The Theoretical Population-Level Impact of a Prophylactic Human Papilloma Virus Vaccine

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Background. The ongoing development of a vaccine against human papillomavirus (HPV) raises important questions about the impact of various vaccination strategies.
Methods. Two mathematical models are developed to explore the population-level impact of an HPV vaccine. The first model focuses on the infection process and the second on the disease process (specifically, cervical carcinoma *in situ* and cancer).
Results. Both population characteristics (*ie*, sexual mixing and rates of sex partner change) and vaccine characteristics affect the steady state prevalence of HPV that would be expected if a vaccine program is implemented. Under a particular set of assumptions, we find that vaccinating both men and women against a specific HPV type would result in a 44% decrease in prevalence of that type whereas vaccinating only women would result in a 30% reduction. We also find that if a vaccine gives protection against some, but not all, high risk types of HPV, the reduction in disease may be less than the reduction in HPV because the remaining high risk HPV types may replace the disease caused by the eliminated types.
Conclusions. A multivalent vaccine containing the majority of disease-causing HPV types would greatly reduce the need for colposcopy, biopsy and treatment. However, it is unlikely that Pap-screening programs would become redundant unless the vaccine is highly effective and coverage is widespread. In contrast to less common infections that are primarily restricted to core groups, targeting the vaccine towards the most sexually active individuals is less effective for a common sexually transmitted infection such as HPV.
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Key words: papillomavirus, human, cancer, cervical, vaccine, model, theoretical.

Cervical cancer is a leading cause of mortality among women in developing countries.[1] In developed countries, screening programs have greatly reduced cervical cancer mortality although cervical dysplasia remains a leading cause of morbidity. In the United States alone, treatment for cervical dysplasia results in annual health care costs in excess of $1.5 billion,[2] whereas pap smear screening costs an additional $2 billion.

Editors' note: *An invited commentary on this article appears on page 622.*

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Most, if not all, cases of invasive cervical cancer and cervical dysplasia are attributable to infection with a subset of human papilloma virus (HPV) types (especially types 16, 18, 31, 33, 35, 39, 45, 51, 52, 55, 58, 59 and 68). For this reason, a prophylactic vaccine against HPV has the potential to have a substantial impact on HPV infection and cervical disease. Indeed, phase 2 trials of candidate vaccines are currently underway in the United States and phase 3 trials are being planned.[3] However, even if a vaccine is shown to be effective in preventing infection from one or more types of HPV, there is considerable uncertainty about the most effective strategy for vaccination and the likely impact of vaccination on HPV and cancer incidence. Should vaccines be focused on high-risk groups or administered more widely? Must both men and women be vaccinated or can a program targeted at only women be effective? These questions can be addressed via modelling.

Mathematical models of the transmission dynamics of infectious disease provide a framework within which patterns of infection and disease can be understood and the potential impact of interventions explored. Models describing the impact of vaccines against childhood infections such as measles, mumps and rubella have a long

history and have played an important role in the development of new vaccination programs.[4,5] Recently, models describing the public health impact of hepatitis B vaccines[6] and potential human immunodeficiency virus (HIV) vaccines[7,8,9] have been developed. These models illustrate the potential gains that can be achieved by moderate levels of vaccine effectiveness, as well as the difficulties in attempting to eradicate such infections.[8] A number of authors have developed mathematical models of the natural history of HPV and cervical cancer, primarily to evaluate the cost-effectiveness of various screening strategies for cervical cancer.[10,11] Garnett and Waddell discuss some issues that are unique to an HPV vaccination program.[12] In this paper we use mathematical modelling to address these issues quantitatively. We develop two models. In the first, we examine the impact of a type-specific prophylactic HPV vaccine on the prevalence of that HPV type in the general population. We investigate the potential impact of the vaccine on HPV prevalence under various assumptions about the vaccine characteristics, population structure and vaccination strategies. In the second model we look at the impact of reductions in the incidence of individual HPV types on the incidence of carcinoma *in situ* (CIS) and invasive cervical cancer (ICC).

Model Description and Parameterization

Model 1

To model the transmission of HPV and the introduction of a vaccine, a simple compartmental model of heterosexual HPV transmission dynamics was developed (see Anderson and May[13] for a review of such models). The population was divided into three sexual activity groups defined by differences in rate of sex partner change. A vaccine that could have a wide range of properties, including reducing susceptibility to infection, reducing the transmissibility of virus, and reducing the mean duration of infectiousness of breakthrough infections, was introduced into this population. Vaccination could fail (1) by having no effect in some people; (2) by reducing, but not fully eliminating, susceptibility in those immunized; or (3) through the loss of protective immunity with time. These three modes of vaccine failure are referred to as "take," "degree" and "duration," respectively.[6] The model is shown graphically in Figure 1 and algebraically in Appendix 1. Table 1 lists the default values used for the parameters in this model. These are the values used for the model runs described below unless otherwise indicated.

Model 2

In model 2 the incidence of CIS or ICC is related to the age-specific incidence of HPV infection and the rate of progression from infection to disease. A cohort of women is divided into four sexual activity classes. These women become at risk for HPV infection (become "susceptibles") at some age that we will arbitrarily designate as time zero (*eg*, assume that individuals become sexually active at 16 years of age). The risk of HPV infection in the susceptibles is assumed to vary with age and sexual activity group, which reflects the known heterogeneity in risk for acquiring a sexually transmitted infection.

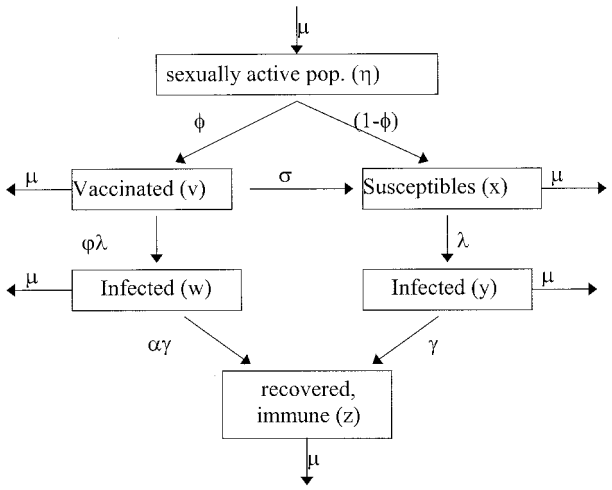

FIGURE 1. Graphical depiction of model 1.

Once infected, individuals progress to the outcome of interest (CIS or ICC) at a rate that depends on how long infection has been present. The age-specific risk of disease development is the product of the risk of disease development at a particular time since infection and the number of (surviving) individuals who acquired infection at that time in the past, accumulated over all times since infection for that age group. When cancer is the endpoint, a proportion σ of the cancers does not occur because of early detection of a precursor lesion (this proportion will likely be somewhat less than the proportion of women receiving regular screening because even the best screening programs cannot detect all incipient cancers). Screening may also reduce the risk of CIS, depending on how aggressively clinicians treat lower-grade lesions. Women who screen positive for dysplasia (and are presumably treated) or who have had a hysterectomy are assumed not to be at risk of developing disease. Figure 2 depicts this model graphically. The model equations are given in Appendix 1, and Table 2 gives the default parameter values used in the model runs.

More details on both models and the choice of parameter values are given in supplementary Appendix S-1 (available with the electronic version of this article http://www.epidem.com).

TABLE 1. Default Parameter Values for Model 1*

Description	Symbol	Type	Default Value(s)
Overall			
Mean duration in the sexually active population (yr) (*ie*, period for which $c > 0$)	$1/\mu$	D	15
Mixing parameter	ε	D	0.7
Activity-group specific			
Proportion in activity group l	ω_l	D	0.03, 0.15, 0.82†
Effective partner change rate for activity group l (partners/yr)	c_l	D	9.0, 3.0, 1.4†
Gender-specific			
Transmission rate from infectious individual of sex k′ to susceptible of sex k	β_k	B	0.7, 0.8‡
Relative risk for transmission of a vaccinated individual with breakthrough infection compared with an unvaccinated individual with natural infection	r_k	V	1.0
Relative susceptibility to infection of vaccinated individuals of sex k compared with unvaccinated individuals of sex *k* ("degree")	φ_k	V	0.25
Mean duration of vaccine protection (yr)	$1/\sigma_k$	V	10.0
Mean duration of infectiousness for individuals of sex k (yr)	$1/\gamma_k$	B	1.5
Relative rate of recovery from (breakthrough) infection in vaccinated individuals of sex k compared with unvaccinated individuals	α_k	V	1.0
Gender/activity-group specific			
Proportion of individuals of sex k and activity group l who are effectively vaccinated (includes the vaccine "take")	$\phi_{k,l}$	V	0.9 for all groups

* Symbol refers to the symbol in the model equations in Appendix 1. The codes for parameter type are D = demographic; B = biologic/natural history of HPV; V = vaccine.
† High, medium, and low activity groups, respectively.
‡ Female-to-male and male-to-female, respectively.

Results

Endemic Prevalence of HPV Infection

Using model 1 we explore the effects of sexual mixing and vaccine characteristics on the effectiveness of various vaccination strategies. The outcome in Figures 3–6 is the endemic prevalence of a specific HPV type (*eg*, HPV 16). This is the proportion of individuals who are detectably HPV DNA positive after a long period of vaccine use under steady-state conditions. Figure 3 shows the relation between (endemic) HPV 16 prevalence and vaccine coverage for an ideal vaccine (*ie*, 100% effective in providing long-lasting immunity for both sexes) in a sexually heterogeneous population. The figure emphasizes the important role that heterogeneity in levels of sexual activity within the population plays in determining the response to different levels of vaccine coverage. The figure shows three scenarios, each of which corresponds to a weighted mean partner change rate (defined as

$$\sum_l \omega_l c_l .$$

using the notation in Table 1) of 1.87. Anderson and May[13] show that for an ideal vaccine the critical level of coverage necessary for disease eradication (π_c) in an

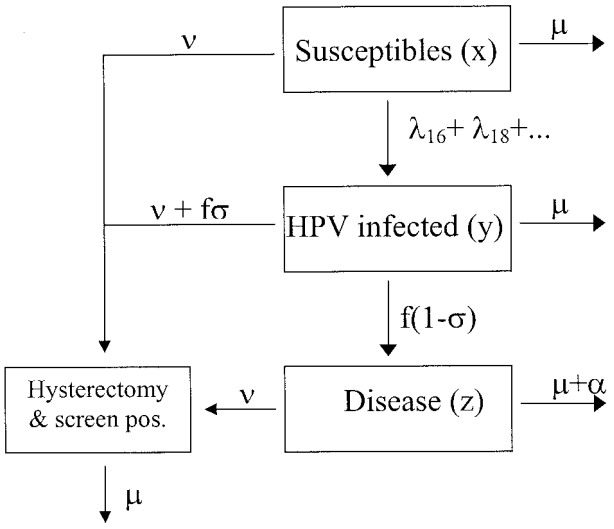

FIGURE 2. Graphical depiction of model 2.

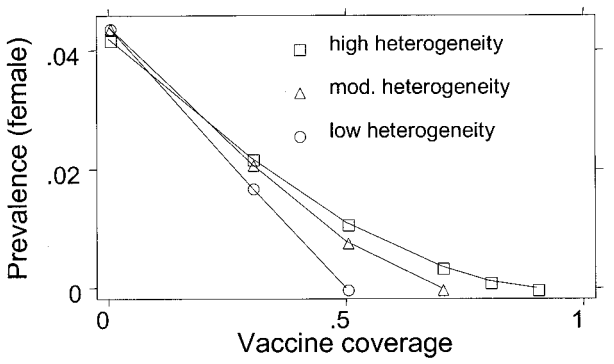

FIGURE 3. Predicted prevalence of HPV by vaccine coverage (ϕ in Table 1) from model 1. The vaccine is given to both sexes and assumed to be 100% effective in providing long-lasting immunity to all individuals receiving it. The population is stratified into three levels of sexual activity with proportions 0.82, 0.15 and 0.03. Low heterogeneity corresponds to an effective partner change rate (*c*) of 1.87 in each stratum. Moderate heterogeneity corresponds to $c = 1.4$, 3 and 9, respectively. High heterogeneity corresponds to $c = 1$, 3 and 20, respectively. Mixing between strata is assumed random ($\epsilon = 1$).

TABLE 2. Default Parameter Values for Model 2*

Description	Symbol	Default Value(s) CIS	ICC
Increased risk of death with disease	α	0.0	0.223
Detection rate in areas with screening	σ	0.30	0.75
Probability of progressing to disease (× 1000) as a function of years since HPV infection (assuming no hysterectomy or death first)	f		
0–5		23	0.14
6–10		22	1.2
11–15		13	3.0
16–20		8.4	4.0
21–25		4.6	4.3
26–30		1.9	4.0
31–35		0.0	3.5
36–40		0.0	3.2
41–45		0.0	2.7
46–50		0.0	2.4
51–55		0.0	2.2
56–60		0.0	1.9
Proportion in activity group l	N_l		
High		0.10	
↓		0.20	
		0.35	
Low		0.35	
Hysterectomy rate (per 1,000 per yr)	ν_a		
16–25		0.5	
26–30		3.7	
31–35		6.0	
36–40		9.5	
41–45		12.5	
46–55		9.8	
56–65		0.35	
66–75		0.30	
Death rate (per 1,000 per yr)	μ_a		
16–25		0.6	
26–30		0.85	
31–35		0.85	
36–40		2.0	
41–45		2.0	
46–55		4.6	
56–65		13.5	
66–75		26.0	
Annual HPV incidence rate (× 1,000) (all high-risk types)†	$\lambda_{a,l}$		
16–20		83	
21–25		50	
26–30		25	
31–45		6	
46–50		5	
51–75		3	

* Symbol refers to the symbol in the model equations in Appendix 1.
† Rates given are pooled over all activity groups. See Appendix S1 in the online version of this article (http://www.epidem.com) for age/activity group-specific rates.

unstratified (homogeneous with respect to rate of partner change) population is given by the relation

$$\pi_c = 1 - \frac{\mu + \gamma}{\beta c} \qquad (2)$$

where μ, γ, β and c are the rate of entry/exit from the sexually active population, the rate of recovery from HPV infection, the per partner transmission rate of HPV, and the effective partner change rate, respectively. Using the values of $\beta = 0.75$ and $c = 1.87$ for the hypothetical population examined here leads to a critical value of $\pi_c = 0.48$ for an unstratified population. However, as heterogeneity in the population increases, the critical level of vaccine coverage needed for disease elimination increases. Heuristically, this is because infections are relatively easily maintained in the proportion of the population that is unvaccinated and has a high rate of partner change. Technically, the value of c that must be used in Eq 1 for a stratified population (assuming random mixing) is equal to the mean + variance/mean of the stratum-specific partner change rates. Thus, increasing heterogeneity in sexual activity levels leads to large increases in c and a corresponding increase in π_c; the principle is the same under nonrandom mixing assumptions although the computation of π_c is more difficult.

The degree of mixing between the strata also plays a role in determining the endemic disease prevalence, particularly at lower levels of vaccine coverage. In model 1 mixing between the sexual activity groups is quantified by the mixing matrix ρ, which may vary from fully assortative (corresponding to $\epsilon = 0$) to fully random ($\epsilon = 1$) using a parameterization described by Garnett and Anderson.[14] Figure 4 shows, for various values of the mixing parameter ϵ, the endemic prevalence for various levels of vaccine coverage under the same assumptions used in Figure 3. Although different values of ϵ result in substantially different values of π_c (*ie*, from $\pi_c = 0.69$ for $\epsilon = 1$ to $\pi_c = 0.90$ for $\epsilon = 0$), the endemic prevalence is uniformly low for coverages above 0.7.

Increasing the size of the highest activity subgroup tends to result in a proportional increase in endemic prevalence but has little effect on the shape of the curves shown in Figures 3 and 4 (data not shown). For the remainder of this section we assume $\epsilon = 0.7$ for three sexual activity groups that comprise 0.82, 0.15 and 0.03 of the population, with $c = 1.4$, 3 and 9, respectively.

Figures 3 and 4 show the expected effects for an ideal vaccine. Table 3 presents results for various vaccine strategies under a more realistic scenario (90% effective coverage with a vaccine that reduces the rate of infections in vaccinated individuals by 75% and confers a mean 10-year protection; breakthrough infections and infections in unvaccinated

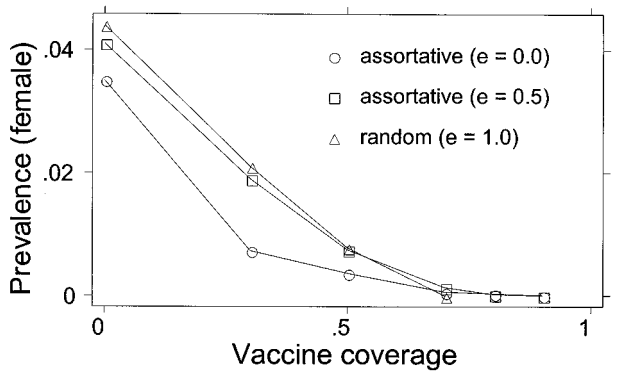

FIGURE 4. Predicted prevalence of HPV by vaccine coverage (ϕ in Table 1) from model 1. The vaccine is given to both sexes and assumed to be 100% effective in providing long-lasting immunity to all individuals receiving it. The population is stratified into 3 levels of sexual activity with proportions 0.82, 0.15 and 0.03 with c = 1.4, 3 and 9, respectively. The degree of mixing varies from random (ϵ = 1.0) to completely assortative (ϵ = 0.0).

individuals have similar natural histories). Note that the steady-state prevalence in men and women in the unvaccinated population differs because the male-to-female transmission rate is assumed to be higher than female-to-male transmission rate. The table suggests that vaccinating only women is a reasonable strategy and provides 68% of the reduction (in HPV prevalence in females) that can be achieved by vaccinating both men and women. On the other hand, targeting the vaccine towards the highest-risk individuals (yet to be identified) is less effective unless there is very little mixing between the highest and lowest activity groups.

A program that targets women for vaccination would likely be easier to implement than one that targets both sexes. However, the reduction in (female) prevalence by

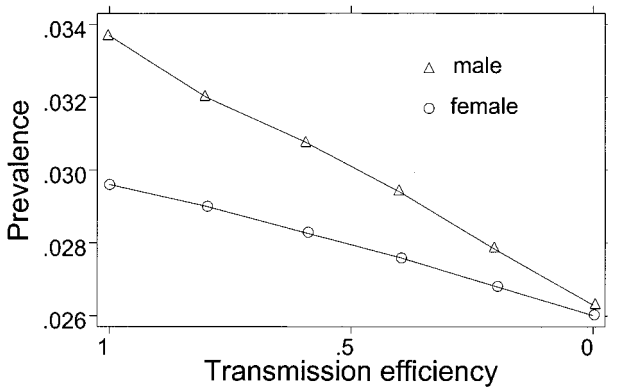

FIGURE 5. Predicted prevalence of HPV by transmission efficiency (r from Table 1) among those vaccinated individuals who experience breakthrough infections. Assumptions: only women vaccinated, 90% coverage, 75% effective; average 10 years of immunity.

a female-only vaccination strategy (relative to vaccination of both sexes) is sensitive to variations in some model parameters. Define the relative reduction as

$$\frac{p^F_{None} - p^F_F}{p^F_{None} - p^F_{MF}}$$

where

$$p^F_{strategy}$$

denotes the prevalence of HPV in females under a given vaccination strategy. Table 4 lists the relative reductions that are predicted by the model as certain parameters are varied. The greatest variation occurs as we move from low heterogeneity in sexual activity (relative reduction = 0.64) to high heterogeneity in sexual activity (relative reduction = 0.73). Thus, as the heterogeneity in sexual activity in the population increases, the additional benefit of vaccinating men decreases.

Among vaccine parameters, the transmissibility of so-called "breakthrough infections" in vaccinated individuals (r) and the percent coverage (ϕ) have the greatest effect on the relative reduction that can be achieved with a female-only vaccination strategy compared with a male and female vaccination strategy. In the case of the transmissibility of breakthrough infections, variations in r have little effect on HPV prevalence in women under the female-only vaccination strategy, but a much stronger effect when both males and females are vaccinated. Interestingly, variations in r have a strong effect on male prevalence under both strategies. This leads to an unusual situation in which the endemic prevalence of infection in men can be essentially equal to (or, under some scenarios, lower than) that in women if the transmissibility of breakthrough infections is low enough. Figure 5 depicts this more rapid reduction of prevalence in men as a function of the transmission probability of breakthrough infections in women. The reduction in women is less because the unvaccinated male population retains the same level of transmissibility whenever infected.

Figure 6 depicts the effects of variations in other vaccine parameters on the endemic prevalence of HPV type 16 under the females-only vaccination strategy, assuming that breakthrough infections have similar transmissibility to natural infections (r = 1). In such a scenario, effective vaccine coverage (the product of the proportion vaccinated and the proportion of vaccine recipients who acquire protection) and efficacy (defined as the proportion of challenges that fail to infect in those "protected") have a strong effect on endemic prevalence in women but only a modest effect on endemic prevalence in men. An increase in the relative rate of recovery from breakthrough infections in vaccinated individuals could

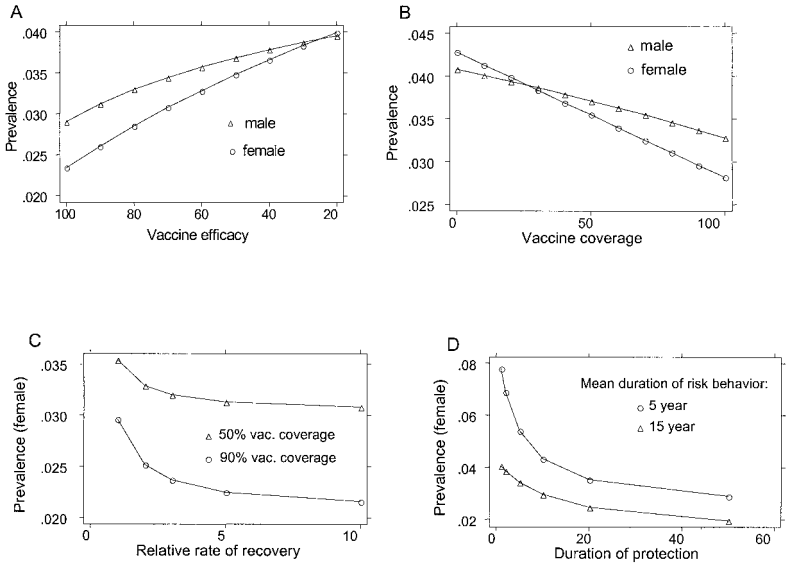

FIGURE 6. Plots showing the effects of (A) percent vaccine efficacy ($1-\phi$), (B) percent effectively vaccinated (ϕ), (C) relative rate of recovery (α), and (D) mean duration of risk behavior ($1/\mu$) and mean duration of protection ($1/\sigma$) on endemic prevalence of HPV infection in a population in which only women are vaccinated. Other parameters are set at the values given in Table 1.

compensate for partial protection, but only to the extent that such breakthrough infections play a role. It should be noted that even if the vaccine has 100% effective coverage or efficacy, other types of failure allow a moderate prevalence of infection to persist. For instance, a vaccine may effectively fail if the duration of protection from infection is less than the duration of risky behavior.

Incidence of Carcinoma *In Situ* and Invasive Cervical Cancer

Using model 2 we explore the effects of reducing the incidence of HPV infections (*ie*, through vaccination) on the incidence of CIS and ICC. We assume that an HPV vaccine is able to prevent 60% of all high-risk HPV infections. This might be reasonable if the vaccine were designed to prevent infection with HPV types 16 and 18. Figure 7 compares the predicted incidence of CIS and ICC by age in a theoretical population in which all high-risk HPV types are present to a population in which HPV types 16 and 18 have been largely removed (*ie*, risk of infection by a high-risk HPV type reduced by 60%). The model predicts that the removal of 60% of high-risk HPV infections results in a 46% reduction in CIS and a 47% reduction in ICC. These results hold for both screened and unscreened populations. This illustrates the potential "replacement effect" in which individuals who would have developed CIS or ICC because of infection with HPV types 16 or 18 now contract the disease because of infection with other high-risk types. This replacement effect also shifts the disease burden towards older individuals. The mean age of CIS is shifted upwards by 1.2 years in the vaccinated population compared with the unvaccinated population, whereas the mean age of ICC increases by 0.6 years (these results are similar in both screened and unscreened populations). Figure 8 shows the predicted percent reduction in CIS for various reductions in the hazard of HPV infection. The curve for ICC is similar, with an approximately one percentage point greater reduction in cases than CIS.

TABLE 3. Effect of Various Vaccine Strategies on Endemic Prevalence of HPV Type 16*

	Steady State Endemic Prevalence	
	Men	Women
No vaccination program	0.041	0.043
Vaccinate men and women	0.022	0.024
Vaccinate women only	0.034	0.030
"Target" high-risk men and women†	0.033	0.035
"Target" high-risk women only†	0.038	0.038

* Assumptions: 90% effective coverage with a vaccine that reduces the rate of infections in vaccinated individuals by 75%; the vaccine confers a mean 10-year protection; and breakthrough infections and infections in unvaccinated individuals have similar natural histories.
† 90% coverage in the two highest-risk groups; 10% coverage in the lowest-risk group.

Discussion

The development of an HPV vaccine would provide a useful addition to the technologies available in the control of cervical cancer. However, a vaccination policy is unlikely to be simple for a vaccine against a sexually transmitted infection that is aimed at preventing the subsequent development of disease and may be restricted in its efficacy. The development of a theoretical framework to explore vaccination impacts with the concomitant collection of appropriate epidemiologic, clinical and virologic data can provide an important aid to the development of rational policy. Here, two mathematical models have been developed to explore the effects of vaccination for genital HPV on the prevalence of HPV infections and the subsequent development of CIS and ICC. We find that under a specific set of assumptions (including: 90% coverage, vaccine 75% effective, mean 10-year immunity), vaccinating both men and women leads to a 44% decrease in the endemic prevalence (in women) of whichever HPV type(s) the

TABLE 4. Sensitivity of the Relative Reduction in (Female) Prevalence Under a Female-Only Vaccination Strategy Compared with a Strategy That Vaccinates Both Sexes*

Symbol†	Values	Relative Reduction
μ	1/5 1/15 1/30	0.698 0.685 0.687
ε	0.1 0.5 0.7 0.9	0.666 0.683 0.685 0.683
c	low medium high#	0.639 0.685 0.732
r	0 0.5 1	0.628 0.641 0.685
φ	0 0.25 0.50	0.715 0.685 0.676
σ	1/5 1/10 1/50	0.681 0.685 0.702
α	1 2 5	0.685 0.713 0.734
ϕ	0.5 0.7 0.9	0.734 0.681 0.685

* Relative reduction is defined as $(p^F_{None} - p^F_F)/(p^F_{None} - p^F_{MF})$ where $p^F_{strategy}$ denotes the prevalence of HPV in females under a given vaccination strategy. Thus, values near 1.0 suggest that vaccinating women only is nearly as efficacious as vaccinating both sexes.
† See Table 1.
# "Low" corresponds to $c = 1.87$ for all three sexual activity level strata; "medium" means $c = 1.4$, 3, and 9; high means $c = 1$, 3, and 20. In all cases the proportion in the three strata are 0.82, 0.15, 0.03, respectively.

vaccine is directed against. Vaccinating only women leads to a 30% decrease in HPV prevalence. However, both vaccine characteristics and sexual behaviors play a key role in determining the predicted prevalence of HPV and the relative efficacy of a female-only vaccination strategy *vs* a strategy in which both sexes are vaccinated. Because population-based estimates of partner change rates and mixing are extremely hard to obtain and because it is not possible to tune the model using existing data, uncertainty about the predicted efficacy of various vaccine strategies remains. However, over a broad range of assumptions, a female-only vaccination strategy would likely be 60%–75% as efficient (Table 4) as a strategy that targets both sexes. In contrast, attempting to target the vaccine toward high-risk individuals appears less likely to succeed, in part because it would be difficult to identify and successfully vaccinate such individuals.

A second finding is that a reduction of 60%, for example, in the incidence of high-risk HPV infections results in a smaller reduction in the incidence of CIS and ICC (46% and 47%, respectively) because some of the HPV-associated lesions that are avoided (through vaccination) are replaced by lesions caused by other high-risk HPV types. This replacement effect is a direct consequence of the assumption in model 2 that individuals who develop disease (CIS or ICC) are permanently removed from the susceptible population. That is, in addition to removing lesions, standard treatments for cervical squamous intraepithelial lesions (SIL) (*eg*, loop electrosurgical excision procedure, cryotherapy, conization, laser) also destroy nonlesional tissue in the cervical transformation zone (where virtually all cervical cancers occur). Because this nonlesional tissue may already be infected by other high-risk types and is susceptible to future infection, standard treatments protect against future disease. Similarly, aggressive treatment against precursor lesions (*ie*, low-grade SIL) resulting from infections by eliminated types also protects against future disease from the remaining high-risk types. Vaccination against a subset of high-risk HPV types will not have this same protective effect because the transformation zone will not be removed and infections with the remaining oncogenic types may lead to lesions in this susceptible epithelium. As a result, the reduction in cases of disease will be proportionately smaller than the reduction in HPV infections. Note that we assume that the various HPV types have independent natural histories, conditional on sexual behavior. Current research suggests this is the case, at least for the most common HPV types.[15] In addition, the model does not account for the possibility that elimination of some HPV infections by vaccination (*eg*, HPV types 6 or 11) may actually increase the oncogenic potential of breakthrough infections with high-risk types (*eg*, HPV type 16) as suggested by some recent research.[16,17]

Although a vaccine for one or more high-risk HPV types should decrease a woman's risk of CIS and ICC, it is unlikely to completely eliminate it. Thus, screening programs must continue in some form. Nonetheless, vaccination may still be cost-effective if it eliminates the need for follow up and treatment of a substantial number of HPV-associated SIL. In addition, it may be possible to reduce the frequency of Pap screening if a successful vaccination program can be implemented.

Although our application of these models has focused on high-risk HPVs and CIS and ICC, the qualitative findings reported here are largely applicable to HPV types that cause genital warts, most notably types 6 and 11. A key difference, however, is that we would not expect to see a differential reduction in disease compared with HPV incidence for genital warts. That is, a given reduction in infections with wart-causing HPV types should lead to a concomitant reduction in warts. The assumption that individuals who develop disease (warts) are permanently removed from the susceptible population would not be reasonable in a model of HPV and genital warts. In contrast to treatment of cervical SIL, genital wart treatments are largely lesion-specific. Even with successful treatment, large areas of genital epithelium remain susceptible to development of warts by other wart-associated HPV types. Thus, we expect less of a replacement effect with wart-causing HPVs.

Our models of cervical carcinoma have focused separately on the transmission dynamics of infection and the incidence of disease. The logical next step would be to combine the two models to provide an age-structured

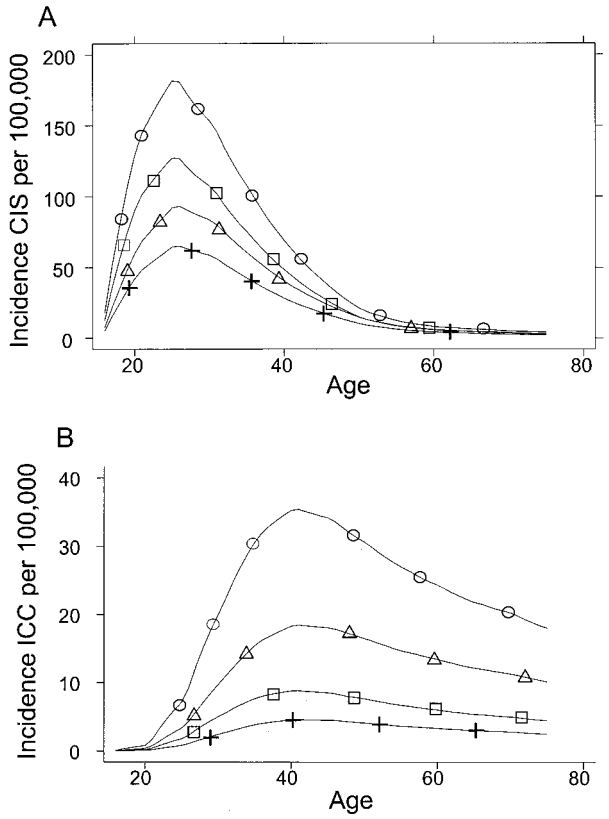

FIGURE 7. Model 2 for (a) CIS and (b) ICC, with and without the presence of HPV 16 and 18. ○ = All high-risk HPV. △ = All high-risk HPV except types 16 and 18. □ = All high-risk HPV, with screening. + = All high-risk HPV except types 16 and 18, with screening. Screening is assumed to prevent 30% of CIS and 75% of ICC.

model of the transmission of HPV and progress to disease. Such a model could be used to explore the impact of different vaccination and screening strategies. However, the addition of further model complexity will accentuate the gaps in our knowledge of HPV biology and reliable behavioral parameter estimates. Although any mathematical model is necessarily a simplification of reality, this is perhaps especially true of models of sexually transmitted infections in which patterns of partner change and mixing are crucial to disease spread but about which relatively little is known except in selected subgroups. In the absence of detailed information regarding how these factors change with age, we are forced to make simplifying assumptions.

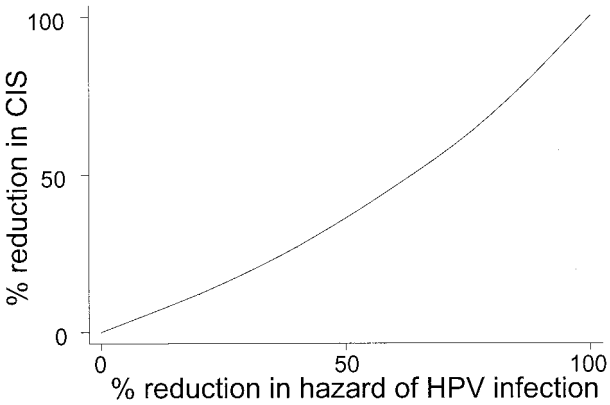

FIGURE 8. Predicted percent reduction in CIS cases as a function of the percent reduction in the hazard of HPV infection.

As data on the population level impact of large-scale sexually transmitted disease interventions become available, it will be possible to evaluate the reasonableness of these assumptions. At present, however, data from such experiments are lacking. Similarly, our knowledge of the natural history of HPV infection, cervical dysplasia and cervical cancer is substantial but still incomplete, especially with respect to longer-term consequences. For example, relatively little information is available on the carriage and infectiousness of HPV over the long-term after resolution of primary infection. If infected individuals remain sporadically infectious (perhaps at a lower level) over long periods, then a vaccination program that prevents such infections would be even more attractive. Finally, the deterministic structure of the models presented here does not allow for stochastic effects, which could lead to disease eradication at low levels of endemic infection.[13]

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Appendix

The following equations define model 1:

$$\frac{dx_{k,l}}{dt} = 0.5\ \mu\omega_l(1-\phi_{k,l})\eta - (\lambda_{k,l}+\mu)\,x_{k,l} + \sigma_k\nu_{k,l}$$

$$\frac{dy_{k,l}}{dt} = \lambda_{k,l}x_{k,l} - (\mu+\gamma_k)\,y_{k,l}$$

$$\frac{dz_{k,l}}{dt} = \gamma_k y_{k,l} + \alpha_k\gamma_k w_{k,l} - \mu z_{k,l}$$

$$\frac{dv_{k,l}}{dt} = 0.5\ \mu\omega_l\phi_{k,l}\eta - (\lambda_{k,l}\varphi_k + \mu + \sigma_k)\,\nu_{k,l}$$

$$\frac{dw_{k,l}}{dt} = \lambda_{k,l}\varphi_k\nu_{k,l} - (\mu+\alpha_k\gamma_k)w_{k,l} \qquad (5)$$

$$\lambda_{k,l} = c_l\beta_k\sum_m\left[\rho_{l,m}\left(\frac{y_{k',m}+r_{k'}w_{k',m}}{N_{k',m}}\right)\right]$$

$$N_{k,m} = x_{k,m} + y_{k,m} + z_{k,m} + \nu_{k,m} + w_{k,m}$$

$$\rho_{l,m} = (1-\varepsilon)\,\delta_{l,m} + \varepsilon\left[\frac{c_m N_m}{\sum_s c_s N_s}\right]$$

where $\eta = \sum_k\sum_m N_{k,m}$.

Model 2 is defined as follows:

$$x_l(0) = N_l$$

$$\frac{dx_l(a)}{da} = -(\lambda_l(a)+\mu(a)+\nu(a))\,x_l(a)$$

$$\frac{\partial y_l(a,\tau)}{\partial a} + \frac{\partial y_l(a,\tau)}{\partial \tau} = -y_l(a,\tau)(f(\tau)+\mu(a)+\nu(a))$$

$$y_l(a,0) = \lambda_l(a)\,x(a)$$

$$\frac{dz_l(a)}{da} = \int_0^a y_l(a,\tau)\,f(\tau)\,(1-\sigma_l)d\tau - (\mu(a) + \alpha + \nu(a))\,z_l(a) \qquad (6)$$

$$\frac{dw_l(a)}{da} = \nu(a)(x_l(a)+z_l(a) + \int_0^a y_l(a,\tau)d\tau + \int_0^a y_l(a,\tau)\,f(\tau)\sigma_l d\tau - \mu(a)w_l(a)$$