Integrating epidemiology, psychology, and economics to achieve HPV vaccination targets

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Human papillomavirus **(HPV) vaccines provide an opportunity to reduce the incidence of cervical cancer. Optimization of cervical cancer prevention programs requires anticipation of the degree to which the public will adhere to vaccination recommendations. To compare vaccination levels driven by public perceptions with levels that are optimal for maximizing the community's overall utility, we develop an epidemiological game-theoretic model of HPV vaccination. The model is parameterized with survey data on actual perceptions regarding cervical cancer, genital warts, and HPV vaccination collected from parents of vaccine-eligible children in the United States. The results suggest that perceptions of survey respondents generate vaccination levels far lower than those that maximize overall health-related utility for the population. Vaccination goals may be achieved by addressing concerns about vaccine risk, particularly those related to sexual activity among adolescent vaccine recipients. In addition, cost subsidizations and shifts in federal coverage plans may compensate for perceived and real costs of HPV vaccination to achieve public health vaccination targets.**

game theory | mathematical modeling

An estimated 11,000 women in the United States were diagnosed with invasive cervical cancer in 2007 (1). Vaccination against human papillomavirus (HPV) can reduce morbidity and mortality from cervical cancer and genital warts. The Centers for Disease Control and Prevention (CDC) recommends vaccination for 11- to 12-year-old girls as well as catch-up vaccination for 13- to 26-year-old women (2).

Mathematical models of HPV vaccination have previously evaluated whether a proposed combination of screening and vaccination efficiently uses health budget dollars by calculating the monetary costs of the program against a measure of its relative health benefits (3). Increasingly complex models have been used to incorporate both direct and indirect costs and benefits of vaccination (4, 5). However, recent concerns have been raised about potential adolescent promiscuity when young adults are vaccinated against a sexually-transmitted infection and about the high cost and potential side-effects of the vaccine itself (6). Models of HPV vaccination have typically assumed that vaccination rates will linearly increase during the first five years of implementation and reach at least 70% of the eligible population (7, 8). Yet less than one quarter of eligible women have received even one of the three recommended doses of the HPV vaccine, despite its approval and marketing almost three years ago (9). Therefore, it may be prudent to examine the impact of the target population's perspectives or behaviors on the efficacy of HPV vaccination programs. In the past, vaccination programs have been stymied by such public perceptions (10).

Game theory has recently been integrated with disease models to examine how public perceptions can affect public health goals (11–15). In game theoretic analyses, the level of vaccination in a community stabilizes at a "Nash equilibrium" where individual cannot reduce their perceived risks or increase their perceived benefits by switching to a different decision (16). The individual's perceptions may not be rational or even well-informed, but may depend on public rumors, economic or social constraints, and on the community incidence of disease (11). The purpose of such models is not to attempt to predict human behavior, but to examine incentives and disincentives for vaccination

Here, we used game theory and epidemiological models to examine the impacts of public perceptions and economic costs on incentives for HPV vaccination in the U.S (17) (Fig. 1). We used a survey of the perceived risks and benefits of vaccination among parents of vaccine-eligible children to calculate the percentages of the females and males that could have sufficient incentive to vaccinate at the Nash equilibrium, which we refer to as the "Nash vaccination levels." We examined how alternative public health policies related to federal immunization programs may provide further incentives for individuals that could meet population-level vaccination targets. The "socially optimal" targets were defined as the female and male vaccination levels that maximized health-related benefits and minimized health-related costs for the overall population, in terms of both population health and health-related expenditures.

Results

Survey Results. Responses to our survey revealed that the perceived risk of cervical cancer if vaccinated was significantly lower than the perceived risk if not vaccinated (paired-sample t (164) = 7.72, $P < 10^{-4}$; Table 1). Similarly, the perceived risk of genital warts if vaccinated was significantly lower than the perceived risk if not vaccinated (paired-sample t (321) = 11.86, $P < 10^{-4}$, including parents of boys). However, participants had relatively low expectations for vaccine efficacy; the mean perceived relative risk reduction was 54% for cancer and 32% for warts. Screening for cervical pathologies was thought to be required significantly less frequently with vaccination than without (paired-sample t (164) = 4.38, $P < 10^{-4}$). Survey recipients also believed that adolescent sexual behavior would increase among those vaccinated by a factor of 1.8 on average.

Estimates of Vaccine Impact. Before conducting the game theoretic analysis, we calculated the vaccine's cost-effectiveness to compare it to prior cost-effectiveness studies. At the current cost of $360 per vaccine series, the cost-effectiveness ratio for vaccinating 70% of women with a 95% effective vaccine conferring lifelong immunity was $14,800 (95% CI: $14,140–15,540). The incremental cost of such vaccination was $248.55 for discounted quality-adjusted life years (QALY) gain of 0.01679 from a baseline discounted life expectancy of 29.328 years. This value is close to the $13,650

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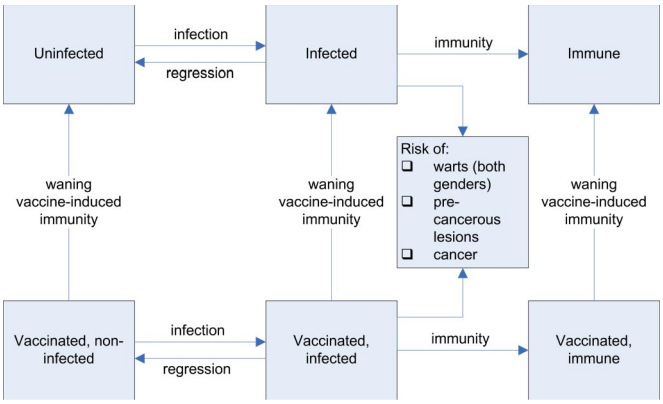

Fig. 1. Flow diagram for the model. Four types of HPV infection (16, 18, other high-risk types, and low-risk types) were simulated among seven age classes, including the most common co-infections and type-specific immunity. See SI for equations and sexual activity patterns among males and females among age classes.

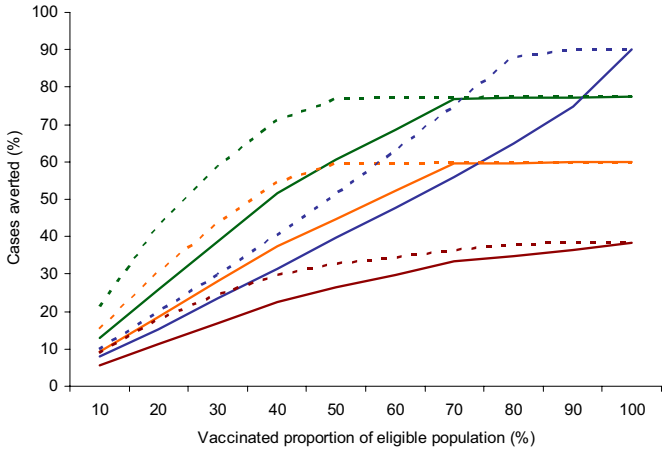

Fig. 2. Percent cases averted through vaccination in a scenario with a 95% effective vaccine conferring lifelong immunity, without changes to screening or sexual risk behavior. Vaccine-preventable HPV infections (types 16, 18, 6, and 11) constitute 77% of cervical cancers, 39% of cervical intraepithelial neoplasias grade 1 (CIN1), 60% of CIN2/3, and 90% of genital warts cases at baseline (0% vaccination). Solid lines reflect female-only vaccination (red, CIN1; orange, CIN2/3; green, cancer; blue, warts); dashed lines reflect vaccination of both genders. The transmission dynamics of low-risk HPV types differs from that of the high-risk types, hence the impact of vaccination on warts produces a qualitatively different trajectory from vaccination's impact on cancer and precancerous lesions. Cases averted plateaus due to other strains not covered by the vaccine.

average (range: $3,000–24,300) from commonly-cited cost-effectiveness analyses (7, 18–20). The discounted cost, QALY, and life expectancy values are also similar to those estimated by the prior studies (range: $244–362, 0.0077–0.0286 years, and 27.720–28.798 years, respectively) (7, 18–20).

Cancerous pathologies from vaccine-types of HPV were eliminated when more than 68% of females were vaccinated in our model. Vaccinating males has an epidemiological benefit that diminishes with increasing vaccination coverage in women (dashed lines in Fig. 2). For example, if 40% of males are vaccinated, the level of female vaccination required to eliminate vaccine-type HPV pathologies drops from 68% to 55%. If both genders are vaccinated to the same level, approximately 50% of both genders required vaccination to achieve vaccine-type elimination. However, the cost per QALY gained from vaccinating 50% of both genders was larger than the cost per QALY gained from vaccinating 68% of females only. Vaccination of both genders accumulated incremental discounted costs of $356.80 versus $248.55 when only females are vaccinated, for a total discounted QALY benefit of 0.01585 years versus 0.01679 years.

Game Theoretic Results. We found that the socially optimal target vaccination level in this model was 67% vaccine uptake among females (95% CI: 64–80%) and 0% among males (Fig. 3). At any level of female vaccination below the threshold for elimination of vaccine-types of HPV, increasing the vaccination level among females had a greater incremental benefit than increasing the level among males. Levels of vaccination above the threshold did not outweigh the costs of additional vaccination in both health-related QALY and costs at a standard QALY-to-dollar conversion ratio of $50,000 per QALY. However, at higher levels of willingness to pay for each QALY, the impact of further reducing warts-related QALYs and costs did increase the socially optimal vaccination level (Fig. 3).

We found that the social optimum was sensitive to vaccine efficacy and to the duration of vaccine-elicited immunity. The optimum was reduced from 67% female vaccination at 95% efficacy to 58% in the case of a perfectly effective vaccine, because the same disease burden was achieved with less vaccination and lower cost. Conversely, vaccination at the social optimum increased by 3% for a vaccine with 85% efficacy. Reducing the duration of immunity increased the optimum level of vaccination, as further vaccination became necessary to achieve the same epidemiological benefit. Optimal vaccination reached 100% by 31 years of vaccine-induced immunity, assuming 95% efficacy. The optimum remained at 100% as the duration of induced immunity was further reduced, until a threshold of 11 years. Below this threshold, the cost of the vaccine exceeded its benefits, decreasing the optimal level to 0%.

We found that Nash vaccination levels were lower than the social optimum at all levels of willingness-to-pay for health. The female vaccination level was only 32% at the baseline willingness-to-pay

Table 1. Responses to questionnaire items by parents of 11- and 12-year-olds

Questionnaire item	Mean (95% CI)
What do you think your child's chance of getting cervical cancer is if she is NOT vaccinated against HPV?*	29.4% (25.6–33.2%)
What do you think your child's risk of cervical cancer is if she were to be vaccinated against HPV?*	12.3% (9.4–15.2%)
What do you think is your child's risk of ever getting genital warts is, if they are NOT vaccinated against HPV?	30.3% (27.3–33.3%)
What do you think is your child's risk of ever getting genital warts is, if they were to be vaccinated against HPV?	11.0% (8.9–13.1%)
How long do you think the vaccine will protect a recipient against HPV?	40.2 yrs (36.4–44.0 yrs)
What influence would the vaccine have on the number of sexual partners in their lifetime? (Decrease, increase, or stay the same by a factor of X)†	Increase by factor of 1.8 (1.6–1.9)
If your child was NOT vaccinated against HPV, how frequently would you recommend her to have a Pap smear?*	1.07 times per year (0.81–1.33)
If your child was vaccinated against HPV, how frequently would you recommend her to have a Pap smear?*	0.93 times per year (0.63–1.23)

Mean and 95% confidence intervals to survey questions are displayed.
*Question administered to parents of women children only, $N = 165$; $N = 322$ for other items.
†Asked of a convenience sample of 286 college students.

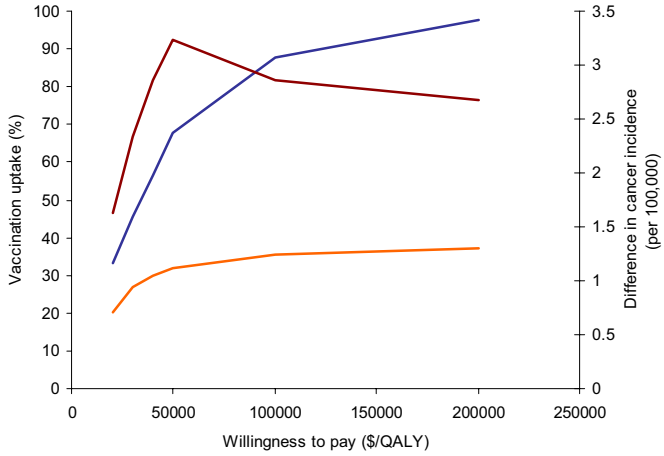

Fig. 3. Varying the conversion ratio between dollars and QALYs. The social optimum vaccination level (blue) and Nash female vaccination level (orange) were compared while the willingness to pay for each QALY was varied. The difference in cancer incidence per 100,000 between the Nash and optimum levels (green) peaked after the utilitarian reached a maximum threshold of cancer cases averted (while higher socially optimal levels of vaccination conferred further benefits from reduced warts at higher levels of willingness to pay).

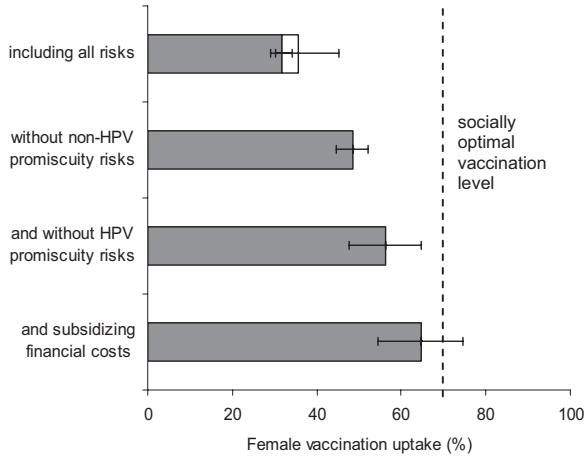

Fig. 4. Nash vaccination levels are displayed against different perceived risks of vaccination. ''Without non-HPV promiscuity risks'' describes risks of other major STDs (HIV, herpes, gonorrhea, *Chlamydia*, syphilis) and teenage pregnancy under the perception that HPV vaccination would increase risky adolescent sexual behavior; ''HPV promiscuity risks'' similarly refer to HPV-related health consequences from promiscuity; ''subsidizing financial costs'' refers to full coverage of the uninsured by the VFC and vaccine-manufacturer programs, as well as coverage of non-vaccine costs to patients (patient time costs, administration fees, and doctors' visit costs).

level of $50,000/QALY (Fig. 3). The social optimum was much more sensitive than the Nash vaccination levels to the willingness to pay per QALY. Thus, as the willingness to pay for each QALY increased, the discrepancy between the Nash vaccination level and the social optimum increased as well. At $100,000/QALY, the optimal level of vaccination among women was 88%, but the Nash vaccination level only increased to 35%. The optimum was higher than the 68%, because further QALY benefits were accrued by reducing warts when people are willing to pay for the QALYs associated with warts risks (Fig. 2). We found that up to 3.2 cases of cancer per 100,000 could be averted by aligning the Nash levels with the social optimum (Fig. 3). At the willingness-to-pay level of $50,000/QALY, achieving the social optimum was estimated to achieve a 73% decline in cancer incidence from the baseline level of 9.7 per 100,000 per year.

Although Nash vaccination levels were low as a result of risk perceptions, the perceived reduced need for screening among survey recipients also indirectly lowered the Nash vaccination levels. The vaccination level at the Nash equilibrium would have increased by 11% had vaccine recipients not reduced their level of screening, because the reduced level generated a higher burden of pathologies from HPV types not included in the vaccine, and thus reduced the incremental benefits of high levels of vaccination.

Public Perceptions Regarding Adolescent Promiscuity. Public perceptions regarding adolescent promiscuity had the most significant impact on the Nash vaccination levels among the topics we analyzed. We first simulated the case in which all perceived risks of promiscuity (increased HPV-related disease, other sexually-transmitted diseases, and teenage pregnancy) were included in the Nash calculation. We then simulated the case in which these different concerns about adolescent promiscuity were dispelled.

When perceived costs of sexually-transmitted diseases (other than HPV) and teenage pregnancy were included among vaccine risks, the Nash vaccination strategy was 32% for females (95% CI: 29–34%) and 3.9% for males (95% CI: 0–12%). The male vaccination level was above zero given the larger benefits to males of avoiding genital warts when few females have been vaccinated (an absence of herd immunity benefits).

When the risks of non-HPV sexually-transmitted infections and pregnancy were removed from the risk calculation, such that only HPV-related disease risks were considered, the Nash vaccination level for females rose to 49% (45–52%). At these higher levels of female vaccination, herd immunity benefits eliminated incentives for men to vaccinate. Thus, the Nash vaccination level for males reduced to 0%. Further removal of all perceived adolescent promiscuity risks, including perceived risks related to increased HPV disease from adolescent promiscuity, elevated the Nash female vaccination level to 56% (47–65%), but did not reach the social optimum of 67% (Fig. 4).

Our model predicted that no vaccination would occur at the social optimum if the fears of adolescent promiscuity that were recorded in our survey were actualized, given the dramatic perception that sexual risk among adolescent vaccine recipients would nearly double (Table 1). The real-world health and economic costs of such sexual behavior repercussions outweighed vaccine benefits if these perceptions were borne out, because the near-doubling of sexual activity produced a profound increase in the costs of sexually-transmitted disease to the community. It is notable that such an increase in sexual behavior has never been observed to our knowledge and thus would be highly unlikely.

Economic Incentives. Economic costs to individuals significantly impacted Nash vaccination levels. Private insurers typically follow the recommendations of the CDC's Advisory Committee on Immunization Practices (21), which recommends HPV vaccination (2). However, an estimated 13% of children are uninsured for vaccines (22). Although the government Vaccines for Children Program (VFC) subsidizes the cost of the vaccine itself, it permits providers to pass administration costs and doctor's visit fees onto patients (23). In addition, there are the implicit work time, transport, and related expenses associated with making three doctor's office visits to receive all three doses of the vaccine (23). Similarly, the vaccine manufacturer's free vaccine program covers only a minority of low-income patients given its eligibility requirements (see *Methods* for details) (24). We estimated that if the VFC continues to reach 50% of those children without insurance coverage for vaccination (25) and the manufacturer's vaccination program continues to reach an additional 15% of the uninsured, an average household would still have to bear a cost of $181 to provide a child with the complete vaccine series.

By reaching all of those children without insurance coverage for

vaccination, the VFC only increased the Nash vaccination level by 3% (1–5%) to 59% in our calculations. This increase was modest, because the majority of costs remaining with vaccinated children's families were costs related to lost work time and doctor visit fees associated with making three visits to the physician, rather than from the vaccine's cost itself. If subsidies were offered to cover these administration-related costs, the Nash vaccination level would increase by 9% to 65% for women (55–75%), nearly in line with the social optimum (Fig. 4). To maintain the same VFC budget, however, we estimated that the cost of the vaccine itself would need to be reduced by $55 per dose (from a baseline price of $120 per dose) for the program to bring the Nash and optimal vaccination levels into alignment by redistributing funds to cover administration-associated patient expenses. At this vaccination level, an estimated 48% of cervical cancer cases could be averted, when accounting for reduced screening rates among vaccine recipients from the survey data.

Discussion

We performed a game theoretic analysis of HPV vaccination based on survey data collected to assess public perceptions about the risks and benefits of HPV vaccination. While no mathematical model can predict human behavior, the purpose of game theoretical analysis is to examine incentives and disincentives for vaccination that could influence levels of vaccine uptake and disease risk within different social and economic contexts. The model revealed that the perception that sexual promiscuity would increase among vaccinated adolescents could have a significant impact on vaccination levels at the Nash equilibrium. The Nash vaccination level was far below a level that, on balance, maximized overall health-related benefits and minimized overall health-related costs for the population, in terms of population health and health-related expenditures. When the perceived costs of promiscuity, including the consequences of increased sexually-transmitted diseases other than HPV and increases in teenage pregnancy rates, were taken into account, the Nash vaccination level among females was only 32%, rather than the 67% target level.

There is no evidence that perceptions of increased adolescent sexual promiscuity are based on reality. Nonetheless, these perceptions may impact decision making of the public with regard to HPV vaccination. If these perceptions could be minimized through educational programs, the Nash vaccination levels could substantially increase according to this model. This result supports the CDC's ongoing efforts to identify the degree of perceived risk and benefit among the parents of vaccine-eligible children and design educational programs based on these perceptions (26).

Although reduced perceptions of vaccine-related risk promoted vaccination in this model, such risk perception changes alone were not found to be sufficient to elevate the Nash vaccination levels to meet target vaccination levels. The alignment of the Nash equilibrium and social optimum was achieved in this model by the introduction of new economic incentives for vaccination. In our simulations, extensive costs were transferred to patients in terms of doctor's visit fees and administration costs and lost work and related time costs for parents to make three doctor's office visits for their child to obtain the full vaccine series. To align the Nash and utilitarian vaccination levels, subsidizing these costs faced by parents, not just the cost of the vaccine itself, would require the vaccine to be $55 less expensive per dose, if the overall government VFC budget were to remain unchanged. Alternatively, the VFC budget would need to expand by $165 per person vaccinated, based on the assumed costs included in this model. Subsidizing patients' costs increased female Nash vaccination levels to 65% when combined with a successful educational program that averted vaccine risk perceptions among parents.

This result suggested that game theoretic models could become useful for assessing what vaccine prices could help to achieve public health targets. Current vaccine pricing is based on market valuations rather than assessments of public health need and available budgets. The model used in this analysis predicted that the constraints placed upon vaccine manufacturer programs to offer a proportion of vaccines without charge may critically limit their real-world efficacy. Coverage for the HPV vaccine by the manufacturer does not extend beyond office-based clinics. However, much of the low-income population in the United States attends public health clinics that are not eligible to provide free vaccines through the manufacturer's program (24). Hence, the full cost of vaccination is placed upon the portion of the population that currently has the highest rates of cervical cancer and the lowest rates of screening. Our calculations indicated that at current rates of insurance coverage, government subsidization, and manufacturer program accessibility, almost 1 of every 20 vaccine-eligible females would bear the full costs of vaccination, a cost burden equivalent to $525 per child to obtain the full vaccine series.

The cost of HPV-related disease screening and management is estimated to be $2.9 billion per year. Consequently, vaccination may be highly beneficial for the health system, but only if made accessible. Further studies are being conducted to examine how best to integrate new screening technologies and protocols fddddinto the health system in the context of vaccination, as reductions in screening-related costs may be a major health system benefit of vaccination (30, 31). Improvements in screening technologies in the future may permit the realized risk of cancer with HPV infection to decline, but may also be mediated by perceptions of the public concerning the need to visit doctors' offices and obtain screening after vaccination. The perception that screening was of significantly lower importance to vaccinated than unvaccinated women resulted in an increased level of pathology from the types of HPV not covered by the currently-available vaccine in our model. The perception reduced the socially optimal vaccination level in our model by 11% because vaccine-associated reductions in screening created new health costs that generated reciprocal disincentives to vaccinate. This result emphasizes the need for education related to the importance of screening in the postvaccine environment.

As with all mathematical models, this model makes assumptions to examine real-world relationships through a simplified representation of reality. No cross-immunity was incorporated between HPV types, as in prior studies of HPV vaccination (5, 7, 18–20, 27, 28). If the vaccine does confer cross-immunity to other HPV types, the discrepancy between the Nash equilibrium and social optimum would likely be more pronounced, and therefore our results may be viewed as conservative. The potential for type replacement among HPV viruses, improvements in screening, and uncertainties about immunity remain subjects of investigation (18, 29). These factors could lower the socially optimal level of vaccination from the case in which type replacement does not occur, access to screening remains low among significant parts of the population, and the duration of immunity is lifelong. Furthermore, as with cost-effectiveness assessments, we used quality-adjusted life years (QALYs) as an index of health-related utility. However, QALY values will vary among different members of the population and merely serve as rough estimates to quantify intrinsically qualitative aspects of health (30). Hence, we examined the differences between QALY estimates across a broad range of potential utilities and levels of willingness-to-pay for health. Because sexual promiscuity became a subject of controversy during the course of this analysis, we supplemented our survey of parents with a sexual behavior perception survey among a convenience sample of college students. Actual perceptions of sexual behavior may differ between parents and our convenience sample. Finally, we simulated vaccination of 11- to 12-year-olds, as they are the long-term focus of the CDC vaccination programs. The current catch-up vaccination program for the 19- to 26-year-old age class may be even more challenging to implement, given this group's underinsured status in the United States (24).

Our analysis provides a framework for integrating perceptions of risk into health policy models, which can be refined and extended as the social study of risk perceptions produces greater understanding of the factors that impact the acceptance of new public health interventions. Determining the risk perceptions that play into the willingness of parents to have their children vaccinated is a difficult challenge to achieving vaccination targets. The results from a model of HPV vaccination suggest that subsidizing administration-related costs of vaccination, in addition to costs of the vaccine itself, may be important to encourage eligible families to seek HPV vaccination. Our findings also emphasize the importance of educational programs in addressing concerns that could inhibit effective vaccine uptake.

Methods

Survey. We surveyed 326 adults matched to U.S. demographic statistics; 165 were the surrogate decision-makers for 11- to 12-year-old girls and 157 were decision-makers for 11- to 12-year-old boys (4 subjects were excluded due to incomplete responses). The supporting information (SI) provides demographic statistics on the sample. Following this initial survey, public concerns arose that HPV vaccination could increase sexual activity among adolescents. We further assessed this perception in a convenience sample of 286 college students (42% women) to gain a sense of how prevalent this idea was in a current recipient population and to what extent sexual behavior was thought likely to increase in the context of vaccination. Table 1 summarizes the questionnaire items developed for the parameterization of the mathematical model.

Model Assumptions. A deterministic age-structured mathematical model was used to simulate HPV vaccination, transmission, and disease risks among women and men in the United States. We simulated the vaccination of females and males at ages 11 to 12, followed by HPV transmission in the age groups of 15 to 19 and each of six subsequent decades of life, allowing for explicit aging between classes while holding the population demography stable in the age distribution observed in the 2005 U.S. Census (31). We adopted a modified susceptible-infected-recovered-susceptible (SIRS) structure (Fig. 1) simulating transmission of four representative HPV types (16; 18; other high-risk, HR, types that can induce cancer; and low-risk, LR, types that can confer genital warts), including the potential for type-specific immunity and co-infections. Vaccination averted type 16, 18, and a fraction of LR infections (reflecting the burden of types 6 and 11, covered by the vaccine), conditional upon vaccine efficacy and the duration of induced immunity. Sexual activity rates and mixing patterns were incorporated through a ''who acquires infection from whom'' matrix (10), which is detailed with the model equations in the SI.

The HPV parameters used in the model are specified in the SI. To estimate the transmission rates and proportion of infected persons acquiring natural lifelong type-specific immunity after infection, a Bayesian calibration procedure described previously (32) was adopted to calibrate the model against age-specific HPV prevalence data (33). Monte Carlo iterations, burn-in, and thinning were calculated using the Raftery-Lewis diagnostic (34), and standard autocorrelation and convergence criteria were used to confirm the robustness of the results (35, 36). To calculate the probability of subsequent disease associated with each type of infection, we used Bayes' rule, such that the age-specific probability of disease from each type of infection was estimated as the product of the proportion of disease attributable to that HPV type (metaanalysis in the SI) and the probability of the disease in the population, divided by the probability of infection by that type, where the latter two components were taken directly from publicly-available age-specific datasets (33, 37–39). This serves as an alternative to compartmentalizing all disease stages and rates of flow between them, which has led to numerical identifiability problems in the context of fitting large models to limited data (40). Such problems do not merely add to parameter uncertainty, but also produce bias and skew in outcome mean and confidence interval calculations because of multimodality in the landscape of parameter values that can fit limited data (41–43). The above approach prevents identifiability biases, while implicitly accounting for current rates of screening, diagnosis and medical intervention in the risk calculation. Five types of disease were considered in the model—three types of precancerous lesions (cervical intraepithelial neoplasia (CIN) grades 1 through 3) as well as genital warts and cervical cancer (including squamous cell, adenocarcinoma, adenosquamous, and other cervical carcinomas).

Costs and Health-Related Utility. We incorporated the cost of the currently-available quadrivalent HPV vaccine ($120 per dose ×3 doses) (44), vaccine administration costs ($15 per dose ×3 doses) (23), patient time costs ($20 per visit ×3 visits) (18, 28), and clinician fees to patients ($15 per visit ×3 visits) (18, 28). For disease states, we included the costs of managing incident CIN1 ($1,739), CIN2 ($3,233), CIN3 ($3,671), cervical cancer ($31,120), and prevalent genital warts ($425) (8). We calculated the disease risk per prevalent HPV infection, hence current screening rates are implicit in the risk calculation. Rates and costs of screening will not be differentially affected by vaccination after already accounting for disease risk rates per HPV type and the risk change upon vaccination (below), hence we did not need to tally additional screening costs, which would subtract out from the calculations described below. We also included the economic productivity costs due to lost work from cancer, of $9,686 per case when adjusting a per-death estimate by the probability of death per case (45).

In one iteration of the model, detailed further below, we incorporated the potential economic consequences if surveyed perceptions of increased sexual promiscuity among vaccinated adolescents were actualized. We tallied the economic costs of the most common sexually-transmitted infections and teenage pregnancy. These were the lifetime management costs per new case of HIV ($199,800), genital herpes ($417, women; $511, men), *Chlamydia* ($244, women; $20, men), gonorrhea ($266, women; $53, men), syphilis ($444), and teenage pregnancy ($7,177, women only; estimated as the differential cost of supporting a household with teen pregnancy, versus that when pregnancy is delayed until adulthood) (46, 47). All costs were tabulated in 2005 U.S. dollars using the Consumer Price Index (48).

In addition to financial costs, we tallied the health-related survival and quality of life costs related to HPV and potentially averted by vaccination. The health-related ''utility'' of each year of life, conditioned upon disease, was computed in standard quality-adjusted life years (QALYs) (30), such that a year of healthy life had a QALY value of 1. Other QALY values incorporated into the analysis were 0.91 for CIN1 and warts, 0.87 for CIN2/3, 0.70 for cancer, 0.83 for HIV, 0.993 for genital herpes, 0.93 for *Chlamydia* and gonorrhea among women, 0.997 for *Chlamydia* and gonorrhea among men, 0.88 for syphilis, and 0.94 for teen pregnancy (7, 49–51). All costs and QALYs were discounted at a 3% annual rate (30).

Nash and Social Optimum Calculations. To calculate vaccination levels at the Nash equilibrium and social optimum, we calculated individual and population utilities. The utility to individuals was different for women and men given their different risks and benefits from HPV infection and vaccination. We defined total utility as the sum of QALYs and costs, varying the QALY-to-dollar/willingness-to-pay conversion ratio.

QALY losses to females included the perceived risks of cancer and warts with and without vaccination, weighted by the probability of vaccination among women and the perceived duration of protection, multiplied by the QALY disutilities of cancer and warts. The perceived risks at any given vaccination level were the estimated risks from the model at that vaccination level, multiplied by the ratio of the survey-based perceived risks and the model-given true risk in the absence of vaccination (52, 53). Latin Hypercube Sampling was used to sample from the joint distribution of survey responses to propagate heterogeneities in perceived risk responses from the survey data to the utility calculation (54, 55). Male QALY losses were similarly calculated, including only genital warts.

Dollar costs to individuals included the probability of vaccination multiplied by the time cost of vaccination and associated physicians' fees to patients, listed above. We then added the cost of the vaccine itself multiplied by the probability of lacking vaccine insurance coverage (0.13) and neither being covered by the VFC (which covers 50% of the uninsured) or the vaccine manufacturer's subsidization program (which covers 15% of the uninsured) (22, 24, 25). From this dollar cost, we subtracted the disease costs saved by vaccination, multiplied by the proportion of the population that would normally pay for disease costs themselves (15%) (56). We also subtracted the income loss saved by vaccination as a result of averted cancer, estimated by the model.

In light of the survey results (Table 1), we evaluated a scenario in which the relative risk of non-16/18 HPV cancers increased as a result of reduced screening among vaccine recipients (estimated to be a RR = 1.18, 95% CI: 1–1.87 from a prior analysis, ref. 57). We also evaluated the scenario in which the sex level among adolescents in the model increased in accordance with the surveyed perceptions. The sex level increase led to increases in HPV pathologies calculated by the model and new non-HPV STDs and teen pregnancies calculated by multiplying the perceived change in the sex level among adolescents by the linear regression coefficients between sex rates and rates of STDs and pregnancies in the United States (21, 58) ($\rho > 0.96$, $R^2 > 0.92$). Costs and QALYs were multiplied by these new cases and added to the cost and QALY losses of individuals in these scenarios.

To calculate Nash vaccination levels, the vaccination level for each gender was found at which the total health-related disutility was minimized, using a simulated annealing search algorithm (59). The disutility is the sum of QALY losses and dollar losses, where the willingness-to-pay per QALY was varied as per Fig. 3. The social optimum level of vaccination was calculated by maximizing the difference between long-term marginal benefits and long-term marginal costs of vaccina-

tion with regard to both health-related quality of life for the population, and economic costs irrespective of who pays for them. The cost of vaccination was multiplied by the vaccinated proportion per gender, times the proportion of the population eligible for vaccination. HPV disease-related costs averted from vaccination and productivity costs gained through averted cancer cases were subtracted from this tally of dollars lost. The net dollars lost, converted to QALYs, were added to QALYs lost from disease based on the model's disease predictions at each vaccination level. Simulated annealing was also used to calculate the socially optimal vaccination levels to minimize the total disutility for the population. Uncertainty analysis was performed by Latin Hypercube Sampling from the parameter ranges (SI) to estimate the impact of parameter uncertainty on model outcomes (54, 55).

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