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Examining Future Adolescent HPV Vaccine Uptake With and Without a School Mandate

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Abstract

Purpose—To develop a model of adolescent HPV vaccine utilization that explored future HPV vaccination rates with and without a school mandate for the vaccine at middle school entry.

Methods—A dynamic, population-based, compartmental model was developed that estimated over a 50 year time horizon HPV vaccine uptake among female adolescents living in the U.S. The model incorporated data on parental attitudes about this vaccine and adolescent health care utilization levels.

Results—Without a mandate, our model predicted that 70% coverage, a lower threshold value used in many previous modeling studies of HPV vaccination, would not be achieved until a mean of 23 years after vaccine availability. Maximal coverage of 79% was achieved after 50 years. With a school mandate in place, utilization increased substantially, with 70% vaccination coverage achieved by year 8 and maximal vaccination coverage, 90%, achieved by year 43.

Conclusions—Our results suggest that vaccine utilization is likely to be low for several years, though strong school mandates might improve HPV vaccine uptake. These results impact the interpretation of previous modeling studies that estimated the potential clinical impacts of HPV vaccination under assumptions of very high vaccine utilization rates.

Keywords

human papillomavirus; vaccines; adolescent; papillomavirus vaccines; Markov chain

INTRODUCTION

Human papillomavirus (HPV) is a common sexually transmitted infection that is associated with a variety of cancerous and non-cancerous clinical conditions.[1] In 2006 the U.S. Food and Drug Administration licensed a highly effective quadrivalent HPV vaccine that provides protection against 4 types of HPV associated with cervical cancer and genital warts.[2,3] A second, bivalent, HPV vaccine that affords similarly high protection against cervical lesions,

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but does not include antigens associated with genital warts, was approved in the U.S. in 2009.[4]

Modeling studies have been used to explore the potential population-level clinical impacts resulting from HPV vaccination and to examine the impact that HPV vaccine programs might have on cervical cancer screening guidelines. To date, more than 17 different mathematical models exploring these issues have been developed.[5,6] Though these models differ in their assumptions, dynamics, and structure, they uniformly conclude that if widely implemented, HPV vaccines could drastically reduce the prevalence of HPV-related diseases.

An important caveat of these previous modeling studies, however, is that they aimed to evaluate the “best case” scenario with regards to the potential clinical impacts of HPV vaccination. To do so, they simulated very high levels of vaccination (70–100%) among adolescents and assumed these were achieved at, or within a few years of, vaccine introduction. [7–11] Numerous lines of evidence indicate that these assumptions are likely to be unrealistically high. First, historical review of vaccine introduction patterns suggests that adolescent vaccination may be difficult to implement[12,13] and that decades can pass following initial vaccine introduction before high levels of coverage are achieved among this population.[14] Second, numerous studies have documented that for HPV vaccines specifically, there is hesitancy on the part of parents and medical providers to provide this vaccine to adolescents, particularly for younger adolescents for whom the vaccine is preferentially recommended.[15–19] Third, recent examinations of current adolescent health care utilization patterns have demonstrated that this population is significantly less likely than other childhood age groups to participate in health maintenance exams where vaccines are preferentially provided. [20] Taken together, these findings suggest that the actual clinical impacts of HPV vaccines may be substantially lower than what has been predicted by previous modeling studies because vaccine utilization will be substantially less than what these models assumed.

Because adolescents under the age of 18 generally require parental consent for vaccination, parents’ views about the HPV vaccine are a critical factor for high uptake. Numerous studies have defined several parental attitudinal and demographic characteristics associated with adolescent HPV vaccine utilization including previous experience with HPV-associated illnesses, perceived risk for HPV infection, and beliefs about the benefits of HPV vaccination, among others.[21–23] The commonality of these factors among geographically and socio-economically diverse groups of parents strongly suggests their influence on future adolescent utilization of the HPV vaccine. Despite this, to our knowledge there have been no cost-effectiveness studies that have used parent attitudinal data to inform expectations of adolescent HPV vaccine use. Similarly, very little has been done to incorporate data on adolescent health care utilization into previous HPV vaccination models.

To address these issues, we developed a model of HPV vaccine utilization among adolescents that incorporated data on parental attitudes about the vaccine and adolescent health care utilization levels. Our primary goal was to evaluate future levels of HPV vaccine utilization among adolescents under current conditions, but we also used our model to explore the potential impact that a school mandate for HPV vaccination might have on this outcome. Historically, school mandates for vaccination have been an effective policy for improving vaccination rates.[24] As of 2009, 22 states had HPV vaccine-related school mandate proposals under consideration, and two mandates requiring the vaccine for school entry had been passed (VA and D.C.) with implementation to begin in the 2009 school year. [25]

METHODS

Model description

We developed a dynamic, population-based, compartmental model to estimate over a 50 year time horizon HPV vaccine uptake among 11–17 year old female adolescents living in the US. This model was conceptually based on components from three validated health behavior theories: a) The Transtheoretical Model (i.e. Stages of Change) model;[26] b) the Health Belief model;[27] and c) the Theory of Reasoned Action.[28]

In our compartmental model two policy scenarios were considered – one where school mandates for HPV vaccination were not enacted, and the other where an HPV vaccine school mandate was in place at the onset of vaccine introduction (i.e. at the beginning of the 50 year time period). The model compartments are illustrated in Figure 1. A detailed description of model parameterization and structure is available in a technical Appendix that accompanies this manuscript. Briefly, each compartment (box) represents the amount of individuals in different states of the vaccination process. At every time step individuals are allowed to change states or remain in their current compartments according to pre-specified probabilities. The arrows between compartments indicate the possible changes of state, while the semi-circular arrow starting and ending in the same compartment denote the possibility of individuals remaining in the same state as in the previous time period.

Simulation Approach

The model tracked cross-sections of 11–17 year old females for every calendar month from 2008 to 2058 and for every month of age between 11 years, 0 months and 17 years, 11 months. The size and distribution of the initial cross section of 11–17 year-old females, as well as the size of future 11 year-old cohorts, were derived from US Census Bureau estimates.[29] Based on data from our own university health system[30] and anecdotal reports of few 9–10 year olds receiving the vaccine, our model assumed that no vaccination occurred before age 11, so every month a new cohort of unvaccinated 11 year old girls entered the model. Adolescents exited the model by reaching age 18 or by dying; a uniform mortality rate for adolescent females was applied throughout the simulation period.[31]

The model treated adolescents and their parents as a cohesive unit such that movement of the adolescents through the various model compartments was driven by parameters specifying parents' attitudes about HPV vaccination and, in some cases, the likelihood of the adolescent accessing medical care. Adolescents/parents entered the model through different compartments based on estimates of parents' general awareness of HPV vaccination, as well as their baseline attitudes towards the vaccine (see Figure 1 and further description below). In the no mandate scenario, the proportion of parents unaware of the vaccine was set to decrease exponentially over time, going from 40% to 5% over 10 years. At each time step (monthly) the adolescent subjects could remain in their current compartment or move to a different one according to a specified probability distribution.

Each dose of the vaccination series was assessed separately, with the model requiring a minimum of 2 months between the first and second doses and 4 months between the second and third doses of vaccine, in accordance with recommended HPV vaccination schedule.[1] Interaction with a medical provider was modeled explicitly for receipt of the first vaccine dose, but subsequent doses incorporated this factor into the overall transition probability for compartments where vaccine doses were received.

Parameter Development

Our model incorporated the effects of parental attitudes about HPV vaccination and adolescent health care utilization levels on HPV vaccine uptake. When available, we used published literature to inform parameter development. For parameters where empirical data were not available, values were based on opinions of a panel of vaccination experts. Specific values for those parameters as well as a description of the process we employed to obtain them are available in the associated Appendix.

Briefly, parameters specifying parents' overall attitudes about the vaccine (the probability of wanting the vaccine for their daughter) were derived by taking the weighted average of three different parental attitudinal sub-domains that had been shown in previous studies to be influential factors affecting parental HPV vaccine acceptability.[15,23,32] These included a) the influence of the vaccine's cost on parents' attitudes; b) the influence of normative beliefs (i.e. perceived society and peer acceptance of the vaccine) on parents' attitudes; and c) the influence of parents' personal experiences on their attitudes. For model compartments that simulated interaction with the physician, the influence of physician's recommendation on parents' attitudes was included as a fourth attitudinal sub-domain in this calculation. The relative influence of these different attitudinal sub-domains was different for the parameter specifying vaccine initiation (receipt of first dose) than for those specifying receipt of subsequent (second and third) doses.

Modeling HPV Vaccine Mandate

Though school mandates for vaccination are known to improve vaccination rates,[24] to our knowledge there is no published data that provides specific information on how these mandates affect parental decision-making about vaccines or the ability of adolescents to access medical services. After consulting with a panel of vaccination experts, we made assumptions in our model that the implementation of a school mandate for HPV vaccination would affect three aspects of the vaccine administration process: 1) parental attitudes about the vaccine (which we included as a fifth attitudinal sub-domain in the calculation of overall parental attitudes about the vaccine in the mandate scenario); 2) the likelihood that an adolescent would interact with a medical provider; and 3) the likelihood that the provider would have the vaccine available for patients wanting it. The effects of an HPV vaccine school mandate on model parameters is summarized in Table 1, which demonstrates the base case values, and the parameter ranges considered in sensitivity analyses. The effect of the mandate on parameters and their distribution is described in greater detail in the accompanying Appendix.

Model outputs

The primary outcomes assessed from the model were the mean number of 11–17 year-old girls vaccinated with the first, second and third doses of HPV vaccine each month over the simulated time period. Monte Carlo runs were conducted to ascertain the impact of uncertainty in the model's parameters on the output, generating 90% confidence intervals for all results. The model was programmed to present annualized data based on the mean number of girls vaccinated for each time period. Post-processing of the mean annualized values was then used to calculate the mean cumulative proportion of the eligible population of girls vaccinated with first, second and third doses over time.

Sensitivity analyses

The overall effect of parameter uncertainty was gauged by the 90% confidence intervals generated by Monte Carlo runs. We also performed one-way sensitivity analyses to assess

relative impact of each individual parameter on the model's output. These data are presented in the accompanying Appendix.

Software

The model was coded in Visual Basic, using a Microsoft® Excel 2007 spreadsheet interface. Sensitivity analysis was conducted using @Risk for Excel (version 5.0.1, Palisade Corporation) simulation software.

RESULTS

Cumulative Vaccination

The predicted mean cumulative proportion of 11–17 year old girls vaccinated with the first, second and third doses of the HPV vaccine series under no mandate and mandate conditions is depicted in Figure 2. Without vaccine mandates, mean utilization one year after the vaccine is introduced was estimated at 25%, 17% and 7% for the first, second and third doses, respectively. Vaccination series completion did not reach a 70% coverage level, the lower threshold value used in some previous studies assessing the clinical impacts of HPV vaccination, until 22 years had elapsed. Maximal mean vaccination coverage was achieved in the last year of model simulation (year 50) and was 78%. Though little data is available with which to calibrate the model's output, our results were consistent with recently published national estimates of HPV vaccine utilization during the first full year of vaccine availability among females 13–17 years old which demonstrated uptake of first, second and third doses of vaccine by 25%, 17% and 6%, respectively.[33] National data on the second year of HPV vaccine utilization were recently released by the Centers for Disease Control and Prevention (CDC) and were also consistent with our model outputs, though estimations of third dose utilization were slightly less consistent in the model's second year of output (CDC –18.6%, our model 23%).[34] Our results were also consistent with longer term trajectories of uptake for newly implemented vaccine recommendations.[12,35]

With a school mandate for HPV vaccination in place, mean utilization after one year of vaccine availability was 42%, 34% and 19% for the first, second and third doses, respectively. The 70% series completion threshold was reached after 7 years and maximal vaccine utilization, 91%, was achieved by year 42.

Annual Doses Used

The annual number of HPV vaccine doses used (first, second and third doses combined) is depicted in Figure 3. Consistent with the population uptake of HPV vaccination described above, mean utilization was lower under baseline conditions (panel 3A) than in the setting of a school mandate (panel 3B). In both scenarios vaccine utilization was highest in the first several years following vaccine implementation, due to the high proportion of un- or incompletely vaccinated adolescents in the population. Vaccine doses utilized then declined rapidly, reflecting decreases in the proportion of the population who were not vaccinated. After approximately 7 years, annual increases in vaccine utilization doses used reflected only population growth, rather than increases in the proportion of the population vaccinated (data not shown).

Sensitivity Analyses

One-way sensitivity analysis demonstrated that the monthly probability of an adolescent accessing medical care was the most influential parameter in the model (see Appendix for sample sensitivity analysis results). Over a parameter range of 0.024 – 0.075, the mean number of vaccine doses utilized during the first year (first dose only) ranged from 2.49–

5.67 million. All other parameters had substantially smaller effects on the model's outputs (see Appendix).

DISCUSSION

A growing body of data on the factors associated with HPV vaccine acceptability among parents has emerged in the years surrounding the vaccine's licensure. Our model of HPV vaccine utilization is one of the first to incorporate such data on parental attitudes and also to incorporate data on utilization of adolescent preventive health care services. Our model predicted that it would take decades before a level of 70% HPV vaccine utilization (a value typically used in previous modeling studies of HPV vaccination) among adolescent girls was realized. This finding, which is consistent with uptake patterns of other newly introduced adolescent vaccines, [12] suggests that previous estimations of the potential population-level effects of HPV vaccination on HPV-related clinical outcomes must be interpreted with caution. This is because these examinations were based on models with simplifying assumptions of high levels of adolescent HPV vaccine coverage that coincided with the onset of vaccine availability – i.e. the best case scenario for impacting HPV-related diseases. Because our model indicates that adolescent vaccine utilization is likely to well below the Healthy People 2010 goal of 90% uptake for many years, the population-level health effects of HPV vaccination are likely to be substantially more modest than that previously described by these models.

Our results suggest that mandating the HPV vaccine for middle school entry could significantly improve uptake of HPV vaccine among adolescents. Since the vaccine was licensed in 2006, 24 states have proposed legislation centered on HPV vaccines for females entering middle school and of these, proposals in two locations, Virginia and the District of Columbia, have been passed.[25] In our simulation, we found that implementation of an HPV vaccine school mandate at the onset of vaccine availability resulted in both a substantially more rapid uptake of the vaccine, as well as a much higher maximal level of vaccine utilization. Though this finding is in keeping with historical data on the influence of school mandates on vaccine uptake,[24] our results should be interpreted with caution because there is considerable uncertainty regarding the mechanisms by which school mandates exert their effects on population uptake of vaccines. We simulated mandate implementation by increasing parental willingness for vaccination, while also increasing the likelihood that an adolescent would interact with the medical provider and that the provider would have the HPV vaccine available. These assumptions were based on agreement among a panel of vaccination experts. However, additional research will be needed to confirm the extent to which HPV-vaccine-related mandates exert their effects through these, or other, avenues.

There is currently wide variability in the stipulations of HPV vaccine-related school mandates currently under consideration in the legislature, and many of these diverge significantly from vaccine-related mandates of the past. For example, in several states HPV vaccine “mandates” simply require that parents receive information about HPV rather than requiring the students to actually get the vaccine for school attendance. Similarly, among states where administration of the vaccine *is* being considered as a requirement for school entry, many also include generous “opt out” clauses that allow parents to forgo HPV vaccination of their daughter without the need of medical, philosophical or religious justification. Our mandate analysis attempted to simulate a historically “typical” school mandate for vaccines (one that has a fairly strong requirement for vaccine administration) because several states are considering enacting this type of mandate, and because this enables the effects of an HPV vaccine mandate to be more directly compared to those related to other vaccines. However, future analyses will undertake a more detailed

exploration of HPV mandates by evaluating alternative approaches to simulating mandates in our model. We believe this will enable us to capture important differences between how “typical” HPV vaccine mandates and the more “alternative” types of HPV vaccine mandates also under consideration (i.e. information-only or universal opt-out option mandates) might exert their effects. For example, it is reasonable to hypothesize that mandates requiring the receipt of HPV information, rather than actual vaccine administration, could affect parent attitudes about the vaccine (as in our model) but not provider availability of the vaccine.

Limitations of our study primarily relate to the simplifying assumptions that were used in our model. In addition to assumptions about how mandates might affect vaccine-seeking behaviors, we did not differentiate between parental *intentions* for vaccination versus parental *willingness* for vaccination, which may be affected differentially by a variety of factors. Another major assumption in our model was that parent/adolescent behaviors and attitudes were unrelated to any demographic characteristics such as age, race or income. Previous work demonstrates that HPV vaccine acceptability among both parents and medical providers is significantly higher for older adolescents (15–17 years) when compared to younger adolescents (11–13 years).[15,17–19] In contrast, increasing age has been shown to be associated with a decreased likelihood of participating in routine “check-ups.” It is difficult to predict how the lack of age-related variability in attitudes and behaviors in our model might have affected our results since increased HPV vaccine acceptability for older adolescents is likely to be somewhat counterbalanced by decreased access to preventive care visits where vaccine are known to be preferentially provided.[36] While we believe that our model captured the main issues related to expected future use of adolescent HPV vaccine, future iterations of the model should explore the potential effects of age-related variability in vaccine-seeking behaviors.

Similarly, future HPV vaccine utilization models should also consider incorporating the effect of other adolescent or parent demographic characteristics. Factors such as race, religion and education have all been implicated as associated with variability in HPV vaccine utilization by adolescents.[15,21,30,37–39] Our previous work suggests there are important racial and insurance-related disparities in HPV vaccination use.[30] This finding has implications for the potential for this vaccine to impact cervical cancer rates in the U.S. Future models should attempt to incorporate heterogeneities in HPV vaccine utilization by demographic characteristics such as these as this may inform where interventions and outreach activities are particularly critical.

Conclusions

Our model’s results point to a need to re-evaluate public expectations for the clinical impacts of HPV vaccination at a population-level and to further explore the role of social policies such as school mandates for HPV vaccination. While there is little doubt that HPV vaccination can result in health benefits, the high levels of HPV-related disease prevention predicted by previous models may not be achieved based on current parental perceptions about the HPV vaccine and adolescent health care utilization patterns. “Normalizing” HPV vaccination such that it becomes an accepted, and even expected, part of adolescent health care services, is one way that higher HPV vaccination uptake levels might be realized. This could potentially be achieved by implementing adolescent immunization via schools which have been shown in other countries to be effective at achieving high vaccination rates among the adolescent population.[40] Equally important however, our model suggests that increasing adolescent participation in preventive care visits is also imperative. Focusing immunization provision on the medical home has several advantages including more comprehensive care and the ability to incorporate other health care services into appointments where vaccines are provided.

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Technical Appendix to Accompany

Modeling Future Adolescent Human Papillomavirus Vaccine Uptake: Inclusion of parent attitudes, adolescent health care utilization levels and a school mandate

Model Overview

This appendix describes the constructs of a dynamic, Markov compartmental model that incorporates census data, adolescent health care utilization levels and parental attitudes about HPV vaccination. The model tracks serial cross-sections of adolescent girls, aged 11–17 years, over 50 years. The following diagram (Figure 1) outlines the structure of the model's compartments, and movement of individuals within the model:

MODEL DYNAMICS—The compartments (boxes) in Figure 1 represent the amount of individuals in different states of the vaccination process. At every time step (1 month), individuals are allowed to change states or remain in their current compartments according to pre-specified probabilities. The arrows between compartments indicate the possible changes of state, while the semi-circular arrows starting and ending in the same compartment denote the possibility of individuals remaining in the same state as in the previous time period.

To populate the model initially, a cohort of 11–17 year old girls entered the model. Because our model was based on a time step of 1 month, the 11–17 year old cohort was divided into 84 age categories corresponding from age 11 years-0 months to age 17 years-11 months. Starting populations for each of the age categories were identical, and were derived by dividing the total population of 11–17 year old females estimated by U.S. Census Data (14,163,515 individuals) by 84.¹ Every month thereafter a new cohort of 11 year-0 month old girls (bundled with their parents, a.k.a. subjects) entered the model, based on annual projections from U.S. Census Data¹ that were divided by 12 to derive monthly estimates (Table 1).

Immediately upon entering the model, the subjects are classified into one of three categories: Their parents are unaware of the HPV vaccine (compartment [C]1, Figure 1); their parents are aware of the vaccine and want to vaccinate their daughters (C2); or their parents are aware of the vaccine but do not want to vaccinate their daughters (C3). The subjects are then allowed to circulate among those initial compartments or to progress into visiting a physician at which point they are all aware of the existence of the vaccine and are again classified as wanting it or not (C5, C4, respectively). Those who want the vaccine can progress to obtain the first dose (C6), and then are classified into wanting or not wanting the second dose (C8, C7, respectively). Those who want the second dose can then progress to obtain it (C9) and are then classified into wanting or not wanting the third dose (C10, C11, respectively). Finally, those who want the third dose can progress to obtain it (C12). At any time step, subjects leave the model either by death or by reaching 18 years of age. Receipt of first, second and third doses are tracked for the 11–17 year old cohort monthly.

The model was implemented using a time step equal to one month. All model parameters were adjusted accordingly. We ran the model for 50 years; $t=0$ corresponds to January 1, 2008 while $t=600$ corresponds to January 1, 2058. Ages (a) in the model are also shown in simulation months; for example, $a = 0$ stands for 11 year – 0 month olds, and $a = 83$ represents 17 year – 11 month olds.

The mathematical specification of the model is as follows:

$$X_{i,a}(0) = \lambda_i(0)P_a(0) \text{ for } i = 1, 2 \text{ \& } 3; a = 0, \dots, 83$$

$$X_{i,a}(0) = 0 \text{ for } i = 4, \dots, 12; a = 0, \dots, 83$$

$$X_{i,a}(t) = \lambda_i(0)P_a(t) \text{ for } i = 1, 2 \text{ \& } 3; t = 1, \dots, 600$$

$$X_{i,a}(t) = 0 \text{ for } i = 4, \dots, 12; t = 1, \dots, 600$$

$$X_{i,a}(t) = (1 - \mu) \left[\sum_{k=1}^{k=12} p_{k,i} X_{k,a-1}(t-1) \right] \text{ for } i=1, \dots, 12; a=1, \dots, 83; t=1, \dots, 600$$

Where:

$X_{i,a}(t)$ = number of adolescent girls age a , in compartment i at time t

$P_a(t)$ = estimated number of adolescent girls age a at time t in the U.S.

$p_{k,i}$ = probability of moving from compartment k to compartment i in one time step.

$\lambda_i(t)$ = probability that an incoming cohort of 11 year-olds belong to compartment i ($= 1, 2$, or 3) at time t .

μ = mortality rate for females aged 11–17 (43/10,000/12, or 3.58×10^{-5} per month).²

PARAMETERS

Base Case – No mandate

Variable values that were used to create the parameters were selected by combining published data with expert judgment. A panel of nationally recognized vaccination experts (Dr. Gary Freed and Dr. Matthew Davis, University of Michigan) reviewed all parameters used in the model and provided input into parameters where published data were not available.

The mean $\lambda_1(0)$, $\lambda_2(0)$, $\lambda_3(0)$ were estimated to be 0.40, 0.27 and 0.33 respectively. These probabilities were computed by first estimating the proportion of subjects unaware of the HPV vaccine as 0.4.³ Among those who are aware of the vaccine, the proportion of those wanting the vaccine was estimated to be 0.55.^{4,5} This latter value was derived using a weighted average that combined information about the relative perceived influence of cost, normative beliefs and personal attitudes about the vaccine (Table 2). This value, multiplied by the likelihood of being informed about the vaccine (0.6), specified $\lambda_3(0)$.

After $t = 0$, the proportion of uninformed subjects was assumed to decrease exponentially from its initial value of 0.4 and reach a steady state level of 0.05 after 10 years (120 months) according to the following scheme: $0.05 + 0.35 \times \exp(-0.035404 \times t)$. $\lambda_1(t)$, $\lambda_2(t)$ & $\lambda_3(t)$ were altered accordingly.

Parameter values used for the transition probabilities among compartments were derived following a procedure similar to those used to derived the λ 's. These transition probabilities are assumed to be static; their values are shown in Table 3, below.

Parameter values - Mandate Effect

With a mandate in place, the probability of a subject being unaware of the vaccine (λ_1) was estimated to be .05 from the outset, with no changes in the value over time, in contrast to the non-mandate scenario. Among those aware of the vaccine, the proportion of subjects wanting the vaccine was estimated to be 0.81, by again combining the perceived influence of cost, normative beliefs and personal attitudes about the vaccine, plus now also including the perceived influence of a mandate (Table 2). This process yielded .05, .19 and .76 values (mean of Monte Carlo runs) for λ_1 , λ_2 & λ_3 respectively for all t after adjusting for the probability of being aware of the vaccine.

As before, parameter values for the transition probabilities among compartments were derived using a similar procedure, but adding the perceived effect of a mandate. Mandates had effects only on those parameters associated with parent attitudes (Table 2 of Appendix and Table 1 of accompanying manuscript), likelihood of knowing about the vaccine without first seeing a medical provider (described above), physician availability of the vaccine (transitions C5→C6, C8→C9, and C11→C12) and adolescent access to care (see Table 1 of accompanying manuscript, affects transitions emanating from C1, C2 and C3). Transition values used in the mandate scenario are shown in Table 4, below.

Sensitivity Analysis

We performed extensive sensitivity analysis to appraise the impact of uncertainty in parameter values on our results. Employing Monte Carlo simulation, we imposed a triangular distribution on all parameter values, specifying lowest possible, most likely and highest possible value for the parameters, with and without the effect of a mandate. Table 3 and Table 4 show the values used in our simulations. For every transition probability, the tables show the highest value used (blue background), the mean (yellow), and the lowest value used (orange). Note that the entries on the blue and yellow rows of the tables show the extreme values achieved by individual parameters, and therefore may not add up to 1.

We also performed 1-way sensitivity analyses where parameter values were held at a fixed value (the most likely value in the triangular distribution) and parameters were tested individually over their specified ranges. This analysis demonstrated that the variable specifying adolescent's access to care was the most individually influential parameter in the model (Figure 2, panels A and B).

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Figure 1. Population-based compartmental Markov model incorporating attitudinal and action states related to HPV vaccination for parents of adolescent females

Note: Not shown – subjects may exit model at each stage due to adolescent death or adolescent aging >17 years-0 months.

A)

B)

Figure 2.
Cumulative Mean HPV Vaccine Utilization Among Eligible Adolescent Girls Under No Mandate (panel A) and Mandate (panel B) Conditions.

A)

B)

Figure 3.
Mean Annual Number of HPV Vaccine Doses Utilized under No Mandate (panel A) and Mandate (panel B) Conditions

Figure 1. Model Compartments

Arrows indicate movement between compartments (numbered in parentheses). *Note: Not shown – subjects may exit the model at each stage due to adolescent death or adolescent aging >17 years-11 months.*

(A)

(B)

Parameter Description	Range of Parameter Values Tested	Range of Mean Number of First Doses Delivered**	
		Low	High
Weighting value for cost; transition λ_1	3-15	3913061	4098424
Weighting value for normative beliefs; transition λ_1	6-20	3939614	4068130
Weighting value for personal experience; transition λ_1	10-25	3937731	4041634
Monthly probability of being un-informed (λ_1)	0.1-0.5	3983036	4003839
Monthly probability of accessing care (incorporated into multiple parameters)	0.02-0.08	1963140	5918779
Weighting value for cost; all transitions emanating from C2	3-10	3932815	4088142
Weighting value for normative beliefs; all transitions emanating from C2	1-8	3941766	4071212
Weighting value for personal experience; all transitions emanating from C2	10-40	3982261	4002793
Monthly probability of changing mind to no vaccine, no Dr. visit (C3 $\rightarrow$ C2)	0.05-0.20	4316474	3685635
Monthly probability of changing mind to wanting vaccine after Dr. visit (C4 $\rightarrow$ C5)	0.01 – 0.10	3683522	4416446
Monthly probability of getting first dose once desired and seen Dr. (C5 $\rightarrow$ C6)	0.90 – 0.99	3980241	4010313

**Out of 100 Simulation Runs

Figure 2. Example Results From One-Way Sensitivity Analyses: First Year of Vaccine Utilization Under the No-Mandate Scenario Depicted in Graphical (A) and Tabular (B) Forms
Legend. Each line represents first dose utilization at the end of year 1. Each individual model parameter or sub-parameter is adjusted over a range of pre-specified change from the most likely value while all other parameters are held at their most likely values. *Note: Similar results are found under mandate conditions and for other years or doses in the model.*

Table 1

Parameters Values Differing Between No-Mandate and Mandate Scenarios

Parameter	No Mandate	Mandate	Reference
	Most Likely Value [§] (Range)	Most Likely Value [§] (Range)	
Probability Parents are Unaware of the Vaccine	0.4 [‡] (0.1–0.5)	0.05 (0.03–0.07)	28
Monthly Probability of Adolescent Visiting the Doctor	0.042 (0.02–0.08)	0.0498 (0.024–0.096)	29, 18
Probability of Parent Changing From Not Wanting to Wanting the Vaccine After Seeing Doctor, First Dose	0.02 (0.01 – 0.10)	0.10 (0.05 – 0.20)	E.P., 17
Probability of Parent Changing Mind from Not Wanting to Wanting the Vaccine, Second/Third Dose	0.10 (0.05 – 0.20)	0.75 (0.25–0.80)	E.P., 17
Probability of Getting the Second/Third Dose Once Parent Decides they Want It	0.8 (0.5–0.99)	0.95 (0.9–0.99)	E.P., 30

[§] Most likely value in the triangular parameter distribution used in the Monte Carlo analysis.

[‡] This value was set to decrease exponentially over time. See Appendix for further details. E.P. – Expert panel consensus

Table 1

Annual birth cohort of 11 year olds entering the model*

Model Year	Annual Birth Cohort
1	1912943
2	1903820
3	1917564
4	1941954
5	2026875
6	2029016
7	2042042
8	2057328
9	2075321
10	2094497
11	2114500
12	2136150
13	2158321
14	2179879
15	2199633
16	2217143
17	2232725
18	2246509
19	2258874
20	2270334
21	2281483
22	2292954
23	2304970
24	2317432
25	2330041
26	2342627
27	2355740

Model Year	Annual Birth Cohort
28	2369657
29	2384706
30	2399362
31	2413859
32	2430087
33	2447992
34	2467326
35	2487149
36	2507289
37	2527804
38	2548521
39	2569247
40	2589735
41	2609835
42	2629518
43	2648677
44	2658711
45	2669293
46	2680520
47	2691601
48	2702807
49	2713793
50	2724887

* Annual cohort values were divided by 12 to derive the monthly 11 year-0 month birth cohorts that entered the model.

Weighting Schema for Select Model Parameters

Table 2

Parameter	Sub-parameters	Starting Value of Sub-parameter [†]	Relative Weight of Sub-parameter [†]	Final Value [‡]		Refs.
				No Mandate	With Mandate	
<i>Probability of Wanting Vaccine Among Informed¹</i>	Mandate	0/1 [*]	10			4_12
	Cost	0.86	5	0.55	0.81	
	Normative Beliefs	0.75	8			
	Personal Attitudes	0.7	16			
<i>Probability of Inherently Changing Mind to Wanting Vaccine Outside of Dr. Visit²</i>	Mandate	0/1 [*]	20			
	Cost	0.3	5	0.08	0.47	
	Normative Beliefs	0.25	2			
	Personal Attitudes	0.1	25			
<i>Probability of Wanting 2nd/3rd Dose After Receiving 1st Dose³</i>	Mandate	0/1 [*]	10			
	Cost	0.86	5			
	Normative Beliefs	1	8	0.78	0.97	
	Personal Attitudes	1	15			
	Physician Recommendation	0.95	15			

¹ A component of λ_3

² A component of the transition probability for C2 $\rightarrow$ C3

³ Transition C6 $\rightarrow$ C8

^{*} When no mandate is in effect, the starting value=0. When a mandate enacted, the starting value = 1.

[‡] Most likely value shown. However, a range of weight factors were used in the Monte Carlo simulation.

Table 3
Transition Probabilities Among Compartments in the Model with No Mandates

	To Compartment											
	1	2	3	4	5	6	7	8	9	10	11	12
From Compartment	1	.931	.024	.031	.032	.053						
	2	.905	.020	.028	.017	.030						
	3	.874	.017	.024	.007	.013						
	4		.903	.068	.067	.015						
	5		.862	.091	.040	.008						
	6		.818	.114	.017	.003						
	7		.200	.921	.088							
	8		.117	.832	.052							
	9		.050	.727	.022							
	10			.990	.100							
	11			.957	.043							
	12			.900	.010							
From Compartment	1				.100	.990						
	2				.053	.947						
	3				.010	.900						
	4						.263	.815				
	5						.217	.783				
	6						.185	.737				
	7						.950	.200				
	8						.883	.117				
	9						.800	.050				
	10						.010	.500	.990			
	11						.006	.231	.763			
	12						.003	.006	.500			
From Compartment	1									.135	.906	
	2									.109	.891	

To Compartment													
	1	2	3	4	5	6	7	8	9	10	11	12	
										.094	.866		
	10										.950	.200	
											.883	.117	
											.800	.050	
	11										.010	.543	.890
											.006	.307	.687
										.003	.105	.452	

Transition probabilities from (y-axis) one compartment to (x-axis) another. Yellow rows indicate value specified as the most likely in the triangular distribution used in the Monte Carlo analysis. Least likely (orange) and most likely (blue) values are also depicted.

Table 4

Transition Probabilities among Compartments in Mandate Model

	To Compartment											
	1	2	3	4	5	6	7	8	9	10	11	12
From Compartment	1	.927	.010	.040	.013	.086						
	2	.896	.009	.038	.007	.050						
	3	.859	.008	.036	.002	.021						
	4		.595	.589	.030	.094						
	5		.504	.440	.011	.045						
	6		.359	.350	.000	.017						
	7		.200	.912	.105							
	8		.117	.821	.062							
	9		.050	.707	.027							
	10			.950	.200							
	11			.883	.117							
	12			.800	.050							
From Compartment	1				.100	.990						
	2				.053	.947						
	3				.010	.900						
	4						.040	.982				
	5						.029	.971				
	6						.018	.960				
	7						.750	.800				
	8						.400	.600				
	9						.200	.250				
	10						.010	.095	.990			
	11						.006	.048	.947			
	12						.003	.003	.900			
From Compartment	1									.020	.991	
	2									.014	.986	

To Compartment												
	1	2	3	4	5	6	7	8	9	10	11	12
										.009	.980	
										.745	.800	
										.400	.600	
10										.200	.255	
										.010	.186	.891
										.006	.142	.852
11										.003	.101	.811

Transition probabilities from (y-axis) one compartment to (x-axis) another. Yellow rows indicate values specified as the most likely in the triangular distribution used in the MonteCarlo analysis. Least likely (orange) and most likely (blue) values are also depicted.