the program to the individual states. The federal funds pass from the Office of Management and Budget through the Centers for Medicare and Medicaid Services to the Centers for Disease Control and Prevention (CDC). The CDC then purchases vaccines at a reduced rate and the funds, now in the form of vaccines, resume their journey from the CDC to the states, usually through the state health departments who send it on to VFC providers.

Individual states vary in their establishment of child and provider eligibility for VFC participation. Some restrictive states limit private providers to using VFC vaccines for certain VFC eligible children, such as Medicaid eligible children, but require providers to send other VFC eligible children, such as underinsured children, to state health departments for VFC vaccines. Mississippi, with one of the lowest HPV vaccination rates in the country, uses this type of restrictive policy. Less restrictive states add their own vaccines to the VFC supply and provide vaccines to public and private providers for vaccination of all children, regardless of VFC eligibility. New Hampshire, a state with one of the highest HPV vaccination rates in the country, utilizes this universal VFC policy. The variation of VFC policies among states is extensive within these two extremes, including policies requiring a VFC provider to carry all recommended vaccines, or other policies that prohibit Medicaid reimbursement for a recommended vaccine (requiring that the Medicaid patient receive VFC funded vaccine from a VFC provider), making vaccination complex, confusing, and vulnerable to inequities.

In addition to the complexity of VFC funding and administration, Section 317 of the Public Health Services Act provides grants for states to support the cost of immunizations and reduce vaccine preventable illness. Like VFC, Section 317 funds are intended to provide support for groups without a means of paying for vaccines and are administered by states and therefore subject to significant variation for individuals based on residency and budget shifts. Unlike VFC funds though, they are often used for individuals with insurance but without immunization coverage specifically, and may be used for adult vaccination. While not a comprehensive solution to the cost of immunization, Section 317 funds are yet another contribution at the federal policy level that may be used to support HPV vaccine uptake, intended to provide some support for improving vaccination and decreasing disease in the United States.

In conclusion, federal public policy influenced Gardasil® through three mechanisms. First, the FDA approved the vaccine for the prevention of cervical cancer and genital warts, and later vulvar and vaginal cancers. Next, the ACIP recommended Gardasil® for all females age nine to 26 years old. Finally, the ACIP voted to include Gardasil® in the VFC program to provide federal funding for Gardasil® vaccination. The next level of policy influence was at the state level, specifically vaccine school entry requirement legislation.

State Policy: School Entry Requirements

After June 2006, with the federal policy decisions established including FDA approval, the ACIP recommendation, and VFC funding, the states were left to establish their own HPV vaccination policies while riding a wave of public support. According to the National Conference of State Legislatures, 41 states and the District of Columbia

have introduced some type of HPV vaccine legislation and 19 states have passed legislation involving HPV vaccination since Gardasil® was approved in 2006. While most states are addressing HPV vaccination policy, the type of legislation varies significantly in scope and outcome from state to state, including legislation ranging from education to funding to school entry requirements (National Conference of State Legislatures, 2010).

While HPV vaccination education may be a publicly acceptable form of legislation to support, vaccinating a large population often requires a more active approach. One of the most effective ways to achieve high vaccination rates in general is through the inclusion of vaccines in school entry requirements (Averhoff et al., 2004; Jacobs & Meyerhoff, 2004; Orenstein & Hinman, 1999).

...school laws establish a system for immunization, a system that works year in and year out, regardless of political interest, media coverage, changing budget situations, and the absence of vaccine-preventable disease outbreaks to spur interest (Orenstein & Hinman, 1999, p. S23).

The challenge, of course, is passing legislation. In the United States, the efficacy of the intervention in achieving the desired outcome is often overshadowed as the debate transforms into one of parental rights and individual freedoms. Satisfying the variety of stakeholders- including state health departments, state-based professional organizations, medical societies, legislators, citizens, vaccine manufacturers, parents organizations, and insurance companies- while dealing with cost issues, the media, anecdotal stories and politics can turn the process into an enormous challenge (Horlick, Shaw, Gorji, Fishbein, & Working Group on Legislation, Vaccination and Adolescent Health, 2008).

Furthermore, as school entry requirements are increasingly referred to as controversial, public support for HPV vaccine inclusion in school entry requirements decreases

(Gollust, Dempsey, Lantz, Ubel, & Fowler, 2010). The following two sections provide case examples of two different state approaches to HPV vaccination and school entry requirements.

Texas: The Case of Executive Order Backlash

Texas became the first state in the country to pass a school entry requirement for the HPV vaccine, an achievement that quickly backfired. On February 2, 2007, less than a year after the HPV vaccine was approved by the FDA and recommended by the ACIP, the Republican governor Rick Perry signed an executive order to require the HPV vaccine for all sixth grade girls. Governor Perry proposed to begin the policy in September 2008, a policy that included a provision to allow parents to easily decline vaccination. Bypassing the state legislature relieved representatives from having to take a public position on HPV vaccination and school entry requirements, a position they recognized as being potentially politically controversial due to the sexual transmission of HPV. Supporters of the executive order hailed it as triumph for women's health. The president of the advocacy group The Texas Freedom Network remarked,

Today's decision by the governor is not just a positive step forward in efforts to promote women's health. It is also an important acknowledgement that health and science should not be held hostage to politics and ideology (Blumenthal, 2007a).

In an interesting twist, the attempted removal of politics and ideology from science and health through the use of the executive order may have resulted in the infusion of politics and ideology back into the issue. Within days of the executive order, fellow Republicans introduced legislation to stop the executive order. A group of parents from Dallas swiftly sued the governor to prevent the executive order from taking effect, claiming the order conflicted with the state's abstinence only sex education policies.

Questions and suspicions began to arise when it was revealed that the governor's former chief of staff began a new position as a Merck & Co. lobbyist. By April 25, less than two months after the executive order was signed, the House passed HB1098 with a vote of 135 to 2 to override the executive order. The governor chose not to veto the bill, thus ending the country's first school entry requirement for the HPV vaccine.

The political reasons for the executive override overshadowed the health benefit for women, a risk for any public health issue decided by politicians instead of health care professionals. "This kind of imperiousness [the executive order] offended his base" according to one political analyst (Blumenthal, 2007b), indicating that a personal political offense took precedence over the politician's public policy responsibilities to pass effective legislation. In a commonly cited concern for individual rights over public health benefits, contrary to the evidence based ACIP recommendation for routine vaccination, one state representative commented,

We believe that parents and doctors should make an informed decision based on their daughters' specific personal situation. By no means am I or the members who voted for this bill saying that parents with their own choosing should not give this vaccination to their child (Frosch, 2007).

The effect, however, was that the high vaccination rates school entry requirements produce, and the population-wide public health benefits that result, became less likely to occur. While parents could easily choose to not vaccinate their daughters under the executive order, the loss of availability and financial accessibility afforded to school vaccines meant that instead many parents would not easily choose to vaccinate their daughters.

A unique contribution to the failure of Texas's executive order, and perhaps school entry legislation in other states, was ultimately Merck & Co. itself. Merck & Co.

recognized the enormous profits to be gained through widespread use of its vaccine. With the FDA approval of Gardasil®, Merck & Co. began an intensive and expensive direct-to-consumer advertising campaign, a common practice that earned the 2008 Pharmaceutical Advertising and Marketing Excellence award and Pharma Executive Magazine's brand of the year. Their campaign did not stop with consumers. They provided educational grants to professional medical associations, also a common practice, including the American College of Obstetricians and Gynecologists, the American College Health Association, the American Society for Colposcopy and Cervical Pathology, and the Society of Gynecologic Oncologists to promote Gardasil® (Rothman & Rothman, 2009). While many new products undergo direct-to-consumer advertising and provide educational grants for professionals, Merck & Co. also began funding intense lobbying efforts for school entry requirements for Gardasil®, which was not a common practice. The lobbying efforts included contributions to the bi-partisan, non-profit group of state legislators, Women in Government, in an effort to establish school entry requirements as a reliable source of long-term vaccine sales, as well as contributions to Governor Rick Perry's campaign.

Merck & Co.'s lobbying campaign initially appeared successful. By February 2007, when the Texas governor signed his executive order, 20 states were considering legislation to include the HPV vaccine in school entry requirements. However, around that time, the public began hearing stories of Merck & Co.'s funding of state lobbying efforts for school entry requirements and its contribution to Governor Rick Perry's campaign. People began to question the ethics of this type of lobbying activity. As the

public backlash began to emerge, Merck & Co. recognized the potential political harm of such intense lobbying and ceased funding the effort.

With the passing of time, Merck & Co.'s lobbying efforts were no longer considered influential. In a study of key informants across the United States involved in legislating the HPV vaccine, conducted between 2008 and 2009, the newness of the vaccine and the cost of the vaccine were both cited as influential factors in the legislative decisions in Texas (Colgrove, Abiola, & Mello, 2010). These more practical concerns, however, were not the focus of the public debate in 2007.

After a five year "softening up" period, the heated battle opposing required HPV vaccination has cooled to indifference- perhaps a move in the direction of acceptance. Texas Rep. Jessica Farrar, who voted against the executive order in 2007, introduced HB 2220 in March 2009, which would give the Executive Commissioner of the Health and Human Services Commission the authority to require HPV vaccination. The bill continues to languish in committee (National Conference of State Legislatures, 2010). Meanwhile, Texas' HPV vaccination rate remains just below the national average at 48% (Centers for Disease Control and Prevention, 2011).

In retrospect, Texas Governor Rick Perry consistently supported his decision to utilize the executive order until it returned to the spotlight in 2011 in his run for the Republican party nomination for President of the United States. In an interview during September 2011 he commented,

I think anything that a state can do to fight cancer is a wise and a thoughtful approach. Did I make an error in how I went about this? Yes, I've readily admitted that I shouldn't have used an executive order. I should have had an opt in, and I should have worked through the legislative process (Stengel & Halperin, 2011).

Despite his recent change in perspective, he still has not rescinded his support for HPV vaccination, only his executive order. Time will determine if the brief highlight of his past as a result of his presidential aspirations is enough to rekindle the national debate that could lead to substantive public policy changes.

Virginia and Washington, DC: Success Through Legislative Process

Following the legislative failure in Texas, across the United States only Virginia and Washington, DC managed to pass legislation that included the HPV vaccine in school entry requirements. The two locations benefited from the initial wave of public support, but avoided the controversy surrounding Texas's executive order by utilizing the legislative process. In April 2007, the General Assembly of Virginia passed a bill 81 to 17 in the House and 40 to zero in the Senate requiring that all girls entering sixth grade receive the HPV vaccine. To pass the bill, Del. Phillip Hamilton commented that, "We built in safeguards to make sure it was a cautious approach" (Smith, 2007). The safeguards included scheduling the requirement to begin October 1, 2008, effectively delaying its initiation until the start of the 2009 school year, more than two years after the legislation was approved. This two year delay gave parents ample time to become comfortable with and learn more about the requirement. In addition to delaying the start of the school entry requirement, the legislation included an amendment by Governor Timothy Kaine, a Democrat, liberalizing the parental exemption option for the HPV vaccine. Specifically, the amendment stated

Because the human papillomavirus is not communicable in a school setting, a parent or guardian, at the parent or guardian's sole discretion, may elect for their child not to receive the human papillomavirus vaccine, after having reviewed materials describing the link between the human papillomavirus and cervical cancer approved for such use by the board

(An Act to amend and reenact §32.1-46 of the Code of Virginia, relating to requiring the human papillomavirus vaccine, 2007).

In what may be a reflection of people's discomfort with the sexual transmission of HPV, Virginia differentiates the HPV vaccine from other required vaccines protective against diseases that are "not communicable in a school setting." To opt out of the hepatitis B vaccine, which became a requirement following the failure of a risk-based vaccination strategy, parents must sign a waiver. To opt out of the HPV vaccine, no action is required. The distinction, in practice, makes the HPV vaccine a recommendation for parents in Virginia rather than a requirement, but still allows females access to the funding and insurance coverage that accompany required vaccines.

Shortly after Virginia passed their legislation, the Washington, DC city council also passed, by a vote of seven to three, an HPV vaccine requirement for girls entering sixth grade. Like Virginia, the city council delayed the effective start date of the legislation until the 2009 school year to allow time for implementation, and like Virginia, the legislation included a very liberal opt out option, allowing parents to refuse HPV protection for their daughters, for any reason, by simply filling out a form.

Both Virginia and Washington, DC succeeded in including the HPV vaccine in school entry requirements by passing legislation through state congressional bodies or through city council members elected by the public, rather than resorting to the unilateral executive order that backfired in Texas. They appreciated the potential controversy that could result from the public's discomfort with an issue linked to sexual activity and postponed the initiation of legislation to allow people time to become comfortable with the vaccine. In addition, they expanded the opt out criteria so that parents may opt out for any reason, which differs from other immunizations that require a religious (in 48

states) or philosophic (in 19 states) exemption. This relaxed opt out option appeased parents and advocates of individual rights over public health. These concessions will likely result in lower HPV vaccination rates, as decreased complexity of opt out options results in increased numbers of parents opting out (Rota, et. al., 2000). However, the policies allowed for the successful passage of publicly acceptable legislation that should improve access for much of the population and improve HPV vaccine acceptability among parents who may view school vaccines as standard. The 2009 school year marked the start of the HPV vaccine school entry requirement in both Virginia and Washington, DC and the policies were carried out with little public fanfare. Since then, legislation was introduced in 2010 in Virginia to overturn the requirement, but has remained in committee. The impact of legislation on vaccination rates will be measured in the coming years.

In conclusion, states influenced Gardasil® vaccination policy primarily through support, or lack of support, for school entry requirement legislation. Because states, with the exception of Virginia and Washington, DC, chose not to include Gardasil® in school entry requirements, they passed along policy responsibility for vaccinating the public to the next level: individual health care organizations and providers. Planned Parenthood Mid and South Michigan is one example of a health care organization that struggled to establish organizational policies in response to federal and state policies, described below.

Health Care Organization Policy:

The Case of Planned Parenthood Mid and South Michigan

Planned Parenthood has provided health care for females and males for over 90 years (Planned Parenthood Federation of America, 2011). Planned Parenthood Mid and South Michigan (PPMSM) is a Planned Parenthood affiliate serving 62,000 mostly young female patients annually in 15 health centers across mid and southern Michigan (Planned Parenthood Mid and South Michigan, 2010). Planned Parenthood Federation of America (PPFA) oversees PPMSM and 83 other Planned Parenthood affiliates across the United States (Planned Parenthood Federation of America, 2011). PPFA operates on the national level supporting women's reproductive health through policy advocacy and education, while guiding local affiliates in the provision of evidence based health care at more than 800 health centers (Planned Parenthood Federation of America, 2011).

When the HPV vaccine was first approved by the FDA in June 2006, Cecile Richards, President of PPFA was in Kalamazoo, Michigan and commented, "Planned Parenthood looks forward to making sure that this vaccine is accessible and available to young women everywhere in this country" (Meehan, 2006). Despite its availability elsewhere, almost four years passed after Richards' statement before the vaccine became available at PPMSM, on May 1, 2010, in two of its 15 health centers.

Initially, the primary reason PPMSM chose not to carry Gardasil® was that they awaited the outcome of state policy development (M. Steuber, PPMSM Vice President for Medical Affairs, personal communication, October 2009). PPMSM waited for the state legislature to pass school entry requirements that would effectively vaccinate the younger population who would later become PPMSM patients, eliminating the need for PPMSM to vaccinate. The bill (SB1416) however, failed (State of Michigan 93rd Legislature, December 15, 2006, p. 3289-3291), as described below.

Michigan Policy History

The state of Michigan was the first state to propose legislation to include the HPV vaccine in school entry requirements. In September 2006, SB1416 was introduced in the state Senate (State of Michigan 93rd Legislature, September 12, 2006, p. 2060), requiring all girls entering sixth grade to receive the HPV vaccine. The bill was introduced by Republican Senator Beverly Hammerstrom (State of Michigan 93rd Legislature, September 12, 2006, p. 2060), recommended for passage by the Senate Committee on Health Policy (State of Michigan 93rd Legislature, September 19, 2006, p. 2166), supported by all 11 female senators (State of Michigan 93rd Legislature, September 20, 2006, p. 2193-2195) and the female governor Jennifer Granholm (Heinlein, 2006), and passed 36 to one by the Republican run Senate (State of Michigan 93rd Legislature, September 20, 2006, p. 2193-2195). When the bill was then sent to the Republican run House, the House Committee on Health Policy supported the bill, and the House initially supported the bill 58 to 45 on December 14, 2006 but then agreed to temporarily postpone consideration (State of Michigan 93rd Legislature, December 14, 2006, p. 3279-3289). Michigan requires bills to be passed by a majority of members elected, not a majority of members voting, so the next day, December 15, 2006, the bill failed to produce majority support from the full component of 110 legislators, with a final vote of 53 legislators voting in favor and 48 opposing the bill (State of Michigan 93rd Legislature, December 15, 2006, p. 3289-3291). Two legislators showed up late, missing the vote, and the remaining seven were absent (State of Michigan 93rd Legislature, December 15, 2006, p. 3289).

Opposition came from Republican lawmakers arguing in favor of parental control specifically, not necessarily against the HPV vaccine generally. According to Republican Representative Kevin Elsenheimer,

I am the father of an 11 year old daughter. My wife and I may decide to have her receive the vaccine at some point in her future. The vaccine clearly shows great promise - some have said it's miraculous. My no vote is premised upon a concern that the government is rushing to 'correct a wrong' that can be handled easily through a personal family decision to vaccinate (State of Michigan 93rd Legislature, December 14, 2006, p. 3280).

Republican Representative David Robertson had similar comments. "While I recognize the potential benefit of this, or any vaccine, I cannot support the mandatory aspect of this bill. I believe this should be a matter of parental choice" (State of Michigan 93rd Legislature, December 14, 2006, p. 3281).

Michigan struggled with the public controversy fueled by the media, which the rest of the country was starting to experience. If the excitement of Gardasil's® potential health benefits overshadowed any opposition when it was first approved, Michigan newspaper headlines helped reverse the trend and created controversy. Headlines like "Pre-sex Vaccine Draws Little Opposition - Panel Recommends Shots for Girls as Young as 9 to Prevent Cancer" (The Associated Press, 2006) and "Virginity Patrol not the only irrational ones in HPV debate" (Alberty, 2006) and later "Michigan May Force Girls to Get Vaccine" (Heinlein, 2006) fueled extremist views surrounding the vaccine and school entry legislation in the state. Despite the media's focus on the "controversy" surrounding a vaccine that protects against the effects of a sexually transmitted infection and its feared contribution to premarital sex, no record of the premarital sex argument was made in the Senate (State of Michigan 93rd Legislature, September 20, 2006, p. 2193-2195) or House (State of Michigan 93rd Legislature, December 14, 2006, p. 3279-3289) records.

Eleven variations of HPV vaccination legislation have been and continue to be considered in Michigan, including bills related to information dissemination and insurance coverage, most without proceeding beyond the designated committee and therefore not open to debate (National Conference of State Legislatures, 2010). The only HPV vaccine related bill legislators managed to pass was HB5322 in May 2008 that required HPV vaccine information to be included with other vaccine information if a school district provides vaccine information (State of Michigan 94th Legislature, 2008).

Planned Parenthood Mid and South Michigan Policy History

Without the support of school entry requirements from the state, and with a new PPFA policy requiring that all Planned Parenthood health centers provide the HPV vaccine, PPMSM started to search for ways to carry the expensive vaccine. One option utilized by similar organizations in other states was to depend on their state's health department to provide vaccines free to health care providers. Rhode Island, with the highest vaccination rates in the country (73%), offers this convenience (Centers for Disease Control and Prevention, 2011). However, the Michigan Department of Community Health does not provide vaccines free to all health care providers. Instead, they require that patients make a separate trip to the state facilities to receive Gardasil®, charging a fee of \$15 per injection. Therefore, low-cost vaccine is currently available from the state, but not accessible through PPMSM providers.

Another option examined by PPMSM was reimbursement of the vaccine for patients with Medicaid. However, Medicaid declined to reimburse PPMSM for Gardasil®, which they do for other providers, for unknown reasons (M. Steuber, PPMSM Vice President for Medical Affairs, personal communication, 2010). This prevented any

Medicaid patient from receiving the HPV vaccine at PPMSM unless they were willing to pay over \$500 out of pocket.

Approximately 70% of the PPMSM population was uninsured in 2010 (Small & Patel, 2011), making the Merck Vaccine Patient Assistance program a possible source of financial support for many patients (Merck, 2011). The Merck Vaccine Patient Assistance Program, available to uninsured individuals who meet certain eligibility requirements, necessitates that patients and providers complete an application form, fax it to the company for approval, and wait for a response. If approved, the patient can receive the vaccine for free, and replacement vaccines are sent to the provider quarterly. While time spent completing forms, faxing to the company, and waiting for confirmation would be a burden on both patients and providers, and its lack of weekend availability would limit its usefulness, it could be an option for reduced cost vaccine for some patients.

Without an outside source of funding to pay for the vaccine, nor a source of free or reduced cost vaccine, nor even reimbursement for the vaccine in many cases, and an economic recession straining finances, cash-strapped PPMSM passed the cost of the vaccine on to their patients, limiting accessibility. While the patient cost of most services provided at PPMSM is determined by an income-based sliding scale made possible by Title X federal funding, PPMSM determined the organization could not support the cost of the vaccine on a sliding scale (M. Steuber, PPMSM Vice President for Medical Affairs, personal communication, October 2009). All patients would be charged \$150 for each vaccine injection in addition to a \$30 injection fee, regardless of income, for a total of \$540 if the full three dose series was completed at PPMSM. Even those utilizing the Merck Vaccine Patient Assistance Program would still have to pay the \$30 injection fee,

three times, for a total of \$90. This sum is often more than the cost of the annual exam, which can be free for uninsured patients.

On May 1, 2010, four years after the FDA approved Gardasil®, PPMSM stocked HPV vaccines at two health centers to pilot HPV vaccine administration, and expanded Gardasil® availability to all health centers in 2011. In staff training for implementation, the cost burden of the vaccine was emphasized through oral presentation and power point slides, in conjunction with other aspects of Gardasil® administration. Availability of the vaccine at these two PPMSM facilities improved rates of vaccination from 11% to 17% (Small & Patel, 2011).

In summary, the PPFA requirement that all Planned Parenthood health centers make HPV vaccination available to patients by 2012 has not translated into substantially increased vaccination of Planned Parenthood patients in Michigan. The current climate of political and financial constraints in Michigan raises major cost barriers to vaccine implementation at PPMSM. Political pressure prevented passage of a school-entry requirement, pushing responsibility for attaining high vaccination rates onto health care organizations and providers. For PPMSM, this clinic encounter level responsibility presented challenges, especially challenges around cost issues. Overcoming these constraints is important to the thousands of 19 to 26 year olds served by this organization, with PPMSM being the only source of health care for many of these patients.

The Future: Impact of the Affordable Care Act

This paper has so far discussed Gardasil®'s policy history at the federal, state, and health care organization levels. The next step is to look to the future. As the political landscape changes with each election, priorities shift and HPV vaccine policy may return

to the forefront of debate and consideration, or fade into the background again. Much of the future of HPV vaccine policy remains unknown and will continue to change as new research emerges. Books will be written and discussed analyzing the politics of HPV vaccination. For example, see Wailoo, Livingston, Epstein, & Aronowitz, 2010. However, despite HPV vaccine policy constraints at the federal, state, and health care organization levels in the past, a change in policy at the federal level, specifically the passage of The Affordable Care Act, is the most likely policy influence modification for the near future.

After months of political debate, a final vote of 220 to 207 in the House and 56 to 43 in the Senate, and not a single Republican vote, President Barak Obama signed the Affordable Care Act into law on March 23, 2010. The extensive law focuses mainly on health insurance reform, eliminating over time practices such as denying coverage for pre-existing conditions, cancelling coverage for people who become ill, and imposing lifetime limits on coverage. The law has the potential to shape public policy's influence on HPV vaccine uptake through three provisions: increasing the number of people with insurance, expanding insurance coverage for young adults until age 26, and increasing preventive care insurance coverage, including recommended vaccines and the preventive maintenance visits where immunization is often addressed, for all people.

Increasing the Number of People with Insurance

Perhaps one of the most politically contentious pieces of the Affordable Care Act is the individual mandate for health insurance. By 2014, the law will require uninsured individuals, approximately 32 million individuals, to purchase insurance. The federal and state governments will assist uninsured individuals in purchasing insurance in two ways.

First, the law expands Medicaid coverage for about 16 million people by covering most individuals with incomes up to 133% of the federal poverty level. Second, federal subsidies will help expand access to private insurance for middle-income families through insurance exchanges (The New York Times, 2011).

Because cost and insurance coverage are one of the strongest influences on HPV vaccine uptake (Conroy et al., 2009, Jain et al., 2009), universal insurance coverage will likely decrease much of the HPV vaccine cost burden faced by uninsured individuals, increasing HPV vaccine uptake, especially for those over the age of 18 who do not have access to Vaccines for Children coverage due to their age. An example of this potential influence is the one state with universal health coverage currently- 66% of adolescents in Massachusetts have initiated HPV vaccination, one of the highest percentages in the country (Centers for Disease Control and Prevention, 2011). Insurance coverage may not be the only influence on HPV vaccine uptake, but it does help.

Because the individual mandate does not go into effect until 2014, however, ample time exists for this particular aspect of the Affordable Care Act to be rescinded. Across the country, 31 lawsuits from Republican governors and attorneys general in 26 states are making their way through the court system seeking to overturn the law. The lawsuits focus on the individual mandate, with opponents arguing that government cannot require individuals to engage in commerce by requiring them to purchase insurance and proponents arguing that individuals will inevitably consume health care and therefore should finance health care (Sack, 2011). The final outcome, which has the potential to be decided by the Supreme Court, will determine how much influence the individual mandate will ultimately have on HPV vaccine uptake.

Expanding Coverage for Young Adults Until Age 26

Starting September 23, 2010 (with exemptions for existing insurance plans through 2014), young adults are eligible for coverage under their parents' health insurance until age 26, regardless of marital status, student status, or dependency status (United States Department of Health and Human Services, 2010). Young adults face unique difficulties in accessing insurance coverage. Employment varies and access to employer-based health insurance is often limited while young adults start to establish themselves in the workforce. As a result, 30% of young adults are uninsured, the highest rate of any age group (Center for Consumer Information and Oversight, 2010). The intent of the Affordable Care Act is to reduce the number of uninsured young adults by allowing the group access to their parent's health insurance. As more people become insured, the cost burden of the HPV vaccine on individuals may be eliminated and more people will likely become vaccinated.

Increasing Preventive Care Insurance Coverage

Starting September 23, 2010, new health insurance plans (with exemptions for existing insurance plans), are required to offer preventive services free of charge, without a co-payment or deductible (United States Department of Health and Human Services, 2010). This piece of the Affordable Care Act includes immunizations in general, and HPV vaccination specifically. As described above, cost and insurance coverage in general do influence HPV vaccine uptake. However, research on the effect of smaller costs specifically, such as co-payments, on HPV vaccine uptake is limited.

Impact on Health Care Organizations

The Affordable Care Act has the potential to increase HPV vaccine uptake by reducing the cost burden of the vaccine for many individuals through expanded health insurance coverage. When insurance companies cover the cost of the vaccine for most individuals, the cost burden is almost eliminated for health care organizations, especially those serving a currently largely uninsured population such as PPMSM. Organizations may be able to focus their limited resources on the remaining individuals not covered by the Affordable Care Act, such as immigrants or individuals covered under existing grandfathered insurance plans that are exempt from the requirements. As the Affordable Care Act becomes fully implemented in 2014, researchers, politicians and organizations will begin to evaluate its success or failure in improving health care in the United States and influencing HPV vaccine uptake.

As demonstrated in this chapter, insurance coverage is not the only system influence on HPV vaccine uptake. Public policy at the federal level, including vaccine approval, recommendation, and funding, and at the state level, including school entry requirements, influence health care organizations and individuals. As discussed in the next chapter, Chapter Three, a variety of influences at the health care organization level may also be modified to improve HPV vaccine uptake in individuals.

References

- Advisory Committee on Immunization Practices. (2006). Record of the proceedings June 29-30, 2006. Retrieved from <http://www.cdc.gov/vaccines/recs/acip/downloads/min-jun06.pdf>
- Advisory Committee on Immunization Practices. (2009). Summary report October 21-22, 2009. Retrieved from <http://www.cdc.gov/vaccines/recs/acip/downloads/min-oct09.pdf>
- Alberty, E. (2006, September 15). Virginitiy patrol not the only irrational ones in HPV debate. *Saginaw News*, p. 3A.
- An act to amend and reenact §32.1-46 of the code of Virginia, relating to requiring the human papillomavirus vaccine, §858. (2007). Retrieved from <http://leg1.state.va.us/cgi-bin/legp504.exe?071+ful+CHAP0858>
- The Associated Press. (2006, June 30). Pre-sex vaccine draws little opposition - panel recommends shots for girls as young as 9 to prevent cancer. *The Grand Rapids Press*, p. A4.
- Averhoff, F., Linton, L., Peddecord, K. M., Edwards, C., Wang, W., & Fishbein, D. (2004). A middle school immunization law rapidly and substantially increases immunization coverage among adolescents. *American Journal of Public Health*, 94(6), 978-984.
- Blumenthal, R. (2007a, February 3). Texas is first to require cancer shots for schoolgirls. *The New York Times*, p. 9.
- Blumenthal, R. (2007b, April 26). Texas legislators block shots for girls against cancer virus. *The New York Times*, p. 16.

- Brown, D. R., Schroeder, J. M., Bryan, J. T., & Stoler, M. H. (1999). Detection of multiple human papillomavirus types in condyloma acuminata lesions from otherwise healthy and immunosuppressed patients. *Journal of Clinical Microbiology*, 37(10), 3316-3322.
- Center for Consumer Information and Oversight. (2010, April 20). Young adults and the affordable care act: protecting young adults and eliminating burdens on families and businesses. Retrieved from http://cciio.cms.gov/resources/files/adult_child_fact_sheet.html
- Centers for Disease Control and Prevention. (1994). Reported vaccine-preventable diseases-United States, 1993, and the childhood immunization initiative. *Morbidity and Mortality Weekly Report*, 43(4), 57.
- Centers for Disease Control and Prevention. (2009a). Advisory committee on immunization practices (ACIP). Retrieved from <http://www.cdc.gov/vaccines/recs/acip/default.html>
- Centers for Disease Control and Prevention. (2009b). CDC vaccine price list. Retrieved from <http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm>
- Centers for Disease Control and Prevention. (2009c). Genital HPV Infection: CDC Fact Sheet. Retrieved from <http://www.cdc.gov/std/HPV/STDFact-HPV.htm>
- Centers for Disease Control and Prevention. (2010). Vaccine safety. Retrieved from <http://www.cdc.gov/vaccinesafety/vaccines/HPV/gardasil.html>
- Centers for Disease Control and Prevention. (2011). National and state vaccination coverage among adolescents aged 13 through 17 years-United States, 2010. *Morbidity and Mortality Weekly Report*, 60(33), 1117-1123.

- Colgrove, J., Abiola, S., Mello, M. M. (2010). HPV vaccination mandates- lawmaking amid political and scientific controversy. *The New England Journal of Medicine*, 363(8), 785-791.
- Conroy, K., Rosenthal, S. L., Zimet, G. D., Jin, Y., Bernstein, D. I., Glynn, S., & Kahn, J. A. (2009). Human papillomavirus vaccine uptake, predictors of vaccination, and self-reported barriers to vaccination. *Journal of Women's Health*, 18(10), 1679-1686. doi:10.1089/jwh.2008.1329
- Dempsey, A. F., Abraham, L. M., Dalton, V., & Ruffin, M. (2009). Understanding the reasons why mothers do or do not have their adolescent daughters vaccinated against human papillomavirus. *Annals of Epidemiology*, 19(8), 531-538. doi:10.1016/j.annepidem.2009.03.011
- Dunne, E. F., Unger, E. R., Sternberg, M., McQuillan, G., Swan, D. C., Patel, S. S., & Markowitz, L. E. (2007). Prevalence of HPV infection among females in the United States. *The Journal of the American Medical Association*, 297(8), 813-819. doi:10.1001/jama.297.8.813
- Focus on the Family. (2009). About Focus on the Family. Retrieved from http://www.focusonthefamily.com/about_us.aspx
- Finger, R. (2011a). Home. Retrieved from <http://www.regfinger.com/index.html>
- Finger, R. (2011b). HPV Vaccine. Retrieved from <http://www.regfinger.com/5.html>
- Frosch, D. (2007, March 14). Texas house rejects order by governor on vaccines. *The New York Times*, p. 14.
- Gold, R. B. (2007). Challenges and opportunities for U.S. family planning clinics in providing the HPV vaccine. *Guttmacher Policy Review*, 10, 8-14.

- Gollust, S. E., Dempsey, A. F., Lantz, P. M., Ubel, P. A., & Fowler, E. F. (2010). Controversy undermines support for state mandates on the human papillomavirus vaccine. *Health Affairs*, 29(11), 2041-2046. doi:10.1377/hlthaff.2010.0174
- Greer, C. E., Wheeler, C. M., Ladner, M. B., Beutner, K., Coyne, M. Y., Liang, H.,...Ralston, R. (1995). Human Papillomavirus (HPV) type distribution and serological response to HPV type 6 virus-like particles in patients with genital warts. *Journal of Clinical Microbiology*, 33(8), 2058-63.
- Harris, G. (2006, June 30). Panel unanimously recommends cervical cancer vaccine for girls 11 and up. *The New York Times*, p. 12.
- Heinlein, G. (2006, September 13). Michigan may force girls to get vaccine - sixth-graders would be required to get shot to prevent cervical cancer. *The Detroit News*, p. 1A.
- Horlick, G., Shaw, F. E., Gorji, M., Fishbein, D. B., & Working Group on Legislation, Vaccination and Adolescent Health. (2008). Delivering new vaccines to adolescents: The role of school-entry laws. *Pediatrics*, 121(Suppl 1), S79-84. doi:10.1542/peds.2007-1115I
- Jacobs, R. J., & Meyerhoff, A. S. (2004). Effect of middle school entry requirements on hepatitis B vaccination coverage. *Journal of Adolescent Health*, 34(5), 420-423. doi:10.1016/j.jadohealth.2003.08.014
- Jain, N., Euler, G. L., Shefer, A., Lu, P., Yankey, D., & Markowitz, L. (2009). Human papillomavirus (HPV) awareness and vaccination initiation among women in the United States, national immunization survey-adult 2007. *Preventive Medicine*, 48(5), 426-431. doi:10.1016/j.ypmed.2008.11.010

- Lacey, C. J. N., Lowndes, C. M., & Shah, K. V. (2006). Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. *Vaccine, 24*, S35-S41.
- Meehan, C. (2006, June 9). Planned Parenthood chief lauds new vaccine. *Kalamazoo Gazette*.
- Merck. (2011). Merck vaccine patient assistance program. Retrieved from <http://www.merck.com/merckhelps/vaccines/home.html>
- Muñoz, N., Bosch, F. X., de Sanjosé, S., Herrero, R., Castellsangüé, X., Shah, K. V.,...Meijer, C. J. L. M. (2003). Epidemiologic classification of human papillomavirus types associated with cervical cancer. *New England Journal of Medicine, 438*(6), 518-27.
- Myers, E. R., McCrory, D. C., Nanda, K., Bastian, L., & Matchar, D. B. (2000). Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. *American Journal of Epidemiology, 151*(12), 1158-1171.
- National Conference of State Legislatures. (2010). HPV Vaccine: State Legislation. Retrieved from <http://www.ncsl.org/default.aspx?tabid=14381>
- Orenstein, W. A., & Hinman, A. R. (1999). The immunization system in the United States - the role of school immunization laws. *Vaccine, 17*(Suppl 3), S19-24.
- Planned Parenthood Federation of America. (2011). About Us. Retrieved from <http://www.plannedparenthood.org/about-us/index.html>
- Planned Parenthood Mid and South Michigan. (2010). Planned Parenthood Mid and South Michigan. Retrieved from <http://www.plannedparenthood.org/midsouthmi>
- Raley, J. C., Followwill, K. A., Zimet, G. D., & Ault, K. A. (2004). Gynecologists' attitudes regarding human papilloma virus vaccination: A survey of fellows of the

- American college of obstetricians and gynecologists. *Infectious Diseases in Obstetrics and Gynecology*, 12(3-4), 127-133. doi:10.1080/10647440400020661
- Reiter, P. L., Brewer, N. T., Gottlieb, S. L., McRee, A. L., & Smith, J. S. (2009). Parents' health beliefs and HPV vaccination of their adolescent daughters. *Social Science & Medicine*, 69(3), 475-480. doi:10.1016/j.socscimed.2009.05.024
- Riedesel, J. M., Rosenthal, S. L., Zimet, G. D., Bernstein, D. I., Huang, B., Lan, D., & Kahn, J. A. (2005). Attitudes about human papillomavirus vaccine among family physicians. *Journal of Pediatric and Adolescent Gynecology*, 18(6), 391-398. doi:10.1016/j.jpag.2005.09.004
- Rota, J. S., Salmon, D. A., Rodewald, L. E., Chen, R. T., Hibbs, B. F., & Gangarosa, E. J. (2000). Processes for obtaining nonmedical exemptions to state immunization laws. *American Journal of Public Health*, 91(4), 645-648.
- Rothman, S. M., & Rothman, D. J. (2009). Marketing HPV vaccine: Implications for adolescent health and medical professionalism. *The Journal of the American Medical Association*, 302(7), 781-786. doi:10.1001/jama.2009.1179
- Sack, K. (2011, June 9). Judges weigh limits of health law's powers. *The New York Times*, p. A-17.
- Small, S. L. & Patel, D. A. (2011). Impact of HPV vaccine availability on uptake. *The Journal for Nurse Practitioners*. Manuscript accepted for publication on June 20, 2011.
- Smith, T. (2007, February 22). Bills requiring vaccine advance- mandate for HPV shot goes to Kaine; parents could opt out. *Richmond Times-Dispatch*, p. A-6.
- State of Michigan 93rd Legislature. (September 12, 2006). *Journal of the Senate*, No. 81,

2060. Retrieved from <http://www.legislature.mi.gov>
State of Michigan 93rd Legislature. (September 19, 2006). *Journal of the Senate, No. 84*,
2166. Retrieved from <http://www.legislature.mi.gov>
State of Michigan 93rd Legislature. (September 20, 2006). *Journal of the Senate, No. 85*,
2193-2195. Retrieved from <http://www.legislature.mi.gov>
State of Michigan 93rd Legislature. (December 14, 2006). *Journal of the House of
Representatives, No. 95*, 3279-3289. Retrieved from
<http://www.legislature.mi.gov>
State of Michigan 93rd Legislature. (December 15, 2006). *Journal of the House of
Representatives, No. 96*, 3289-3291. Retrieved from
<http://www.legislature.mi.gov>
State of Michigan 94th Legislature. (May 8, 2008). Act No. 121, Enrolled House Bill
No. 5322. Retrieved from <http://www.legislature.mi.gov>
Stengel, R. & Halperin, M. (2011, September 26). Americans are tired of political
correctness. *Time*, p. 36.
Stein, R. (2005, October 31). Cervical cancer vaccine gets injected with a social issue-
some fear a shot for teens could encourage sex. *The Washington Post*, p. A3.
The New York Times (updated March 4, 2011). Times topics: health care reform.
Retrieved from
http://topics.nytimes.com/top/news/health/diseasesconditionsandhealthtopics/health_insurance_and_managed_care/health_care_reform/index.html?scp=35&sq=affordable%20care%20act&st=cse
United States Department of Health and Human Services. (2010). Understanding the

affordable care act: Provisions. Retrieved from

<http://www.healthcare.gov/law/provisions>

United States Food and Drug Administration. (2006). June 8, 2006 approval letter – human papillomavirus quadrivalent (Types 6, 11, 16, 18) vaccine, recombinant.

Retrieved from

<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm111283.html>

United States Food And Drug Administration. (2008). September 12, 2008 approval letter- Gardasil. Retrieved from

<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm111270.html>

United States Food and Drug Administration. (2009a). October 16, 2009 approval letter- Cervarix. Retrieved from

<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm186959.html>

United States Food and Drug Administration. (2009b). October 16, 2009 approval letter- Gardasil. Retrieved from

<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm186991.html>

Wailoo, K., Livingston, J., Epstein, S., Aronowitz, R. (Eds.). (2010). *Three shots at prevention: The HPV vaccine and the politics of medicine's simple solutions*. The Johns Hopkins University Press.

Chapter Three

Modifiable Influences on HPV Vaccine Uptake at The Clinic Encounter Level:

A Literature Review

This literature review was conducted to identify modifiable influences on HPV vaccine uptake relevant to clinical practice. The investigator electronically searched PubMed using the search term “hpv vaccine.” The search was limited to humans and female participants, as routine recommendation for HPV vaccination is currently limited to females, and the search was limited to publications in English, as the journals reporting results in the United States are published in English. The search was also limited to articles published between January 1, 2009 and June 1, 2011, the time period when researchers began publishing HPV vaccine uptake studies. CINAHL was searched separately using the same search term and time limitations to identify any additional studies not available in PubMed. The author also performed hand searches of reference lists of publications that surfaced in the electronic search and met the inclusion criteria, and added her own research manuscript, accepted for publication on June 20, 2011 in *The Journal for Nurse Practitioners*.

Studies were included if they provided direct measurement of uptake (not simply intention to vaccinate) and used variables the investigator identified as modifiable in clinical practice (see results). Studies were excluded if they examined variables unable to

be modified directly in clinical practice, such as race or ethnicity, age, education level, income, marital status, or number of previous hospitalizations. Studies were also excluded if they were not conducted in the United States, in order to increase relevance to clinical practice within the United States. Each study was analyzed to identify the main findings. Similar variables from the main findings were grouped together to extract summary factors of modifiable influences at the clinic encounter level.

Of the 1074 articles identified through the electronic database search, a total of nineteen articles met the inclusion criteria. Table 3.1 summarizes the findings from these studies. Six modifiable influences relevant to clinical practice were extracted from the studies (see Table 3.2). The six influences were: 1) cost and insurance coverage, 2) provider recommendation, 3) vaccination opportunity, 4) HPV and HPV vaccine knowledge, 5) vaccine safety concerns, and 6) HPV risk (including documented HPV risk factors or perceived HPV risk).

Cost and Insurance Coverage

Cost and insurance coverage is potentially modifiable at the clinic encounter in that organizations may have access to resources for patients who cannot afford to pay. Cost and insurance coverage in general differs greatly between females younger than 19 years of age, who are more often insured and may be eligible for free vaccines through the Vaccines for Children program, and females 19 and older who are less commonly insured and have limited access to vaccine-specific funding. Of the seven studies that addressed cost and insurance coverage as influences on HPV vaccination, (Caskey, Lindau, & Alexander, 2009; Conroy et al., 2009; Dempsey, Cohn, Dalton & Ruffin, 2010; Jain et al., 2009; Moore, Crosby, Young, & Charnigo, 2010; Schluterman, Terplan,

Lydecker & Tracy, 2011; Zimet, Weiss, Rosenthal, Good, & Vichnin, 2010), most found cost and insurance coverage to be a influence in the young adult age group.

Across the eligible age range, in a longitudinal survey of 189 females 13 to 26 year old, Conroy et al. (2009) identified insurance coverage for the vaccine as the strongest predictor of HPV vaccine initiation (OR 5.31, 95% CI 1.61-17.49).

Demonstrating the difference between the two age groups, 27% of 18 to 26 year old females cited cost as a reason for foregoing vaccination, while only 10% of younger females ages 13 to 17 years cited cost as a barrier (Caskey et al., 2009).

Among studies specific to young adults, who are therefore no longer eligible for the Vaccines for Children Program, in an analysis of the 2007 National Immunization Survey-Adult data, Jain et al. (2009) found having health insurance as one of the only variables associated with initiation ($p < 0.05$). In another study of 19 to 26 year old insured females, 24.4% cited uncertainty about insurance coverage as a reason for not vaccinating (Zimet et al., 2010).

Even the type of insurance seems to have an effect on vaccination. In a study of outpatient gynecologic clinics, 47% of the nine to 26 year old females who initiated the HPV vaccine series had public insurance compared to 28% with private insurance ($p < 0.01$) (Schulterman et al., 2011). This finding was replicated in young adults specifically, where having public insurance increased the likelihood of vaccination when compared to private insurance (OR 0.52, 95% CI 0.45-0.59) or no insurance (OR 0.47, 95% CI 0.26-0.85) (Dempsey et al., 2010).

One study evaluated the impact of eliminating cost as a barrier by providing a free vaccine voucher at a university health center. This was the only study that provided an

intervention to evaluate the effect of cost as an influence. As a result, 50% of the participants (n=209) utilized the voucher to initiate vaccination (Moore et al., 2010).

Provider Recommendation

Perhaps the most clinically relevant factor that has repeatedly been shown to influence HPV vaccine uptake is provider recommendation. Seven studies confirmed that discussing the vaccine and receiving a recommendation from a health care provider often results in receipt of the vaccine (Caskey et al., 2009; Conroy et al., 2009; Dempsey, Abraham, Dalton, & Ruffin, 2009; Gerend, Weibley, & Bland, 2009; Gottlieb et al., 2009; Guerry et al., 2011; Rosenthal et al., 2011). One survey of 19 to 26 year old females, in which all participants were insured, found even the strength of the physician recommendation mattered, with patients who perceived a stronger recommendation from their physician having a four times greater likelihood of vaccinating than those who perceived a weaker recommendation from their physician (Rosenthal et al., 2011).

While less modifiable but still important to understand, the specialty of the provider can be influential. One study of Kaiser Permanente's immunization data found that having a Pediatrician as a primary care provider was correlated with vaccine initiation when compared to Family Medicine providers (RR 0.81, 95% CI 0.79-0.83) or Internal Medicine providers (RR 0.93, 95% CI 0.87-1.00) (Chao, Velicer, Slezak, & Jacobsen, 2010). A larger study of clinic visit data confirmed the influence of provider specialty where Pediatric providers were positively correlated with HPV vaccination when compared to Family Medicine (OR 0.92, 95% CI 0.81-1.04) or Gynecology providers (OR 0.24, 95% CI 0.18-0.33) (Dempsey et al., 2010). These findings are consistent with uptake among other vaccines, not just the HPV vaccine, showing

Pediatricians consistently outperforming other provider specialties in vaccine administration.

Provider characteristics other than specialty may also influence vaccine uptake. Having a male primary care provider was inversely associated with vaccine initiation (RR 0.92, 95% CI 0.91-0.93) when compared to female primary care providers (Chao et al., 2010). Also, one of the first studies to explore influences on mothers decisions to vaccinate daughters found that mothers who declined vaccination at a health care visit had more often seen someone other than their usual health care provider. This supports the belief that the strength of the relationship between provider and patient also matters, and not just the provider specialty or gender (Dempsey et al., 2009). No studies were found that have evaluated the influence of nurse practitioners on HPV vaccine uptake.

Vaccination Opportunity

Four studies found that females with a recent health care visit were more likely to have received the HPV vaccine than those without a recent health care visit (Caskey et al., 2009; Chao et al., 2010; Dempsey et al., 2010; Reiter et al., 2010), as the health care visit serves as an opportunity to access the vaccine. A total of 13% of parents interviewed in North Carolina cited the lack of a health care visit as the reason they had not initiated vaccination for their daughters (Gottlieb et al., 2009). However, the frequency of health care visits did not seem to be associated with vaccination (Mathur, Mathur, & Reichling, 2010). Females who attended an outpatient visit (Cook et al., 2010) and females who attended a preventive maintenance visit (OR 5.18, 95% CI 4.64-5.79) (Dempsey et al., 2010) were more likely to initiate HPV vaccination than those attending a problem focused visit. This finding supports the understanding that

vaccination opportunity specifically, rather than health care visits generally, influence vaccination, as preventive maintenance visits are traditionally when vaccination status is addressed (Schaffer, Humiston, Shone, Averhoff, & Szilagyi, 2001).

The author's own research showed that four years after the vaccine became available to the public, vaccine availability at the clinic visit increased vaccination from 11.1% prior to health center availability to 17.0% after it became available at the health center (Small & Patel, 2011).

HPV and HPV Vaccine Knowledge

Knowledge about HPV and HPV vaccines are often modifiable at the clinic encounter as health centers have the opportunity to educate patients and parents about the common virus and vaccine protection available. Eight studies examined HPV and HPV vaccine knowledge, as well as the source of that knowledge, as an influence on vaccination (Brewer et al., 2011; Caskey et al., 2009; Gerend et al., 2009; Gottlieb et al., 2009; Guerry et al., 2011; Licht et al., 2010; Mathur et al., 2010; Zimet et al., 2010). The results were mixed of how important these influences are on vaccine uptake, although knowledge never dissuaded vaccination. Differences may vary among parents of adolescents, whose are deciding whether or not to vaccinate their child, and young adults, who are often deciding to vaccinate themselves.

Among studies of parents of adolescents, knowledge of the HPV vaccine (but not HPV) was correlated with uptake in a small (n=82) study of parents ($t = -3.214$, $p < 0.01$) (Gerend et al., 2009). In an early survey of parents, 14% had not heard of the vaccine (13% had not seen a health care provider) and the most commonly cited (22%) reason for not initiating was the need for more information (Gottlieb et al., 2009). This study was

conducted only a year after Gardasil® became available and only 10% of those surveyed had initiated vaccination. Two later studies supported the finding that needing more information about the HPV vaccine decreased the likelihood of vaccine initiation (aOR 0.08, 95% CI 0.04-0.2) (Guerry et al., 2011) and not needing more information increased the likelihood of initiation (aRR 0.41, 95% CI 0.22-0.76) (Brewer et al., 2011).

Among young adults, in a study of 406 university females, participants who knew that HPV caused genital warts were more likely to be vaccinated (aOR 1.85, 95% CI 1.20-2.93) (Licht et al., 2010). Two years after vaccine availability, 31.7% of females reported lack of information about the vaccine as a reason for not initiating vaccination (Zimet et al., 2010).

The source of vaccine information may also influence vaccine uptake across the eligible age range. A large, nationally representative survey found that vaccinated females were more likely to identify health care providers as their source of HPV vaccine information (69%) than unvaccinated females (28%) and 77% of all participants identified their health care provider as the source of HPV information they trust most (Caskey et al., 2009). This study did not differentiate types of health care providers. One survey of 177 high school females in California asked about the source of HPV vaccine knowledge and found that learning about the HPV vaccine from a physician or nurse was associated with vaccination (Mathur et al., 2010).

Vaccine Safety Concerns

Three studies indicated that vaccine safety concerns influence vaccine uptake (Dempsey et al., 2009; Gerend et al., 2009; Zimet et al., 2010). A study interviewing mothers of 11 to 17 year old females who attended a recent health care visit found eight

of the 19 mothers of unvaccinated daughters cited safety concerns due to its recent availability as a reason for declining vaccination (Dempsey et al., 2009). Even in mothers who chose to vaccinate, seven of 33 expressed concerns about safety, but felt the benefits outweighed the risks (Dempsey et al., 2009). In 19 to 26 year old females less than two years after vaccine approval, participants reported the newness of the vaccine (35.4%) and side effect concerns (24.4%) as reasons for not initiating vaccination (Zimet et al., 2010). In a survey also approximately two years after Gardasil® availability, 24% of parents indicated the vaccine would have to be on the market for more than five years before they would feel comfortable providing it for their daughter (Gerend et al., 2009).

HPV Risk

Eight studies examined HPV risk as an influence on HPV vaccination, either through documented risk factors or risk perception (Caskey et al., 2009; Chao et al., 2010; Cook et al., 2010; Dempsey et al., 2009; Gottlieb et al., 2009; Licht et al., 2010; Moore et al., 2010; Zimet et al., 2010). Two studies examined clinical risk factors for HPV. Chao et al. (2010) found in 18 to 26 year old females that risk factors for HPV, including history of sexually transmitted infections, abnormal Pap smears and oral and transdermal contraceptive use are associated with HPV vaccine uptake. This study examined a mostly insured population and did not investigate why the association exists. Conversely, a study of university females found that sexual activity in the past 12 months, a history of a Pap smear or abnormal Pap smear, or a history of a sexually transmitted infection was not associated with vaccination (Moore et al., 2010).

Six of the studies examined HPV risk perception. Mothers (n=52) who declined vaccination for their daughters cited low HPV risk as a contributing factor in their

decision, and those who chose vaccination protection for their daughters recognized high risk of HPV in their choice (Dempsey et al., 2009). In a larger study (n=889), 12.6% of parents with unvaccinated daughters cited the belief that their daughter was not yet sexually active as a reason for not initiating the vaccine (Gottlieb et al., 2009). Thirty percent of 13 to 26 year old females also reported their lack of sexual activity as a reason for not vaccinating (Caskey et al., 2009). A study of Florida Medicaid patients (n=718,660) found sexual activity to be positively associated with vaccine initiation (OR 1.19, 95% CI 1.15-1.24) (Cook et al., 2010). However, another study of university females found that risk perception (Licht et al., 2010) had no association with vaccination. In a study of 19 to 26 year old females (n=185), the most commonly cited reason for not initiating vaccination was the belief that they were in a monogamous relationship (Zimet et al., 2010).

Discussion and Conclusions

Because of the relatively recent availability of Gardasil®, research is still in the early stages of evaluating uptake. However, a review of nineteen available studies exploring HPV vaccine uptake did reveal six potentially modifiable influences amenable to being addressed at the clinic encounter level: 1) cost and insurance coverage, 2) provider recommendation, 3) vaccination opportunity, 4) HPV and HPV vaccine knowledge, 5) vaccine safety concerns, and 6) HPV risk.

Research on HPV vaccine uptake began to take place soon after vaccine approval in 2006 and began to appear in publications in 2009. The studies reported a wide range of vaccine initiation, from 9% to 65%, which may affect specific findings, but clearly demonstrates that high vaccination rates are possible. Research examining what is

working in those areas with 65% uptake is needed, and also what is preventing vaccination in those areas with 9% vaccination rates.

HPV vaccine research has mostly focused on vaccine initiation, rather than series completion. Four of the studies identified evaluated series completion (Cook et al., 2010; Dempsey et al., 2010; Moore et al., 2010; Schluterman et al., 2011). Research on series completion is often difficult as accurate records of series completion can be difficult to obtain, and the minimum of six months between series initiation and completion may prohibitively prolong the duration of a study. In addition, influences on series completion may vary from influences on series initiation. While this literature review focused on initiation influences, future research should continue to expand to evaluate influences specific to series completion.

Much of the research has focused on adolescents as patients and their parents as providers of consent, as vaccine initiation is recommended at age 11 to 12 years old. However, catch-up vaccination is recommended by the Advisory Committee on Immunization Practices for all females through age 26 (Centers for Disease Control and Prevention, 2007), which encompasses a young adult group that will still benefit from the vaccine but may experience very different influences when facing vaccination. As adolescents transition into adulthood, they begin to make health care decisions without parental consent and often face fragmented health care delivery systems as they transition from pediatric providers to family, internal medicine, or reproductive health providers, and attend fewer preventive care visits (Rand et al., 2007). Further research is needed that focuses on the differences between the 9 to 18 year old and 19 to 26 year old populations.

In addition, much of the clinical research has studied patients who are mostly insured, or are uninsured but under the age of 19 and therefore eligible for the Vaccines for Children program. Vaccines for Children is a federally funded, state-administered program that pays for nearly half of the vaccines given to children in the United States. Young adults are not eligible for the Vaccines for Children program, leaving them with fewer cost coverage options for one of the most expensive vaccines on the market. The 19 to 26 year old age group may face unstable insurance coverage as they move through school, unemployment, or the initial years of adult employment. Further research is needed that focuses on the uninsured population and ways to remove cost barriers.

Much of the research has focused on settings in which vaccination is traditionally managed, such as primary care settings. Reproductive health centers, which often serve as the primary source of health care for young adult females, especially healthy females with primarily reproductive health needs, have been overlooked as a possible alternative means of increasing HPV vaccine uptake. Further research is needed that focuses on reproductive health centers as a means of improving HPV vaccination.

One limitation across the HPV vaccine uptake literature is the number of studies using unpublished, untested, and therefore inconsistent measurement tools to evaluate variables and concepts. Only one study reported reliability statistics for their surveys (Rosenthal et al., 2011), and no studies named the survey instruments used to allow for comparison across multiple studies and confirmation of reliability and validity.

The findings describing the association of provider characteristics with HPV vaccine initiation are limited in that they cannot explain if Pediatricians themselves, for example, are more likely to discuss, recommend, and carry vaccines, as is the case with

other vaccines, or if relationships with Pediatricians have been more longstanding by adolescence thereby increasing trust and influence, or even perhaps if those patients seeing pediatricians are more amenable to vaccination.

The literature on HPV risk as an influence on vaccination is limited, mostly focusing on risk perception rather than actual risk of HPV (Caskey et al., 2009; Cook et al., 2010; Dempsey et al., 2009; Gottlieb et al., 2009; Licht et al., 2010; Zimet et al., 2010). One study that examined HPV risk factors among young adult females did find an association between risk and uptake, which indicates there may be a useful application of HPV risk to improving vaccine uptake. However, most of the studies reviewed demonstrate a gap in our understanding of the use of HPV risk as a means of improving HPV vaccine uptake, especially in the context of organizations with limited financial resources. Many organizations with limited resources, such as Planned Parenthood Mid and South Michigan, use risk-based decision making to determine allocation of limited resources for services such as Pap smears and sexually transmitted infection testing. Further study is required to determine if risk can be used at reproductive health centers as a basis for targeting limited organizational financial resources to improve HPV vaccine uptake, making sure those with the most risk receive the most protection.

Finally, because of the rapid changes occurring since the introduction of the HPV vaccine in 2006, the existing research may already be considered outdated. Initial research at the time of vaccine availability demonstrated high acceptability of the vaccine across a variety of populations (Brewer & Fazekas, 2007), which has not translated into high vaccine uptake, preventing researchers from relying on acceptability research to develop predictors of HPV vaccine uptake. Since then, even intention to vaccinate has

not been shown to be reliable predictor of HPV vaccine uptake, with one study showing only 38% of parents who intended on vaccinating their daughter having done so a year later (Brewer et al., 2011). As a result, researchers will have to continue to study influences and predictors specific to uptake, without relying on acceptability or intention. Since its approval, the vaccination process is rapidly progressing from its initial stages of availability to a time when the health care system has had the opportunity to become knowledgeable about the vaccine, establish systems and mechanisms for its delivery, and incorporate it into routine care. Nevertheless, we know that HPV vaccine uptake remains far below the *Healthy People 2020* goal of 80% (www.healthypeople.gov), so much work remains.