Table 3.2

HPV Vaccine Uptake Studies By Influence

Influence	Study
Cost and Insurance Coverage	Caskey et al. (2009)
	Conroy et al. (2009)
	Dempsey et al. (2010)
	Jain et al. (2009)
	Moore et al. (2010)
	Schluterman et al. (2011)
	Zimet et al. (2010)
Provider Recommendation	Caskey et al. (2009)
	Conroy et al. (2009)
	Dempsey et al. (2009)
	Gerend et al. (2009)
	Gottlieb et al. (2009)
	Guerry et al. (2011)
	Rosenthal et al. (2011)
Vaccination Opportunity	Caskey et al. (2009)
	Chao et al. (2010)
	Cook et al. (2010)
	Dempsey et al. (2010)
	Reiter et al. (2010)
	Small & Patel (2011)
HPV and HPV Vaccine Knowledge	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)
Vaccine Safety Concerns	Dempsey et al. (2009)
	Gerend et al. (2009)
	Zimet et al. (2010)
HPV Risk	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)

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Chapter Four

Using Risk To Target HPV Vaccine Resources In High-Risk, Low-Resource Organizations

Introduction

The human papillomavirus (HPV) is a common and costly virus causing cervical cancer and contributing to other HPV-related diseases such as vulvar cancer, vaginal cancer, anal cancer, oropharyngeal cancer and genital warts. Among 20 to 24 year olds, 45% of females carry the virus at any one time (Dunne et al., 2007). The United States spends five billion dollars per year on the prevention and treatment of HPV, not including vaccination (Insinga, Dasbach, & Elbasha, 2005). Two vaccines are available for preventing infection with HPV-16 and HPV-18, two strains of HPV that cause 70% of all cases of cervical cancer. In 2006, the Advisory Committee on Immunization Practices (ACIP) recommended that all females receive the HPV vaccine starting at age 11 to 12, with catch-up vaccination through age 26 (Centers for Disease Control and Prevention, 2007). Five years after the recommendation was established, HPV vaccine uptake still remains low, especially among young adult females. Estimates suggest that series initiation is only 17% for the young adult population and series completion rates substantially lower (Centers for Disease Control and Prevention, 2010).

Organizations with limited financial resources serving a mostly uninsured population often have difficulty supporting the cost of the HPV vaccines, which is the most expensive routinely recommended vaccine for adolescents and young adults. The private sector cost for the vaccines is $128 to $130 for each dose in the three dose series, and in the public sector the cost is $96 to $108 for each dose. Added to the cost is the additional fee for vaccine administration (Centers for Disease Control and Prevention, 2011). In addition to the high vaccine cost is the problem that organizations with limited financial resources typically serve populations at high risk for HPV, such as young adults and those with multiple sexual partners, who are often un- or underinsured. Thus, organizations must often finance the cost burden associated with HPV-related disease for their patients, such as abnormal Pap smear management or genital wart treatment.

For organizations with limited financial resources it can be difficult to determine whether it is better to use these resources for HPV vaccination versus management of HPV-related diseases, or whether some type of "hybrid" strategy, such as vaccinating only the highest risk individuals, is a reasonable middle ground. Risk stratification to allocate limited resources is already being used by these organization for some services, for example paying for the cost of sexually transmitted infection testing or birth control methods, but only among certain high-risk subgroups such as adolescents or individuals with new sexual partners. It is unknown whether a similar risk-based strategy would be feasible or advantageous for an organization if applied to HPV vaccine administration, even though targeted vaccination is not a feasible strategy at the population level (Dempsey, Gebremariam, Koutsky, & Manhart, 2008). To address this question, we determined the costs and clinical impacts of three different organizational approaches to

female HPV vaccination in a low-resource setting, including vaccinating everyone, vaccinating no one, or vaccinating only those considered high-risk.

Methods

Overall Study Design

Clinical and economic impacts were assessed using decision tree analysis for three different HPV vaccination approaches of young adult females attending low-resource health centers serving a high-risk population. The three HPV vaccination approaches were 1) vaccinating all females in this health center population, 2) vaccinating none of the females in this population, or 3) vaccinating only the proportion of this population that have risk factors identified as being associated with HPV infection and/or disease in this population.

Risk Factors

To increase applicability of the decision tree model to the high-risk population seen by low-resource organizations such as Planned Parenthood, we first assessed whether a variety of behavioral/historical factors identified in other studies (National Cancer Institute, 2010; National Cancer Institute, 2011) were associated with the HPV-related outcomes of abnormal Pap smears and genital warts in this particular patient population. For the risk factor analyses, we considered only those variables that could be readily elicited during a typical clinical encounter and therefore potentially used for delivering a targeted vaccination strategy to this clinical population. The risk factors assessed included whether there had been a sex partner change in the past six months (yes/no), age at first intercourse, condom use (never or sometimes/usually or always), history of forced sex (yes/no), current smoking (yes/no), history of oral contraceptive use

(yes/no), and family history of cervical cancer (yes/no). All risk factors analyzed were dichotomous except the continuous variable "age at first intercourse." To facilitate inclusion in a decision tree analysis, age at first intercourse was transformed into a categorical variable by first converting it to number of years of sexual activity. This continuous variable was then dichotomized, testing all possible points of division. The division with the association with the greatest significance with HPV infection (history of abnormal Pap smear specifically) fell between zero and five years, and six and 15 years of sexual activity. The final categorical variable used in place of age of first intercourse was, therefore, years of sexual activity, zero to five years and six to 15 years.

Associations between these risk factors and HPV-related outcomes (abnormal Pap smears or genital warts) were evaluated based on cross-sectional data derived from two high-risk, low-resource reproductive health centers in the Planned Parenthood Mid and South Michigan (PPMSM) affiliate. Data was collected for the first six months of HPV vaccine availability at the two reproductive health centers, between May 1, 2010 and October 31, 2010. Participants were included in the convenience sample if they 1) attended an annual exam during the six months of data collection, a visit when the necessary history and laboratory results were obtained, 2) were female, as the ACIP recommendation for universal vaccination applied only to females at this time, and 3) were between the ages of 19 and 26, as the reproductive health centers in the study limit vaccine availability to this age group. All patient history forms and laboratory results were identical between the two health centers and routinely used by the health centers for patient care. The University of Michigan Institutional Review Board, Planned

Parenthood Mid and South Michigan, and Planned Parenthood Federation of America, Inc. approved all study activities.

To determine which risk factors might be useful for a targeted vaccination strategy, bivariate associations between the above individual risk factors and each of the two HPV-related outcomes (history of abnormal Pap smear and history of genital warts) were calculated using chi-square tests. Of the two HPV-related outcomes, only history of abnormal Pap smear was found to have significant risk factors. Therefore, history of genital warts was excluded from further analysis. Risk factors found in the bivariate analyses to be significant ($p<0.05$) were then included in a multivariable model to determine independent predictors of the outcome.

Decision Tree Structure

Decision tree analysis utilizes an algorithm approach to assessing uncertainty in costs and probabilities, and quantifies the value of outcomes in different scenarios, allowing for more objective decision-making. To assess the impact of the three different vaccination strategies, a decision tree analysis was used to evaluate resulting costs and clinical endpoints (Figure 4.1). When available, the model was parameterized by using data derived directly from PPMSM data. The decision tree assumed annual costs, probabilities, and projected outcomes over a one- year period. Thus, no discounting for future costs was considered. This time frame was selected as low-resource organizations tend to rely on fluctuating funding that is determined annually, and often have a somewhat transient patient population that may not use care in these settings longitudinally.

Probabilities. We used PPMSM data specifically to define the cost of the vaccine, the probability of being vaccinated with HPV previously (for risk-based vaccination and vaccinating no one strategies), and the probability of having a normal or abnormal Pap smear if unvaccinated. Parameters that could not be defined from PPMSM data directly (costs of normal and abnormal Pap smears) were developed using estimates from the literature (Insinga, Glass, & Rush, 2004). See Table 4.1 for baseline values for the model and ranges used in sensitivity analyses (described below).

Probability of vaccination. When vaccinating everyone, the probability variable for becoming vaccinated was valued at 1.0, recognizing that a 100% vaccination rate may not be able to be replicated in reality, but was used as a best-case scenario for the model. The probability variable for being vaccinated when the organization vaccinated no one was 0.18, as PPMSM data indicated that 18% of the population studied had previously initiated or completed vaccinated elsewhere. When utilizing a risk-based vaccination strategy, the percentage of participants in the two reproductive health centers with the particular risk factor being tested was used as the probability of vaccination variable.

Probability of normal and abnormal Pap smears. To determine the probability variables for normal and abnormal Pap smears if a participant was vaccinated, a best-case scenario was used with all vaccinated individuals assumed to have normal Pap smears. For unvaccinated participants, it was calculated that 12% would have an abnormal Pap smear, based on Pap smear results from the annual exam during the time period studied at the two reproductive health centers.

Costs. The cost of the vaccine was considered to be $90, derived from the cost the two reproductive health centers charged patients in administration fees for receiving

the full three dose series. Costs of the purchase of vaccine itself were assumed to be covered by either the patient's insurance, or more commonly, the Merck Vaccine Patient Assistance Program, which can be utilized by the mostly uninsured, low-income patient population.

Costs for normal and abnormal Pap smears were derived from a study using Kaiser Permanente Northwest data (Insinga, Glass, & Rush, 2004) (See Table 4.1). In this study, the researchers analyzed the costs of cervical HPV from 103,476 health plan participants between 1997 to 2002. The results were applicable to this model as they provided a per person average cost of normal and abnormal Pap smears, although 10% of the overall costs were attributable to invasive cervical cancer which low-resource organizations rarely support due to referral of services.

Sensitivity analyses. A one-way sensitivity analysis on all cost and probability variables was run to determine the impact of parameter uncertainties on the model. A wide range of possible probabilities and costs were applied to increase model utility beyond the specific organization used to develop the model parameters. See Table 4.1 for sensitivity analysis ranges. For the cost of the vaccine, the range included no cost as well as the total cost of the vaccine plus administrative fees charged by the two reproductive health care organizations for patients without insurance or the Merck Vaccine Patient Assistance Program ($540).

Statistics

For the initial analysis to determine which risk factors to use in a targeted vaccination strategy, we used PASWStatistics 18.0 to calculate chi-square results for bivariate associations between risk variables and HPV-related outcomes. We then

performed logistic regression from the statistically significant bivariate associations to establish independent predictors of HPV-related outcomes. Demographic and descriptive data was also calculated using PASWStatistics 18.0. To develop and test the three vaccination strategies, TreeAge Pro 2011 was utilized for decision tree analysis. Sensitivity analyses were then performed on all cost and probability variables to test the base case parameter values described above, also using TreeAge Pro 2011. Participants with missing data for a variable were excluded.

Results

A total of 678 participants were included in the health center sample used to parameterize the model. Most participants (72.8%) were uninsured, while 18.6% were privately insured and 8.6% had public insurance. Very few data points were missing from the sample. See Table 4.2 for complete sample data.

Assessment of Risk Factors

Risk factors described above (partner change in the past six months, years of sexual activity, condom use, forced sex, smoking, history of oral contraceptive use, and family history of cervical cancer) were assessed for associations with two HPV-related outcomes- abnormal Pap smears and genital warts. Of these factors, only years of sexual activity (x^2=35.533, p=0.000) and smoking (x^2=5.349, p=0.021) were significantly associated with a history of abnormal Pap smears. For a complete list of bivariate calculations, see Table 4.3. In a multivariable logistic regression model that included years of sexual activity and smoking, only years of sexual activity remained significantly associated with a history of abnormal Pap smear (p=0.000). Thus, years of sexual activity was used as the decision point in the risk-based vaccination strategy arm of the

model. A cutoff of five years of sexual activity was chosen, as this was the point that showed the largest significance when testing bivariate associations of risk factors for HPV-related outcomes. Figure 4.1 shows the general model structure.

Decision Tree Analysis

The decision tree indicated that the three vaccination strategies produced only small variations in clinical costs and outcomes. The least expensive organizational strategy was to vaccinate no one ($123.42 per person). The organizational strategy to vaccinate everyone prevented the greatest number of abnormal Pap smears (see Table 4.4).

One-way sensitivity analyses were then performed for all probability and cost variables to determine the impact of parameter uncertainties on the conclusions from the model (see Table 4.1). Sensitivity analyses for cost outcomes demonstrated that vaccinating based on risk factors was never the least expensive strategy, even when large ranges in costs and probabilities were considered. Instead, the model overall was most sensitive to varying the cost of the vaccine, the cost of an abnormal Pap smear, the probability of being vaccinated if the organization vaccinates no one (for example, people receive the vaccine elsewhere), and the probability of unvaccinated patients having a normal Pap smear. For example, a threshold value of $81 was found for the cost of the vaccine, such that if the cost of the vaccine was $81 or less, the less expensive strategy from an organizational standpoint was to vaccinate everyone, whereas when the cost of the vaccine exceeded $81, the less expensive strategy was to vaccination no one. See Table 4.1 for all threshold values.

Discussion

Key Results

Prior to the study, it was hypothesized that targeting vaccination, while not a useful strategy for the larger population, may be a useful strategy for high-risk, low-resource organizations. This study found that hypothesis to be incorrect. Under no condition (either using base-case estimates or in any of the sensitivity analyses) in the model was targeting vaccination using risk factors better than vaccinating everyone or no one in terms of costs or clinical outcomes. Instead, under most conditions, vaccinating no one was found to be least expensive strategy, and vaccinating everyone was found to prevent greatest numbers of abnormal Pap smears. However, there was surprisingly little difference in cost among the three strategies tested, indicating the improvement in clinical outcomes when vaccinating everyone may be worth the relatively small increase in cost when vaccinating everyone.

Variability in the cost of the HPV vaccine and abnormal Pap smears, as well as the probability of vaccination outside of the organization and the probability of having a normal Pap smear if unvaccinated, changed the optimal vaccination strategy chosen. Changes in these variables are clinically relevant. If the organization is able to reduce costs of vaccine administration through utilizing outside resources such as the Merck Vaccine Patient Assistance program, the benefits of vaccinating everyone clearly exceed vaccinating no one. Vaccination includes three doses in the series (the immunization impact of receiving fewer doses is unknown), although some patients may end up receiving fewer doses from the organization as a result of series initiation elsewhere, or non-completion of the series.

This model assumed everyone in the 19 to 26 year old age group receives a Pap smear every year. However, updated recommendations by the American College of Obstetricians and Gynecologists for cervical cancer screening advise no Pap smear testing until age 21, and then Pap smear testing every two years thereafter. Decreased frequency of Pap smears overall and decreased probability of abnormal Pap smears influence the probabilities and costs of Pap smears for an organization, which may influence their vaccination strategy decision. However, the model was not found to be sensitive to the cost of normal Pap smears, indicating the updated guidelines may not affect the results of this study.

Finally, the model was sensitive to the number of people vaccinated outside of the organization, which is clinically relevant. As this model suggests, placing the cost burden of vaccination on health care organizations serving young adults may be too great for low-resource organizations to bear. These findings further support the ACIP recommendation for all females to receive HPV vaccination at age 11 to 12 years old.

Limitations

One limitation of the study was that the decision tree variable considerations were limited to costs and probabilities of HPV vaccination and Pap smears. In the population studied, 4.5% of participants reported a history of genital warts and an additional 1.2% were diagnosed with genital warts at the annual exam. Because genital warts was not found to have a statistically significant association with risk in this population sample, and other HPV-related health outcomes such as vulvar or vaginal neoplasia were not diagnosed at any of the annual exams, the additional organizational costs of these HPV-related diseases were not included in the model. However, one of the available HPV

vaccines (Gardasil®) helps protect against genital warts, as well as vulvar and vaginal cancer, and therefore, potential cost savings and clinical outcomes from vaccinating may have been underestimated.

Additional simplifying assumptions were made in the decision tree model to increase model utility in practice but which may have affected the results of the study. For example, it was assumed that once someone became vaccinated, they would not have an abnormal Pap smear, despite the possibility, especially in the 19 to 26 year old age group, that participants may have been infected with HPV prior to vaccination, and that vaccination is believed to reduce abnormal Pap smears by only 30-40% since many HPV types not included in the vaccine result in Pap smear abnormalities. Therefore, people who receive vaccination may still incur an abnormal Pap smear and the associated costs. This assumption may have resulted in an overestimation of the benefits of vaccination in the model.

It was assumed that the organization could receive free vaccine for all patients from either the Merck Vaccine Patient Assistance Program or insurance, and therefore would only support the cost of administration, despite knowing that some uninsured patients would not qualify for the Merck Vaccine Patient Assistance Program and some insurance companies would not pay for vaccination, thereby underestimating the cost of the vaccine for the organization.

A 100% vaccination rate was assumed in the "vaccinate everyone" strategy, despite the possibility of patient refusal of vaccination or allergies to the vaccine, which may have overestimated the probability of vaccination in that strategy and affected results. Vaccine series completion was assumed despite knowing that many people who

start the vaccine series are lost to follow up, which may have resulted in an overestimation of vaccine cost or an underestimation of vaccine benefit.

In addition, some parameter estimates were decided without reference to the literature or PPMSM data, including the probability of 100% vaccination if a strategy of vaccinating everyone is used, and the probability of having a normal Pap smear once a participant was vaccinated. To minimize the impact of these limitations, extensive sensitivity analyses were performed using a wide range of possible cost and probability estimates for all variables. Overall, we found our model to be generally robust in its conclusions.

A final limitation of the study was the use of cross-sectional data among a small population to define parameter estimates. The lack of longitudinal data prevented the predictive ability of HPV infection outcomes from risk factors, and relied instead on statistical associations. Also, using just two reproductive health centers in the population studied limited results. To try to decrease selection bias, the health centers were in large, racially diverse cities in southern Michigan, all female patients presenting for annual exams were included, and two health centers were used instead of just one. However, because targeting was not found to be the preferred vaccination strategy, the significance of this restriction is limited.

Generalizability

This study was specific to a population with higher rates of abnormal Pap smears and a higher rate of uninsured individuals than the greater population. This may limit the generalizability of the study to other populations and organizations. However, sensitivity analyses provided useful threshold values for other organizations considering use of this

model. Furthermore, ranges used in the sensitivity analyses were likely outside of plausible ranges, for example, using the complete range of 0 to 1.0 for probabilities, but the overall model remained robust, which supports the generalizability of the model.

Conclusion

Many health care organizations are able to rely on insurance companies for reimbursement of the cost of HPV vaccines and abnormal Pap smear follow up. However, some organizations supporting a largely uninsured population have to make decisions on how to best allocate limited funds to provide the greatest good. This study showed little difference in cost outcomes whether or not the organization supported the cost of HPV vaccination for everyone, no one, or those at high risk, although vaccinating no one was still the least expensive option, and vaccinating everyone produced the least number of abnormal Pap smears.

The findings and conclusions in this article are those of the author and do not necessarily represent the views of Planned Parenthood Federation of America, Inc.

Table 4.1

Baseline Values for Decision Tree Model

Variable	Baseline Value	Sensitivity Analysis Range	Sensitivity Analysis Threshold	Reference
Cost of Normal Pap	$57	0-$200	not applicable	(Insinga, Glass, & Rush, 2004)
Cost of Abnormal Pap	$732	0-$1,000	$807	(Insinga, Glass, & Rush, 2004)
Cost of Vaccine	$90	0-$540	$81	PPMSM
Probability of Vaccination				
No one	0.18	0-1.0	0.089	PPMSM
Everyone	1.0	0-1.0	not applicable	-
Risk	0.39	0-1.0	not applicable	PPMSM
Probability of Normal Pap				
If vaccinated	1.0	0-1.0	not applicable	-
If unvaccinated	0.88	0-1.0	0.87	PPMSM

Table 4.2

Characteristics of Participants Used to Assess Association of Risk Factors With HPV-Related Outcomes (n=678)

Variable	Result: Total	Result: Clinic A	Result: Clinic B
Age: Mean	22.9 (SD=2.1)	22.9 (SD=2.0)	22.9 (SD=2.1)
Annual Household Income			
Mean	$19,450 (SD=$18,277)	$20,073 (SD=$20,448)	$18,372 (SD=$13,710)
Median	$14,400	$14,400	$14,872
Race			
White	65.4% (n=435)	67.5% (n=283)	61.8% (n=152)
Black/ African American	20.3% (n=135)	17.2% (n=72)	25.6% (n=63)
Other	5.6% (n=37)	6.2% (n=26)	4.5% (n=11)
Asian	4.1% (n=27)	4.8% (n=20)	2.8% (n=7)
More Than One	3.3% (n=22)	3.3% (n=14)	3.3% (n=8)
Native Hawaiian/ Pacific Islander	0.6% (n=4)	0.7% (n=3)	0.4% (n=1)
Native American/ Alaska Native	0.5% (n=3)	0.0% (n=0)	1.2% (n=3)
Choose Not To Answer	0.3% (n=2)	0.2% (n=1)	0.4% (n=1)
Ethnicity			
Non-Hispanic	91.6% (n=619)	89.3% (n=384)	95.5% (n=235)
Hispanic	8.4% (n=57)	10.7% (n=46)	4.5% (n=11)
Marital Status			
Single	90.6% (n=572)	88.9% (n=352)	93.6% (n=220)
Married	4.9% (n=31)	5.6% (n=22)	3.8% (n=9)
Choose not to respond	3.2% (n=20)	34.5% (n=18)	0.9% (n=2)
Divorced	0.8% (n=5)	0.5% (n=2)	1.3% (n=3)
Separated	0.5% (n=3)	0.5% (n=2)	0.4% (n=1)
Insurance			
Private	18.6% (n=126)	20.5% (n=88)	15.4% (n=38)
Public	8.6% (n=58)	5.6% (n=24)	13.8% (n=34)
Uninsured	72.8% (n=492)	73.9% (n=317)	70.9% (n=175)
Age at First Intercourse: Mean	16.4 (SD=2.2)	16.7 (SD=2.2)	16.1 (SD=2.2)
Partner Change in the Past Six Months			
No	68.0% (n=444)	66.3% (n=273)	71.0% (n=171)
Yes	32.0% (n=209)	33.7% (n=139)	29.0% (n=70)
Condom Use			
Never	21.9% (n=146)	22.8% (n=97)	20.2% (n=49)
Sometimes	33.5% (n=224)	31.9% (n=135)	36.6% (n=89)
Usually	23.2% (n=155)	24.7% (n=103)	21.4% (n=52)
Always	21.0% (n=140)	20.7% (n=88)	21.4% (n=52)
No history of sexual activity	0.4% (n=3)	0.5% (n=2)	0.4% (n=1)

History of Forced Sex			
No	89.7% (n=603)	89.7% (n=382)	89.8% (n=221)
Yes	10.3% (n=69)	10.3% (n=44)	10.2% (n=25)
Current Smoking			
No	68.9% (n=464)	72.1% (n=307)	63.6% (n=157)
Yes	31.1% (n=209)	27.9% (n=119)	36.4% (n=90)
History of Oral Contraceptive Pill Use			
No	28.0% (n=189)	28.2% (n=121)	27.5% (n=68)
Yes	72.0% (n=487)	71.8% (n=308)	72.5% (n=179)
Family History of Cervical Cancer			
No	98.5% (n=666)	98.1% (n=421)	99.2% (n=245)
Yes	1.5% (n=10)	1.5% (n=8)	0.8% (n=2)
History of Abnormal Pap Smear			
No	72.0% (n=483)	74.8% (n=318)	67.1% (n=165)
Yes	28.0% (n=188)	25.2% (n=107)	32.9% (n=81)
History of Genital Warts			
No	95.5% (n=644)	96.0% (n=410)	94.7% (n=234)
Yes	4.5% (n=30)	4.0% (n=17)	5.3% (n=13)

Table 4.3

Bivariate Associations Between Risk Factors and HPV-Related Outcomes

Risk Variable	HPV-Related Outcome Variable	Association
Years of Sexual Activity	History of Abnormal Pap Smear	x^2=35.533, p=0.000
	History of Genital Warts	x^2=1.466, p=0.226
Partner Change in the Past Six Months	History of Abnormal Pap Smear	x^2=0.332, p=0.564
	History of Genital Warts	x^2=0.234, p=0.628
Condom Use	History of Abnormal Pap Smear	x^2=3.603, p=0.058
	History of Genital Warts	x^2=1.183, p=0.277
History of Forced Sex	History of Abnormal Pap Smear	x^2=0.065, p=0.798
	History of Genital Warts	x^2=0.000, p=1.000
Current Smoking	History of Abnormal Pap Smear	x^2=5.349, p=0.021
	History of Genital Warts	x^2=1.620, p=0.203
History of Oral Contraceptive Pill Use	History of Abnormal Pap Smear	x^2=0.000, p=1.000
	History of Genital Warts	x^2=0.605, p=0.437
Family History of Cervical Cancer	History of Abnormal Pap Smear	x^2=0.044, p=0.834
	History of Genital Warts	x^2=0.000, p=1.000

Table 4.4

Decision Tree Analysis Outcomes for Three Vaccination Strategies

Outcome	Vaccination Strategy		
	No One	Everyone	Risk
Cost* (per person)			
Expected value	$123.42	$130.80	$141.51
Clinical			
Normal Pap smear	90%	100%	93%
Abnormal Pap smear	10%	0%	7%

** Includes cost of vaccination and cost of normal and abnormal Pap smears*

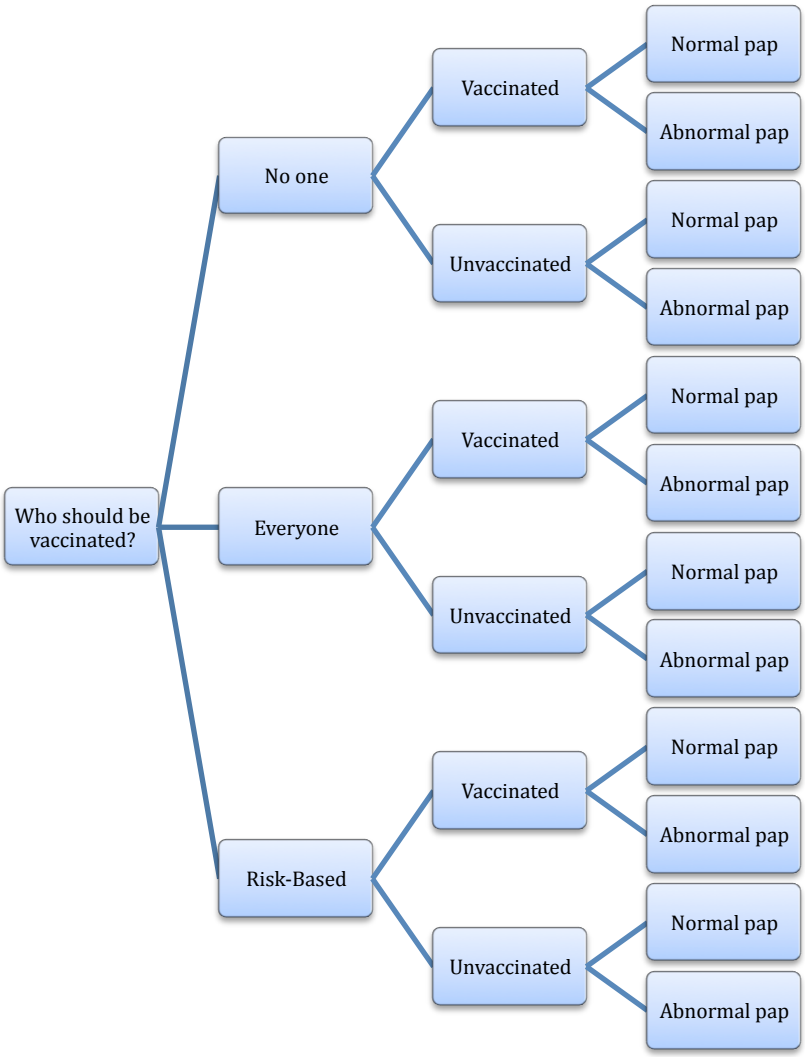

Figure 4.1. Base case decision tree model.

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Chapter Five

Conclusion

This final chapter will serve to synthesize the information provided in the previous chapters of this dissertation. First, the chapter will provide a summary of the major research findings presented in this dissertation, then a discussion of the significance of the research. Next, there will be an overview of the major strengths and weaknesses of the research. Finally, directions for future research will be considered.

Overview of the Major Research Findings

In the Introduction, an ecological model of HPV vaccine uptake was proposed as a conceptual framework for this dissertation and HPV vaccine uptake research more broadly. The ecological model demonstrated that whether or not an individual receives the HPV vaccine results from a variety of influences on many levels, from national and state public policies, to influences of health care organizations, to individual demographics and characteristics. This dissertation focused on national and state public policies (Chapter Two) and health care organization factors (Chapter Three) that influence HPV vaccination and then evaluated a strategy for utilizing those factors to increase HPV vaccine uptake at an organizational level (Chapter Four).

In Chapter Two, a history of HPV vaccine policy was reviewed demonstrating that federal and state public policies were restricted in asserting responsibility for

vaccinating the population, leaving health care organizations to fill the vacuum where large scale population level improvements in vaccination are less likely to occur. The federal government limited its HPV vaccine policy involvement to approving the HPV vaccines through the FDA, recommending evidence-based universal vaccination for all females through the ACIP, and providing some vaccine funding to states for specific subgroups of the population through the Vaccines for Children program.

Once federal policy was established, states began to establish their involvement in HPV vaccination. Initially, a flurry of media coverage surrounded vaccination branding it controversial, and legislation ranged from education to funding to inclusion of the HPV vaccine in school entry requirements. Because vaccine inclusion in school entry requirements is one of the most effective means of increasing vaccination rates in a population, the opportunity for states to significantly influence HPV vaccine uptake was particularly important. However, no states, except for Virginia and Washington, DC, managed to pass legislation to include the HPV vaccine in school entry requirements, and legislation that managed to pass in those locations was weaker than the legislation for other vaccines. Furthermore, the legislation is at risk of future reversal, as a bill has been introduced in Virginia to overturn the initial legislation. States argued in favor of parental rights, abdicating their public health responsibility and opting instead to leave individuals accountable for vaccination. Time will tell if state legislation will have any impact on vaccination rates.

Looking to the future, the Affordable Care Act provides an alternative strategy to improving vaccination by increasing the number of people with insurance, increasing insurance coverage for young adults until age 26, and increasing preventive care

insurance coverage, including vaccines and the preventive maintenance visits during which vaccination is usually addressed. While these measures address a very important influence on vaccination, cost and insurance coverage (see Chapter Three), time will tell if the change is enough to substantially improve vaccination rates population wide.

The literature review in Chapter Three evaluated which factors, modifiable at the patient encounter in health care organizations, influence HPV vaccine uptake. The findings included the stronger influences of cost and insurance coverage and provider recommendation, as well as other influences including vaccination opportunity, HPV and HPV vaccine knowledge, vaccine safety concerns and HPV risk.

Cost and insurance coverage are consistently associated with vaccine uptake, especially among young adults who are not eligible for federally funded programs such as Vaccines for Children. Health care providers, especially Pediatric providers and providers who strongly recommend the vaccine, are influential in vaccination. Similarly, females with an opportunity to vaccinate, such as those with a recent health care visit or a preventive maintenance visit in particular, are more likely to receive the vaccine, and most who receive the vaccine name health care providers as their source of HPV vaccine information. Concerns over vaccine safety influenced vaccine uptake for some in the first couple of years of availability, and parents in particular may base vaccination decisions on the perception that their child is or is not at risk for HPV.

As a result of the findings in Chapter Two and Chapter Three, an evaluation of three possible strategies to increase HPV vaccine uptake at the organizational level was tested in Chapter Four. In Chapter Two, it was found that organizations were largely responsible for vaccinating their own patients, due to the lack of larger effective policies

at the national and state levels. In Chapter Three, it was found that the cost of the vaccine was a significant influence on HPV vaccine uptake for individuals. Therefore, Chapter Four tested three organizational strategies aimed at eliminating the cost of the HPV vaccine for individuals (to increase HPV vaccine uptake) that would also decrease the cost of other HPV-related outcomes for the organization, providing the greatest good for the least cost. The three organizational strategies tested included vaccinating everyone, vaccinating no one, or targeting HPV vaccination to those at highest risk. To determine who was at highest risk, HPV risk factors specific to two Planned Parenthood Mid and South Michigan health centers were identified using information routinely gathered at the annual preventive maintenance visit. The three strategies were then tested using decision tree analysis, which calculated very little difference in cost among the three strategies, although the least expensive strategy was to vaccinate no one, and the strategy with the best clinical outcomes was for the organization to vaccinate everyone.

Significance

This research contributes to the field in that it seeks to place the problem of low HPV vaccine uptake in the context of broader influences, rather than placing responsibility for vaccination entirely on the individual. While it is the individual, or the individual's parent or guardian in the case of minors, that ultimately decides whether or not to vaccinate, for many people the option to vaccinate is pre-determined by decisions made by larger political and organizational entities. For example, when the federal government recommends universal vaccination for all females, and states vote to include the vaccine in school entry requirements, and a health care provider recommends the vaccine, and the cost of the vaccine to the patient is free, those influences, which are

decided by others and beyond the control of the individual, often facilitate the individual's decision to vaccinate. However, if the individual does not realize that they should receive the vaccine because it is not included in the school entry requirements, or their health care organization does not stock it due to cost, or their health care provider does not discuss it, and the cost to an uninsured, low-income patient makes the vaccine unaffordable, then the decision to vaccinate is essentially no longer their own. In these instances, decisions and influences beyond the individual determine their vaccination status. Therefore, while individual influences must still be attended to, we should not lose sight of the power and importance of policy at federal, state and organizational levels to improve HPV vaccine uptake.

Application to Practice: Public Policy Level

By examining the issue of HPV vaccine uptake at a variety of levels in this dissertation, the importance of different influences at various levels was highlighted. At the public policy level, this research demonstrated that for a substantial reduction in HPV-related disease that results in cost-effective vaccination, improvement in HPV vaccine uptake must be addressed at the population level. One of the most effective population level policies for improving vaccine uptake has historically been the inclusion of vaccines in school entry requirements. However, as discussed in Chapter Two, states chose individual rights and parental control over cost-effective population level HPV disease reduction when debating school entry requirements. Furthermore, the school entry requirements that Virginia and Washington, DC did pass were much weaker than school entry requirements for other vaccines, potentially undermining future vaccination efforts for other vaccines as parents learn to easily navigate the opt out system. As such,

policymakers passed along the responsibility for vaccination to health care organizations and individuals where achieving high rates of vaccination is less likely to occur.

In light of the current political and fiscal constraints emphasized in budget negotiations and health care reform debate, cost-effective health care may in the future become a stronger priority for policymakers than individual rights and parental control. Should politicians desire cost-effective health care, they will likely need to re-examine their previous priorities and enact legislation that provides a population level vaccination strategy such as school entry requirements. Support and recommendations for implementation of school entry requirements by organizations such as the National Vaccine Advisory Committee (National Vaccine Advisory Committee, 2008) and the Society for Adolescent Medicine (Society for Adolescent Medicine, 2008) can provide the framework for building legislation.

By choosing to return to school entry requirements, politicians may again face a controversy-seeking media raising concerns about HPV vaccination leading to riskier sexual activity in adolescents, a concern commonly raised with other safer sex interventions such as improving contraceptive knowledge, expanding access to emergency contraception, or increasing condom availability, despite consistent findings that such interventions decrease sexual risk. They may also face parents who believe school-entry requirements take away their right to decline vaccination, despite consistent safeguards in legislation that allow for the parent to refuse vaccine protection for their child. However, if politicians continue to prioritize individual rights and parental control over cost-effective disease reduction, health care organizations and individuals will have to continue to do the best they can to improve HPV vaccine uptake in their own patient

population, finding ways to vaccinate the greatest number of patients possible with the financial resources available to them.

In the meantime, public policy is trying out an alternative strategy to improve HPV vaccine uptake without having to debate HPV vaccination directly or enact school entry requirements specifically. To try to support cost-effective health care delivery, Congress passed the Affordable Care Act, utilizing evidence and recommendations from organizations such as the United States Preventive Services Task Force and the Institute of Medicine, with the intention of eliminating cost as a barrier to individuals and organizations by increasing the number of people with health insurance and requiring that preventive services (including vaccination and the preventive maintenance visits that address vaccination) be covered by insurance. While the overall effect of the Affordable Care Act on population level HPV vaccine uptake remains to be tested, it serves as a potentially viable alternative to the proven difficulties of passing HPV vaccine school entry requirement legislation, and the proven ineffectiveness of trying to fully vaccinate a population with a limited public policy strategy.

If the Affordable Care Act is ultimately overturned, or fails to produce the anticipated health benefits, and policymakers choose not to revisit school entry requirements as a means of improving HPV vaccine uptake, they can hope for improvements resulting from incentives provided by national partners, such as the national Healthcare Effectiveness Data and Information Set (HEDIS). HEDIS, a national survey tool designed to compare health insurance plans, will start measuring HPV vaccination rates for 13 year olds in 2012. Some insurance companies use HEDIS results to incentivize or penalize health care providers to improve health care measures,

including vaccination, which may or may not have an impact on HPV vaccination. Or, policymakers may hope that the recommendations provided by various national organizations such as the ACIP or the Institute of Medicine will translate into other future strategies that will improve vaccination someday.

Ultimately, without a more effective public policy strategy, policymakers have the option of charging health care organizations with the task of improving HPV vaccine uptake on their own by addressing health care organization level influences (Chapter Three), with the understanding that population level disease reduction and cost-effectiveness is less likely.

Application to Practice: Health Care Organization Level

Because federal and state public policymakers have so far chosen to limit their role in developing HPV vaccination strategies, Chapter Three extracted influences organizations can focus on to improve vaccination for their own patients. While the influences were not a comprehensive gathering of all possible influences on HPV vaccination, the influences that organizations have the ability to address and modify were reviewed. As organizations implement their own vaccination strategies, they can use the influences discussed in Chapter Three (cost and insurance coverage, provider recommendation, vaccination opportunity, HPV and HPV vaccine knowledge, vaccine safety concerns and HPV risk) to facilitate an individual's decision to vaccinate, improving vaccination rates, and reducing HPV-related disease and associated health care costs in individuals.

This research in many ways confirms previous research supporting the ACIP-recommended universal vaccination and encouraging the reduction of barriers to

vaccination. Even when testing specific situations where low-resource organizations may be able to target young adult vaccination in an attempt to reduce the cost burden of vaccination to an organization (Chapter Four), the results still indicate very little difference in cost outcomes, and improved clinical outcomes, when investing in vaccinating everyone versus no one or only certain high-risk populations. This research is applicable to practice, suggesting organizations should look beyond the initial cost of the vaccine to the potential savings they receive from the benefits of vaccination.

Major Strengths and Weaknesses of the Work

Strengths

As indicated above, two major strengths of this dissertation are the placement of HPV vaccine uptake within the context of broader influences, and its applicability to practice. The dissertation recognized the complexity of the problem, while avoiding the immobilizing effect such complexity has the potential to render. The information presented and analysis conducted is intended for immediate clinical use, rather than purely for knowledge development or the support of future research. In addition, the literature review in Chapter Three used factors that measured HPV vaccine uptake directly, rather than attitudes, beliefs, or intentions to vaccinate, and the data used for analysis in Chapter Four was based on actual health centers and used a broad range of values with similar conclusions, further anchoring the dissertation in practicality and applicability to settings other than Planned Parenthood.

Weaknesses

While placing HPV vaccine uptake in the context of broader influences is a strength of the dissertation, it can also serve as a weakness. The dissertation does not

measure the direct effect of public policy on HPV vaccination (Chapter Two), but rather describes the history that led to the current state of HPV vaccination policy, and infers from policy research in other scenarios that it would have also influenced HPV vaccine uptake. For example, we can infer from Australia's success with a national policy to vaccinate all females against HPV that the lack of a national vaccine implementation policy in the United States is limiting uptake here and that the Affordable Care Act may or may not serve as a viable alternative national policy. Or it could be inferred that success with high Hepatitis B vaccination rates from state implemented school entry requirements in the United States would have resulted in similarly high HPV vaccine rates had legislation passed among the states.

Placing HPV vaccine uptake in the context of broader influences is also a weakness in that it creates a complex interplay of multiple levels of influence that is difficult, if not impossible, to evaluate in its entirety. To include all variables on all levels with the resulting confounding effects would not only be difficult, it would be impractical in terms of creating change within the health care system that facilitates HPV vaccine uptake. Focusing on those variables that are modifiable (Chapter Three) and most influential (Chapters Two, Three, and Four) to support interventions is necessary, without losing perspective of the more complex system.

An additional weakness of this dissertation is that it does not address individual influences outside of the health care organizations, such as the influence of a partner's vaccination beliefs, or a previous negative experience with vaccination. The practicality of addressing those concerns is limited when planning effective policy or organizational

interventions and should be addressed as needed on an individual basis by health care providers and patients.

Furthermore, while Chapters Two and Three include all ages eligible for vaccination, the hypothetical interventions in Chapter Four are limited to data based on 19 to 26 year old females. HPV vaccine research is often divided into two groups, adolescents and young adults, as they often face different influences from parental involvement to insurance coverage to health care opportunities. And with the potential for more males becoming vaccinated since Gardasil's® approval in 2009 for males, differences in sex, which was not addressed in this dissertation, may become a greater issue for clinicians and researchers.

Finally, an important weakness in the dissertation is the focus on vaccine series initiation in Chapter Three, and an assumption of vaccine series completion in Chapter Four. Because the HPV vaccine is a three dose series, series completion is emerging as a clinical and research challenge. Many individuals are starting the series, but failing to complete the series without adequate follow up. Much of the research focuses on series initiation, as following patients longitudinally for at least six months between the start and end of the series becomes logistically difficult. Therefore, it is important to recognize that research may be focusing on series initiation, but issues of series completion may require a different focus to be effective.

Directions for Future Research

After five years of HPV vaccine availability, the health care community and the general public has had the opportunity to become familiar with the vaccine and millions of doses of the vaccine have been dispensed to eligible males and females. During the

past five years, the research community has had the opportunity to begin to transition from the initial stages of HPV vaccine uptake research, including acceptability and intention to vaccinate, to investigating actual influences on uptake. Now, the most immediate direction for HPV vaccine uptake research in general is to strengthen research establishing the influences on uptake, then move quickly to develop, test, and disseminate interventions to improve uptake. Meanwhile, an ongoing assessment of change and progress requires confirmation that the initial influences on uptake are still relevant and should continue to be addressed to improve HPV vaccine uptake. This dissertation attempted to help strengthen what is known about HPV vaccine uptake influences in Chapters Two and Three, and then began to explore a hypothetical intervention in Chapter Four based on those influences.

There are many directions for future research that result from this dissertation. In keeping with the ecological model of HPV vaccine uptake, research should be conducted at a public policy level into the effect the Affordable Care Act has on HPV vaccination, specifically the amount of influence represented by increased insurance coverage and cost elimination. In addition, research examining the differences between clinics/regions/states with high uptake and those with low uptake, particularly in the 19 to 26 year old population, and what differences are modifiable, is important. This question requires systematic consideration of the public policy level context, including public sector reimbursement rules and insurance coverage effects, as well as school entry requirements in the adolescent population, that can be readily investigated. It also requires inquiry about harder to discover information about logistics, for example, the

distribution of public health vaccines in non-governmental health centers, and the cost of injections in health centers.

At the health care organization level, investigation is needed into what unique attributes reproductive health centers can leverage to influence HPV vaccine uptake in 19 to 26 year olds. This question can be investigated across large organizations like Planned Parenthood Federation of America, Inc. that may create influences as a result of size, smaller organizations like Planned Parenthood Mid and South Michigan that may create influences based on location, or individual health centers that may have the flexibility to adapt to influences not found in larger organizations.

At the individual level, influences that are amenable to change are often outside of the health care system and will perhaps require a different approach to intervention than those implemented by health care organizations or public policy. HPV vaccination is unique among vaccinations in that it is the only one given in adolescence that prevents a sexually transmitted infection. The societal discomfort with adolescents and sexual activity potentially adds an element of individual influence to vaccination that is not replicated in the experience with other adolescent vaccines. Identifying similarities and differences between the HPV vaccine and other universally recommended vaccines may help guide future research.

Finally, as stated previously, most of the HPV vaccine research on uptake focuses on initiation of the series and most of the interventions will be based on the results. However, series completion also requires investigation, as the influences may be different between a person starting vaccination, and the follow up difficulties related to series completion. As vaccine research determines the importance of series completion in

achieving full immunity, uptake researchers will be able to determine where to focus their intervention efforts.

In conclusion, the abundance of HPV vaccine research that has emerged in the past several years is only the start of an exciting future that will mostly likely continue to evolve, offering new opportunities and challenges in the area of HPV vaccine uptake for researchers, practitioners, and patients everywhere. The health care system will be busy continuing to find ways to reduce the prevalence of HPV. Time will pass, history will change, and research will lead the way to ensuring fewer individuals suffer the health consequences of this vaccine-preventable disease.

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