Model for Assessing Human Papillomavirus Vaccination Strategies

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We present a transmission dynamic model that can assess the epidemiologic consequences and cost-effectiveness of alternative strategies of administering a prophylactic quadrivalent (types 6/11/16/18) human papillomavirus (HPV) vaccine in a setting of organized cervical cancer screening in the United States. Compared with current practice, vaccinating girls before the age of 12 years would reduce the incidence of genital warts (83%) and cervical cancer (78%) due to HPV 6/11/16/18. The incremental cost-effectiveness ratio (ICER) of augmenting this strategy with a temporary catch-up program for 12- to 24-year-olds was US $4,666 per quality-adjusted life year (QALY) gained. Relative to other commonly accepted healthcare programs, vaccinating girls and women appears cost-effective. Including men and boys in the program was the most effective strategy, reducing the incidence of genital warts, cervical intraepithelial neoplasia, and cervical cancer by 97%, 91%, and 91%, respectively. The ICER of this strategy was $45,056 per QALY.

Human papillomavirus (HPV) causes cervical intraepithelial neoplasia (CIN); cervical, anal, penile, vaginal, vulvar, and head/neck cancers; anogenital warts; and recurrent respiratory papillomatoses, resulting in disease and death in both women and men (*1*). Cervical cancer incidence and deaths have substantially decreased in countries with organized cervical cancer screening programs (*2*). However, despite this success, cervical cancer is the second most common malignancy among women and a leading cause of cancer death worldwide, with an estimated 493,000 new cases and 274,000 deaths in 2002 (*3*).

In the United States, public health authorities recommend that girls and women 11–26 years of age be vaccinated with the newly licensed quadrivalent HPV vaccine, Gardasil (Merck & Co., Inc., Whitehouse Station, NJ, USA), to prevent cervical cancer, precancerous and low-grade lesions, and genital warts caused by HPV types 6, 11, 16, or 18. Policymakers will need information on the epidemiologic and economic impact of HPV vaccination to formulate guidelines (*4*,*5*). Cohort models provided some of this information but could not fully assess the impact of HPV vaccination (*6*). In particular, vaccination will not only directly protect through vaccine-derived immunity but also indirectly through herd immunity. To account for these direct and indirect effects, a population dynamic model is necessary (*7*). Moreover, a dynamic model can evaluate a broader range of vaccination strategies (e.g., vaccination of boys and men). A few dynamic models exists (*6*,*8*), but only 1 has examined the cost-effectiveness of bivalent HPV (16/18) vaccination strategies (*9*).

We developed a dynamic model to assess the epidemiologic consequences and cost-effectiveness of alternative quadrivalent HPV (6/11/16/18) vaccination strategies. An online Supplementary Appendix (available from www.cdc.gov/ncidod/EID/13/1/28-app.htm) describes in detail the model structure and inputs. Specifically, we examined 2 questions: What is the potential impact of a quadrivalent HPV vaccine on HPV infection and disease in the US population? What is the cost-effectiveness of a quadrivalent HPV vaccine program when added to the current standard of care from the perspective of the US healthcare system?

Methods

Screening and Vaccination Strategies

We assumed that the vaccine will be combined with current screening and HPV disease treatment practices. We defined the reference vaccination strategy to be routine HPV vaccination of girls by age 12 (F12-only) (*10*). We

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also examined the following strategies: 1) routine vaccination of girls and boys by age 12 (F&M12), 2) routine vaccination of girls by age 12 and catch-up female vaccination for those ages 12–24 (F12-only+CUF-only), 3) routine vaccination of boys and girls by age 12 years and catch-up female vaccination for those ages 12–24 years (F&M12+CUF-only), and 4) routine vaccination of boys and girls by age 12 and catch-up female and male vaccination for those ages 12–24 (F&M12+CUF&M).

Dynamic Model Structure

Our dynamic model has demographic and epidemiologic components ([*11*], Appendix). The demographic model defines the demographic characteristics of the population being simulated and describes how persons enter, age, and exit various categories. The heterosexually mixing population is divided into 17 age groups. Each age group consists of persons with low, medium, or high sexual activity.

Twelve-year-old persons enter the population at a gender-specific and sexual activity–specific rate. Persons then move between successive age groups at an age- and gender-specific rate per year (*11*). Persons exit the model upon death at an age- and gender-specific per capita death rate per year. Cervical cancer patients have an additional age- and stage-dependent death rate. Patients with CIN or genital warts do not face an additional risk for death.

The epidemiologic model simulates HPV transmission and the occurrence of CIN, cervical cancer, and external genital warts in this age-structured population. The acquisition of infection and progression of persons from infection to disease follow a similar natural history structure, as assumed in previous models for HPV 16/18 (*6*). We also incorporated HPV 6/11 infection and genital warts, and grouped infections into HPV 16/18, HPV 6/11, or HPV 6/11/16/18. We divided the population into distinct epidemiologic categories, according to the person's status with respect to infection, disease, screening, and treatment (Appendix, Figure 1A–B).

Parameters for Estimates and Sources

A comprehensive search of the literature was conducted to obtain baseline values for the parameters of the model (Appendix Tables A1–A3). We used age-stratified data to estimate cytology screening rates (*12–14*). Estimates of cytology screening sensitivities and specificities were based on published studies (*15,16*).

The degree of protection from the vaccine (the proportion of challenges against which a recipient is protected) against incident infection (HPV 6/11 or 16/18) was 90%; against associated disease the degree of protection was 100% (*17,18*). We assumed the duration of protection was lifelong for the reference case (*6*) and examined a 10-year duration in sensitivity analyses. We assumed the natural course of disease was unaltered following vaccine failure or loss of vaccine-induced immunity. Because Gardasil is a prophylactic vaccine, we did not include any therapeutic benefits to recipients already infected with the vaccine types. We assumed that up to 70% of 12-year-olds received a 3-dose vaccine (*6*). Coverage increased linearly from 0% up to 70% during the first 5 years of the program (e.g.,

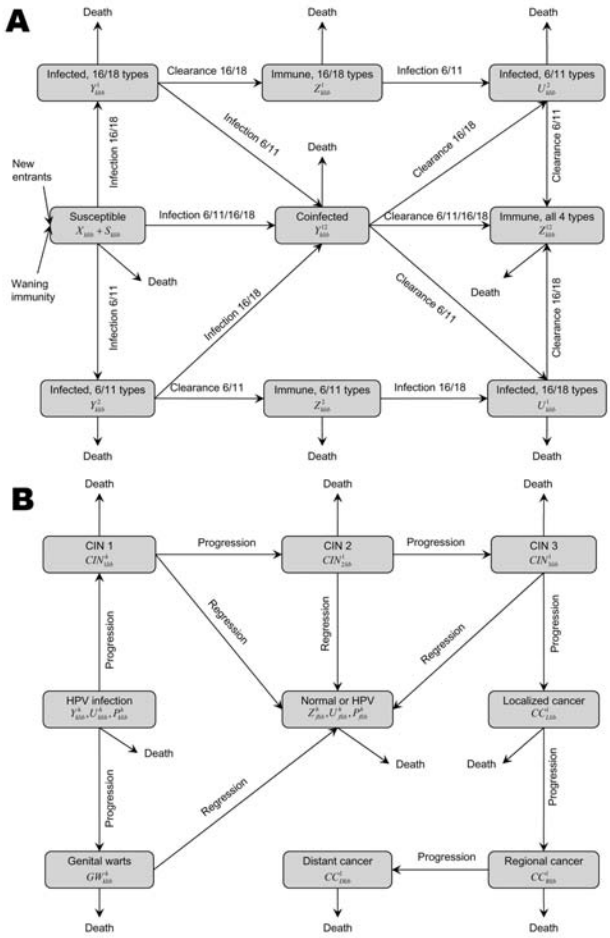

Figure 1. A simplified schematic diagram of human papillomavirus (HPV) infection and disease state transitions, lifetime duration of infection-derived immunity, unvaccinated compartments. A) Persons enter into the susceptible (*X*) compartment and leave all compartments at sex- and age-specific rate. A susceptible host may be infected by either or both HPV types. A host infected with a given type can also be infected with the other type and move into compartment (Y^{12}). An infected person can clear infection with 1 type and can become immune to that type (Z^h) and be infected with the other type (U^h). Infection with and clearance of all types results in lifetime immunity. B) Cervical intraepithelial neoplasia (CIN) develops in females and progresses though several histologic states: infected with a normal cervix; CIN 1; CIN 2; CIN 3; localized, regional, and distant cervical cancer. CIN can regress to normal with or without infection. Genital warts can develop and clear in those infected with HPV 6/11.

14% in year 1, 28% in year 2) and remained at 70% thereafter. Vaccine coverage for the catch-up program increased linearly from 0% up to 50% during the first 5 years (e.g., 10% in year 1, 28% of unvaccinated in year 2), and the program was eliminated after year 5.

We assumed the cost of the HPV vaccine for 3 doses and administration would be US $360 (range $300–$500), consistent with previous analyses (*6*). All costs were updated to 2005 US dollars. Costs and quality-adjusted life years (QALY) were discounted at 3%.

Simulation Method

We assessed the epidemiologic impact and cost-effectiveness of each vaccination strategy over a planning horizon of 100 years. We solved the model for the prevaccination steady-state values of the variables and used them as initial values for the vaccination model. Next, we solved the model for the entire time path of the variables until the system approached a steady-state.

Validation Analyses

We established the face validity of the model by consulting with experts on assumptions regarding the natural history of HPV infection and disease (*19*). The accompanying online Supplementary Appendix allows for further critical review of the model assumptions and provides the mathematical equations necessary to reproduce the results (*19*,*20*). The predictive validity of the model was evaluated by comparing model results with epidemiologic data from unscreened and screened populations in the United States (*2*,*21*–*23*).

Sensitivity Analyses

Because of the large number of equations and inputs, we used a smaller version of the model to determine the most influential inputs. Based on these results, 1-way sensitivity analyses using the full model were performed on vaccine parameters (duration, degree, coverage, cost, target age), quality-of-life weights, discounting, and duration of natural immunity. We also conducted a multivariate sensitivity analysis that examined a pessimistic scenario (i.e., duration of protection = 10 years; vaccine coverage = 50%; health utility for genital warts; CIN 1, 2, 3, and carcinoma in situ (CIS) = 0.97; degree of protection against infection = 75%; and degree of protection against HPV-related disease = 85%). We also examined the role of herd immunity.

Results

Model Validation

Model predictions generally fell within the range of values reported in the literature. Overall, HPV 6/11 steady-state prevalence among females was 0.7%, which is similar to that reported by Giuliano et al. (*24*) for15- to 59-year-old women. The predicted age-specific HPV prevalence curve had a shape and magnitude at peak similar to data reported in the literature (*24*–*28*) (Figure 2). Without screening, the predicted HPV 16/18-attributable cervical cancer incidence curve had a shape and magnitude at peak (39 per 100,000 women-years for ages 45–50) similar to those estimated from unscreened US populations (*22*,*29*). The model predicted that 20% of all cervical cancer cases occurred among women who were never screened, similar to what has been observed in US populations (*30*). Also, the cervical cancer incidence curve (HPV 16/18 attributable) had a shape and magnitude at peak (8.3 per 100,000 women-years for ages 30–39 years) similar to that observed among recent cohorts of US women (*23*). However, the model predicted lower cervical cancer incidence among older cohorts. This approximation may be reasonable given that future cohorts of older women are expected to have lower cervical cancer incidence than women currently in older age groups (fewer women missed screening at younger ages among more recent cohorts [*13*,*14*]). Finally, with screening, the age-specific incidence curves for CIN and genital warts generally had shapes and magnitudes at peak similar to data reported in the literature (*21*,*31*).

Epidemiologic Impact of HPV Vaccination Strategies (Reference Case)

Steady-state HPV prevalence rates were higher for boys or men than for girls or women across all age groups (Figure 2). Overall, HPV 16/18 steady-state prevalence among girls and women ≥12 years of age (2.4%) was higher than that for boys or men (1.7%) and increased with level of sexual activity (data not shown). For both sexes, prevalence increased with age, reached a peak in the 20- to 24-year age group and continuously declined thereafter.

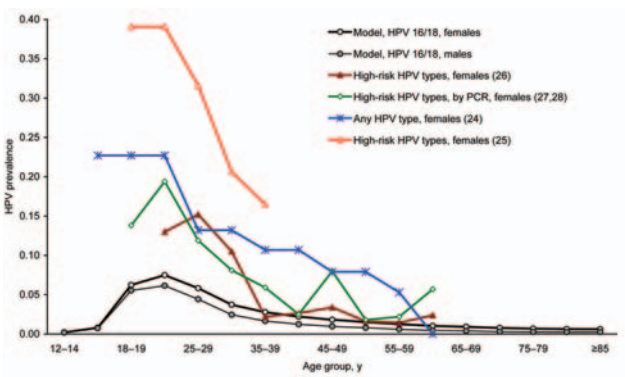

Figure 2. Human papillomavirus (HPV) prevalence by sex and age group, as predicted by the model and reported in selected studies from North America. HPV high risk includes types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82.

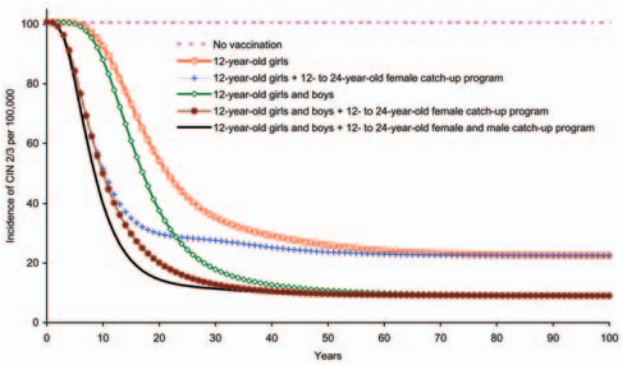

Figure 3. Incidence of cervical intraepithelial neoplasia (CIN) 2/3 due to human papillomavirus 6/11/16/18 infection among girls and women ≥12 years of age, by vaccination strategy.

Across all strategies, the effect of the vaccine was to steadily reduce CIN 2/3 incidence until the system approached a steady state (Figure 3). The largest reduction was accomplished by adopting F&M12+CUF&M. Cervical cancer curves shared the same qualitative features of those of CIN 2/3 (Figure 4). However, because cervical cancer progresses slowly, the effect of vaccination on the reduction in incidence and cancer deaths was more gradual compared with that for CIN 2/3 (Figures 3 and 4).

For genital warts, the reduction occurred sooner (Figure 5A and 5B). Female-only vaccination strategies were effective in reducing genital warts incidence among adolescent girls and women (Figure 5B) and were also effective in reducing the incidence of genital warts among males, but were not as effective as strategies that included male vaccination (Figure 5A).

F&M12+CUF&M had the most effect on the number of cases of genital warts, CIN, and cervical cancer. Compared with screening only, this strategy substantially reduced the long-run, overall number of genital warts (97%), CIN 2/3 (91%), and cervical cancer cases (91%) among adolescent girls and women.

Economic Impact of HPV Vaccination Strategies (Reference Case)

F&M12 was less effective and more costly (dominated) than F12-only+CUF-only (Table 1). The incremental cost-effectiveness ratio (ICER) of F12-only+CUF-only was US $4,666/QALY, and the most effective strategy (F&M12+CUF&M) had an ICER of $45,056/QALY.

Sensitivity Analyses

With 10 years' duration of protection, vaccination reduced disease incidence steadily until ≈10–15 years after vaccination, when the loss of immunity among vaccinated persons and increased numbers of unvaccinated persons reversed these trends and caused the incidence to rise (Figure 6). The rise in incidence continued until years 20–30, after which, it fell steadily until a steady state was approached. The timing and magnitude of the reduction and resurgence in incidence depended on the strategy. The largest reduction and lowest rebound were accomplished by using F&M12+CUF&M. If the duration of protection was only 10 years, long-term reductions in the annual number of cases of genital warts among males, CIN 2/3, and cervical cancer would be 36%, 25%, and 28%, respectively. In addition, ICERs increased by changing the duration of protection from lifelong to 10 years (Table 2).

The long-term cervical cancer incidence and ICER were not very sensitive to changes in the degree of vaccine protection against infection and disease. However, the results were sensitive to varying vaccination coverage. For example, the impact of vaccination on cervical cancer was lower when coverage was 50% compared with 90% (Figure 7). Lower coverage made vaccinating adolescent boys and men more cost-effective (Table 2). Increasing vaccination cost and quality of life weights increased ICERs.

Lower discount rates resulted in higher costs and QALY for each vaccination strategy. Discounting both costs and QALY at 1% decreased ICERs of the nondominated strategies: F12-only+CUF-only had an ICER of $448/QALY, whereas the ICER of F&M12+CUF&M was $28,614 /QALY. With a 5% discount rate, ICERs of these 2 strategies increased to $10,138/QALY and $64,413/QALY, respectively. HPV prevalence and burden of HPV-related diseases increased with shorter duration of natural immunity. A higher background rate of disease made the impact of vaccination look more favorable. For example, with 10-year duration of natural immunity, F12-only+CUF-only was cost-saving, whereas the ICER of F&M12+CUF&M was $11,567/QALY.

When the effects of herd immunity and benefits of prevention of HPV 6/11 were removed, the ICER of F12-

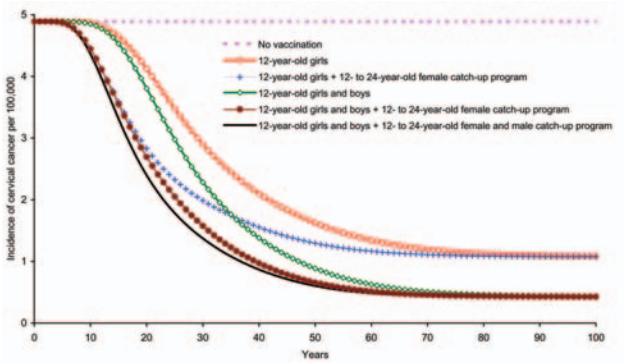

Figure 4. Incidence of cervical cancer due to human papillomavirus 16/18 infection among girls and women ≥12 years of age, by vaccination strategy.

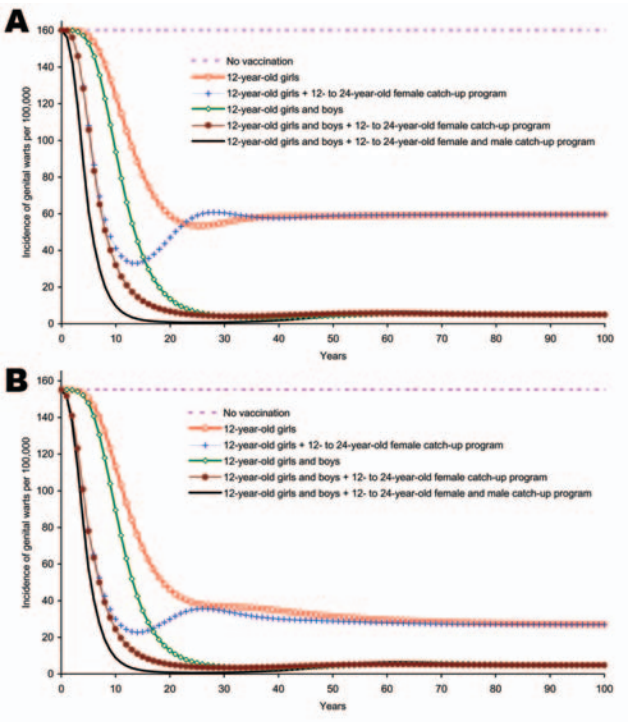

Figure 5. A) Incidence of genital warts due to human papillomavirus (HPV) 6/11 infection among boys and men ≥12 years of age by strategy. B) Incidence of genital warts due to HPV 6/11 infection among girls and women ≥12 years, of age by strategy.

only increased to $21,404. If one assumes a pessimistic scenario, the ICER of the F12-only+CUF-only strategy increased from $4,446/QALY to $29,053/QALY and the ICER of the F&M12+CUF&M increased from $45,056/QALY to $124,063/QALY.

Because vaccination coverage rates are expected to be lower among older age groups, we assumed a rate of 50% among 15- and 18-year-olds. With these rates, F12-only+CUF-only had an ICER of $8,357/QALY compared with delaying age of vaccination to 18 years (Table 3). ICERs of vaccinating by age 12 years increased when coverage rates among persons of ages 15 and 18 years were higher. Increasing the target age of vaccination decreased the benefits of vaccination (Figure 8, Table 3).

Finally, to estimate the additional value of preventing HPV 6/11 infection, we conducted an analysis in which we assumed that persons had no protection against HPV 6/11 infection and related disease. The results of this analysis showed that ICERs of F12-only+CUF-only and F&M12+CUF&M increased to $11,254/QALY and $74,151/QALY, respectively.

Discussion

We developed an integrated transmission dynamic model and economic evaluation to inform HPV vaccine policy recommendations and decisions. We gained valuable insights by comparing various vaccination strategies. In general, the results suggest that a quadrivalent HPV vaccine program that targets female adolescents and women, ages 12–24 years, can be cost-effective ($4,666/QALY) when compared with other commonly accepted medical interventions (*32*). These findings are consistent with other cohort-based cost-effectiveness analyses, which generally show that vaccination of 12-year-old girls can be cost-effective but also illustrate the substantial herd immunity benefits provided by vaccination.

Some results from this model were qualitatively similar to the results of other studies with respect to the finding that male vaccination was more attractive the lower the coverage among girls and women (*9*). However, the results of our base case differ qualitatively from that of Taira et al. (*9*) regarding the conclusion that vaccinating males and females would not be cost-effective. This difference in results may be explained as follows. First, unlike Taira et al., we accounted for the additional benefits conferred by protecting against HPV 6/11 infection among adolescent boys and girls, women, and men. Second, we were able to account for all the benefits and costs of vaccination realized by both those vaccinated and not vaccinated. Third, we assumed lower weights for the quality of life of women

Table 1. Cost-effectiveness analysis of alternative HPV vaccination strategies*

	Discounted total		Incremental		
Strategy	Costs	QALY	Costs	QALY	$/QALY†
No vaccination	72,659,302	2,698,711	—	—	—
12-y-old girls	74,042,990	2,699,178	1,383,687	467	2,964
12-y-old girls and boys	78,707,825	2,699,327	4,664,835	149	Dominated
12-y-old girls plus 12- to 24-y-old females catch-up	74,815,667	2,699,343	–3,892,159	16	4,666
12-y-old girls and boys plus 12– to 24-y-old females catch-up	79,746,357	2,699,461	4,930,690	118	41,803
12-y-old girls and boys plus 12– to 24-y-old females and males catch-up	81,761,210	2,699,506	2,014,853	45	45,056

*Assumes cost of vaccination series is US $360 and duration of protection is lifelong. All costs are measured in 2005 US dollars, and costs and QALY are discounted at 3%. HPV, human papillomavirus; QALY, quality-adjusted life years.
†Compared with the preceding nondominated strategy. Strategy A is dominated if there is another strategy, B, that is more effective and less costly than strategy A.

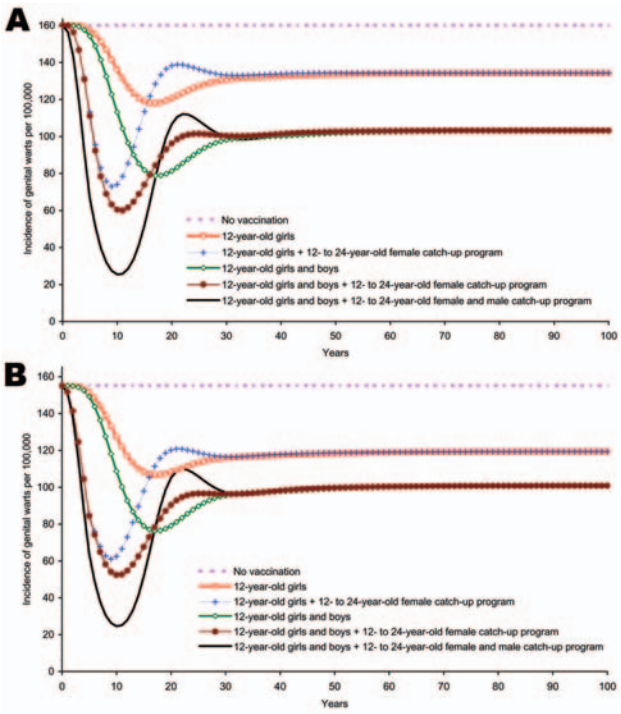

Figure 6. Sensitivity analysis. A) Incidence of genital warts due to human papillomavirus (HPV) 6/11 infection among boys and men ≥12 years of age, by strategy, 10 years' duration of protection. B) Incidence of genital warts due to (HPV 6/11 infection among girls and women ≥12 years of age by strategy, 10 years' duration of protection.

with CIN. However, the comparison is not perfect because our model tracks a population, whereas the model of Taira et al. follows a cohort. Hence, the composition of the numerators and denominators used in the ICERs differs between models. Finally, other methodologic differences occur between the 2 approaches that may explain the differences in results. For example, Taira et al. used steady-state values of HPV infection rates as inputs in their cost-effectiveness model, whereas we measured all outcomes over time, thereby capturing all the effects of transient dynamics generated from widespread vaccination. We also note that the results of the sensitivity analysis, when the effects of herd immunity and benefits of prevention of HPV 6/11 were removed, suggest that the ICER of the female vaccination strategy was $21,404/QALY, which is close to the value of $22,755/QALY reported in another study by Sanders and Taira (*33*).

An important finding from this analysis was that catch-up vaccination can substantially reduce disease in the short term. As a result, the female and male strategy that did not include a catch-up program was less effective and more costly.

One of the influential inputs was vaccine coverage. As female coverage rates decreased, male vaccination became more efficient. Another influential input in the analysis was the quality-of-life weights. The less HPV disease affected quality of life, the more the ICERs increased.

Duration of protection was also an influential parameter. Decreasing duration of vaccine protection to 10 years increased ICERs. However, the impact of this decrease may be mitigated by introducing a booster program. A reasonable approximation for how this program might fare would be to look at the sensitivity of ICERs to changes in vaccination cost. Thus, increasing the cost of the HPV vaccine series to $500 increased ICERs (Table 2). However, all nondominated (i.e., either are less costly or have lower ICERs than more effective strategies) female strategies remained cost-effective. Another influential parameter was the age vaccination was begun. Earlier vaccination resulted in greater benefits. F&M12+CUF&M was cost-effective ($42,697/QALY). However, vaccination by age 12 became less efficient, the higher the vaccination coverage was among older age groups.

Table 2. Sensitivity of incremental cost-effectiveness ratios (US $/QALY) of alternative HPV vaccination strategies to changes in inputs*

Input	F12 only	F12-only+ CUF only	F&M12+ CUF-only	F&M12+ CUF&M†
Baseline	2,964	4,666	41,803	45,056
Cost of vaccination series = $300	997	2,422	33,469	36,161
Cost of vaccination series = $500	7,553	9,900	61,250	65,810
Utility weights for CIN, CIS, GW = 0.97	5,241	7,739	82,700	83,714
Duration of protection = 10 y	Weakly dominated	21,121	54,755	54,928
Degree of protection against HPV 6/11/16/18 = 100%	2,094	4,187	Weakly dominated	51,436
Degree of protection against HPV 6/11/16/18 = 74%	4,273	5,403	39,990	43,930
Degree of protection against disease = 87%	3,116	4,922	40,269	43,974
Coverage with vaccination = 50%	2,636	4,221	23,862	36,235
Coverage with vaccination = 90%	3,449	5,269	Weakly dominated	100,418

*Unless specified otherwise, cost of vaccination series is US $360, and duration of protection is lifelong. QALY, quality-adjusted life years; HPV, human papillomavirus; F12-only, female vaccination by age 12; CUF, catch-up female vaccination for ages 12–24; F&M12+CUF only, female and male vaccination by age 12 and CUF; CIN, cervical intraepithelial neoplasia; CIS, carcinoma in situ; GW, genital warts.
†Compared with the preceding nondominated strategy. Strategy A is dominated if there is another strategy, B, that is more effective and less costly than strategy A. The strategy of female and male vaccination by age 12 that did not include a catch-up program was dominated. A strategy is weakly dominated if there is another more effective program that has a lower incremental cost-effectiveness ratio.

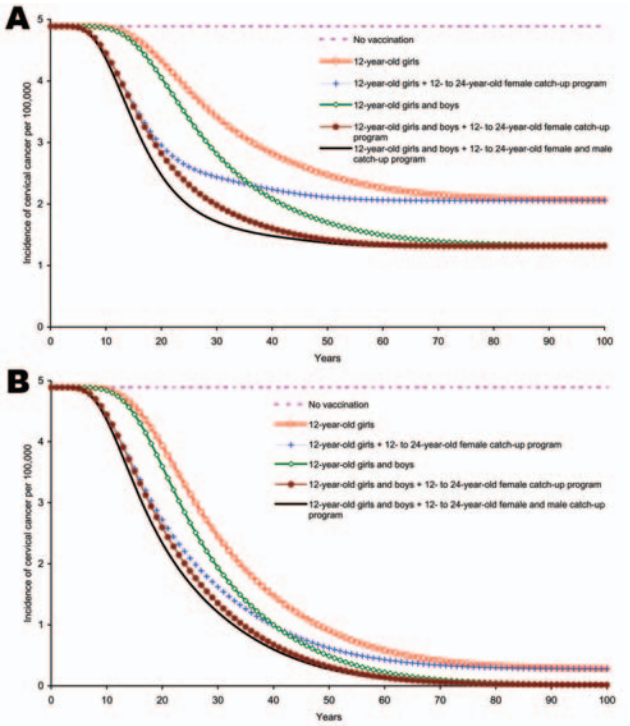

Figure 7. Sensitivity analysis. A) Incidence of cervical cancer due to human papillomavirus (HPV) 16/18 infection among girls and women ≥12 years of age with 50% coverage. B) Incidence of cervical cancer due to HPV 16/18 infection among girls and women >12 years of age with 90% coverage.

Vaccination shifted the age of infection and disease to older age groups. For example, the age of peak cervical cancer incidence increased after introducing vaccination. The upward shifting of age of infection is a common feature of many vaccination programs (*11*).

We believe our modeling approach has several strengths. First, we did extensive validation with existing data. The model is also flexible enough to incorporate better data as they become available. Second, this model accounts for actual screening practices in the United States. Third, because output from this model is population based, the comparison with national registry data is better aligned than comparison of cohort model output with population data (*6*). Finally, all equations and inputs for this model are available to facilitate replication of findings and independent review of the model.

Several enhancements and extensions are desired. First, more relevant data on the natural history of type-specific HPV infection and disease (e.g., HPV transmission probability per sexual contact) are needed. Also, given the influence utility weights have on ICERs, more studies are needed to collect health utilities data on HPV disease states.

Second, we modeled only 4 HPV types and their associated diseases and assumed that HPV types have independent natural histories with no interaction among them. If cross-immunity exists between HPV types, a vaccine that reduces the prevalence of 1 type may promote the prevalence of other types through a process of competitive release. If, however, current or prior infection with 1 HPV type facilitates concurrent or subsequent infection with another HPV type, or if the vaccine provides cross-protection against other types, HPV vaccination could have the additional benefit of reducing the prevalence of HPV infection of types not covered by the vaccine (*34*). The evidence on interaction among HPV types to date is mixed and inconclusive (*35–39*).

Third, we modeled neither coinfection after disease developed in a person nor the coexistence of CIN lesions due to multiple HPV types in the cervix. By accounting for all the cost of vaccinating persons with undetected disease and no benefits for them as a result of the protection against the type that did not cause the disease, our results are biased against the catch-up program.

Fourth, the model assumed that all persons have equal access to healthcare, be it vaccination, screening, or treatment. However, this assumption may not be realistic and may overestimate the benefits of vaccination if women who have limited access to screening are also less likely to get vaccinated. Further studies are required to determine whether those who do not get vaccinated are also likely not to get screened.

Table 3. Incremental cost-effectiveness ratios of alternative HPV vaccination strategies with varying start age of vaccination*

Strategy	Discounted total		Incremental
	Costs	QALY	$/QALY†
18-y-old women plus 18- to 24-y-old female catch-up	73,553,847	2,699,192	1,858
15-y-old female adolescents plus 15- to 24-y-old female catch-up	73,895,046	2,699,214	Weakly dominated
12-y-old girls plus 12- to 24-y-old female catch-up	74,815,667	2,699,343	8,357
18-y-old women and men plus 18- to 24-y-old female and male catch-up	77,535,383	2,699,385	Weakly dominated
15-y-old female and male adolescents plus 15- to 24-y-old female and male catch-up	78,455,750	2,699,404	Weakly dominated
12-y-old female and male adolescents plus 12- to 24-y-old female and male catch-up program	81,761,210	2,699,506	42,697

*Assumes cost of vaccination series is US $360, duration of protection is lifelong, and coverage rate of 50% among age 15- to 24-y-olds. HPV, human papillomavirus; QALY, quality-adjusted life years.
†Compared with the preceding nondominated strategy. Strategy A is dominated if there is another strategy, B, that is more effective and less costly than strategy A. A strategy is weakly dominated if there is another more effective program that has a incremental cost-effectiveness ratio.

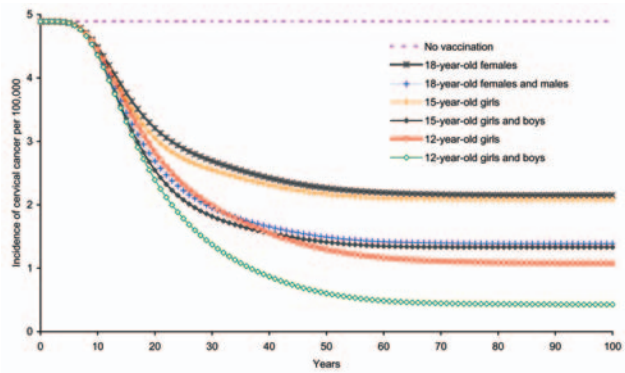

Figure 8. Effect of age that vaccination was begun on cervical cancer incidence due to human papillomavirus 16/18 infection among girls and women ≥12 years of age.

Fifth, the current version of the model focused on heterosexual transmission of HPV and did not incorporate transmission between homosexual and heterosexual persons. Sixth, the scope of the model has been limited to cervical diseases and genital warts. HPV infection has also been associated with recurrent respiratory papillomatoses and cancers of the anus, penis, vagina, vulva, and head and neck. As evidence becomes available, the scope of the model will be broadened to incorporate the potential effects of vaccination on these other HPV conditions. Including these diseases in the model would render more favorable ICERs for vaccination.

Seventh, we did not include death and productivity costs (lost wages), as was done in other analyses (*40*). Including these costs would further reduce ICERs.

Finally, we did not consider vaccination strategies that include infants or mid-adults because current data available on vaccine safety and efficacy are limited to ages 9–26 years (*18*). As data for these other age groups become available, the model can examine these strategies.

In summary, the results from this model suggest that in a setting of organized cervical cancer screening, a prophylactic quadrivalent HPV (16/18/6/11) vaccine can 1) substantially reduce genital warts, CIN, and cervical cancer, 2) improve quality of life and survival, 3) be cost-effective (across a reasonably wide range of assumptions) when administered to girls before age 12 years (with or without a catch-up program), and 4) have a cost-effectiveness ratio near or below (depending on the underlying assumptions of the model) that of several other recommended vaccines, when implemented as a strategy that combines vaccination of both girls and boys before age 12 with a 12–24 years of age catch-up program.

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References

1. Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. J Clin Virol. 2005;32:S16–24.
2. Gustafsson L, Ponten J, Zack M, Adami HO. International incidence rates of invasive cervical cancer after introduction of cytological screening. Cancer Causes Control. 1997;8:755–63.
3. Parkin DM, Bray F, Ferlay J, Pisani P. 2005 global cancer statistics. CA Cancer J Clin. 2005;55:74–108.
4. Markowitz L, Dunne E, Gilsdorf J. Development of recommendations for HPV vaccine use in the United States. Papillomavirus 22nd International Conference and Clinical Workshop 2005, Vancouver, British Columbia, Canada, Apr 30–May 6, 2005.
5. Weinstein MC, Toy EL, Sandberg EA, Neumann PJ, Evans JS, Kuntz KM, et al. Modeling for health care and other policy decisions: uses, roles, and validity. Value Health. 2001;4:348–61.
6. Dasbach EJ, Elbasha EH, Insinga RP. Mathematical models for predicting the epidemiologic and economic impact of vaccination against human papillomavirus infection and disease. Epidemiol Rev. 2006;28:88–100.
7. Edmunds WJ, Medley GF, Nokes DJ. Evaluating the cost-effectiveness of vaccination programmes: a dynamic approach. Stat Med. 1999;18:3263–82.
8. Barnabas RV, Laukkanen P, Koskela P, Kontula O, Lehtinen M, Garnett GP. Epidemiology of HPV 16 and cervical cancer in Finland and the potential impact of vaccination: mathematical modeling analyses. PLoS Med. 2006;3:e138.
9. Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. Emerg Infect Dis. 2004;10:1915–23.
10. Centers for Disease Control and Prevention. Recommended childhood and adolescent immunization schedule—United States, 2006. Morb Mortal Wkly Rep MMWR. 2006;54:Q1–4.
11. Hethcote H. The mathematics of infectious diseases. SIAM Review. 2000;42:599–653.
12. Insinga RP, Glass AG, Rush BB. Pap screening in a U.S. health plan. Cancer Epidemiol Biomarkers Prev. 2004;13:355–60.
13. Hewitt M, Devesa SS, Breen N. Cervical cancer screening among U.S. women: analyses of the 2000 National Health Interview Survey. Prev Med. 2004;39:270–8.
14. Schootman M, Jeffe DB, Baker EA, Walker MS. Effect of area poverty rate on cancer screening across US communities. J Epidemiol Community Health. 2006;60:202–7.
15. Bigras G, de Marval F. The probability for a Pap test to be abnormal is directly proportional to HPV viral load: results from a Swiss study comparing HPV testing and liquid-based cytology to detect cervical cancer precursors in 13,842 women. Br J Cancer. 2005;93:575–81.
16. Coste J, Cochand-Priollet B, De Cremoux P, Le Gales C, Cartier I, Molinie V, et al. Cross-sectional study of conventional cervical smear, monolayer cytology, and human papillomavirus DNA testing for cervical cancer screening. BMJ. 2003;326:733.
17. Koutsky LA, Ault KA, Wheeler CM, Brown DR, Barr E, Alvarez FB, et al. A controlled trial of a human papillomavirus type 16 vaccine. N Engl J Med. 2002;347:1645–51.

18. Villa LL, Costa RLR, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol. 2005;6:271–8.
19. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices–modeling studies. Value Health. 2003;6:9–17.
20. Gold MR, Siegel JE, Russell LB, Weinstein MC, editors. Cost-effectiveness in health and medicine. Report of the Panel on Cost-Effectiveness in Health and Medicine. New York: Oxford University Press; 1996.
21. Insinga RP, Glass AG, Rush BB. Diagnoses and outcomes in cervical cancer screening: a population-based study. Am J Obstet Gynecol. 2004;191:105–13.
22. Gustafsson L, Ponten J, Bergstrom R, Adami HO. International incidence rates of invasive cervical cancer before cytological screening. Int J Cancer. 1997;71:159–65.
23. Surveillance E, Results E. (SEER) Program. Public-use data (1973–2002), National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch. 2005 Apr. Based on the November 2004 submission. [cited 2006 Mar 13]. Available from http://www.seer.cancer.gov
24. Giuliano AR, Papenfuss M, Abrahamsen M, Denman C, de Zapien JG, Henze JL, et al. Human papillomavirus infection at the United States–Mexico border: implications for cervical cancer prevention and control. Cancer Epidemiol Biomarkers Prev. 2001;10:1129–36.
25. Peyton CL, Gravitt P, Hunt W, Hundley R, Zhao M, Apple RJ, et al. Determinants of genital human papillomavirus detection in a U.S. population. J Infect Dis. 2001;183:1554–64.
26. Jacobs MV, Walboomers JM, Snijders PJ, Voorhorst FJ, Verheijen RH, Fransen-Daalmeijer N, et al. Distribution of 37 mucosotropic HPV types in women with cytologically normal cervical smears: the age-related patterns for high-risk and low-risk types. Int J Cancer. 2000;87:221–7.
27. Sellors JW, Mahony J, Kaczorowski J, Lytwyn A, Bangura H, Lorincz A, et al. Prevalence and predictors of human papillomavirus infection in women in Ontario, Canada. CMAJ. 2000;163:503–8.
28. Sellors JW, Kaczorowski T, Kaczorowski J, Mahony J, Lytwyn A, Chong S, et al. Prevalence of infection with carcinogenic human papillomavirus among older women. CMAJ. 2002;167:871–2.
29. Laskey PW, Meigs JW, Flannery JT. Uterine cervical carcinoma in Connecticut, 1935–1973: evidence for two classes of invasive disease. J Natl Cancer Inst. 1976;57:1037–43.
30. Janerich DT, Hadjimichael O, Schwartz PE, Lowell DM, Meigs JW, Merino MJ, et al. The screening histories of women with invasive cervical cancer, Connecticut. Am J Public Health. 1995;85:791–4.
31. Insinga RP, Dasbach EJ, Myers ER. The health and economic burden of genital warts in a set of private U.S. health plans. Clin Infect Dis. 2003;36:1397–403.
32. Center for the Evaluation of Value and Risk in Health. The cost-effectiveness analysis registry [Internet]. Boston: Tufts–New England Medical Center. [cited 2006 Mar 13]. Available from http://www.tufts-nemc.org/icrhps/resprog/cevr/default.asp
33. Sanders GD, Taira AV. Cost-effectiveness of a potential vaccine for human papillomavirus. Emerg Infect Dis. 2003;9:37–48.
34. Elbasha EH, Galvani AP. Vaccination against multiple HPV types. Math Biosci. 2005;197:88–117.
35. Thomas KK, Hughes J, Kuypers J, Kiviat NB, Lee SK, Adam DE, et al. Concurrent and sequential acquisition of different genital human papillomavirus types. J Infect Dis. 2000;182:1097–102.
36. Liaw K-L, Hildesheim A, Burk RD, Gravitt P, Wacholder S, Manos MM, et al. A prospective study of human papillomavirus (HPV) type 16 DNA detection by polymerase chain reaction and its association with acquisition and persistence of other HPV types. J Infect Dis. 2001;183:8–15.
37. Rousseau M-C, Pereira J, Prado JC, Villa LL, Rohan TE, Franco EL. Cervical coinfection with human papillomavirus (HPV) types as a predictor of acquisition and persistence of HPV infection. J Infect Dis. 2001;184:1508–17.
38. Ho GY, Studentsov Y, Hall CB, Bierman R, Beardsley L, Lempa M, Burk RD, et al. Risk factors for subsequent cervicovaginal human papillomavirus (HPV) infection and the protective role of antibodies to HPV-16 virus-like particles. J Infect Dis. 2002;186:737–42.
39. Roden RB, Yutzy W, Fallon R, Inglis S, Lowy DR, Schiller JT. Minor capsid protein of human genital papillomaviruses contains subdominant, cross-neutralizing epitopes. Virology. 2000;270:254–7.
40. Lieu TA, Ray GT, Black SB, Butler JC, Klein JO, Breiman RF, et al. Projected cost-effectiveness of pneumococcal conjugate vaccination of healthy infants and young children. JAMA. 2000;283:1460–8.

Appendix[1]

Demographic Model

The demographic model stratifies the population by gender and 17 age groups (12–14, 15–17, 18–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, and ≥85 years). This age grouping permits age-specific inputs for patterns of sexual activity and cervical cancer screening and allows for age-specific outputs such as rates of cervical human papillomavirus (HPV) disease among girls and women, and genital warts among both males and females. Similar age groupings have been used by other sexually transmitted disease models (*1*,*2*). We further stratified each age group into 3 sexual activity groups (high, medium, low). We defined sexual activity according to the rates of sex partner change per year: low (0–1 per year), medium (2–4 per year), and high (≥5 per year). The number and the initial distribution of new entrants into the population by each gender were chosen to satisfy the Lotka characteristic equation with zero population growth (*3*). This allowed for variation in results across strategies to primarily be due to epidemiologic and program model features and not to changes in the demographic characteristics of the population over time (*3*).

The model starts with 12-year-olds entering the population at a gender-specific and sexual activity–specific rate, and transfers persons between successive age groups at an age- and gender-specific rate per year. The transfer rate depends on the rate of population growth, age- and gender-specific per capita mortality rate, and the number of years within an age group (*3*). We assumed equilibrium in the age distribution with zero population growth.

We set the population size in the model to 100,000 persons divided equally between females and males. Death rates for males and for females without cervical cancer were obtained from Vital Statistics data on gender- and age-specific mortality rates across all races for 2002 (*4*). Death rates among adolescent

[1]Refer to the Appendix References for citations in this Appendix.

girls and women with cervical cancer were obtained from Surveillance Epidemiology and End Results (SEER) Program data for 1997–2002 (*5*). Other demographic data were obtained from US Vital Statistics and the 2000 Census (*4*,*6*).

Epidemiologic Model

The epidemiologic model simulates HPV infection and occurrence of HPV disease (cervical intraepithelial neoplasia [CIN], cervical cancer, and genital warts) in the population. The acquisition of infection and progression from infection to disease follow a similar natural history structure, as assumed in previous models for HPV 16 and 18 (*7*). Building on these previous models, we also incorporated HPV 6 and 11 infection and genital warts and modeled infection by using 3 groups of HPV types (HPV 16/18, HPV 6/11, or HPV 6/11/16/18).

To simulate the occurrence of CIN, genital warts, and cervical cancer among those infected with HPV, we divided the population into distinct epidemiologic categories, according to the population's susceptibility to infection or the population's status with respect to infection, disease, screening, and treatment. These categories were similar to what has previously been defined in other models (*7*). The following, along with Figure 1, describes the movement of the population through these categories.

HPV Infection: Acquisition and Transmission

The epidemiologic model begins with 12-year-olds entering into the susceptible category *X*. Susceptible persons acquire HPV infection with a given type (HPV 16/18 infected only, HPV 6/11 infected only, or HPV 6/11 and HPV 16/18 infected) at a rate dependent upon gender, sexual activity group, age, and time. The rate at which persons of a given gender, sexual activity group, and age class at a given time acquire infection with a certain type (per capita force of infection) depends on the number of sexual partnerships and how these persons form partnerships with persons of the opposite sex, the fraction of infected sex partners, and the transmission probability per partnership. The formation of sexual partnerships is governed by a conditional probability sexual mixing matrix. Each cell in the mixing matrix represents the probability of a person of a given gender, sexual activity group, and age class having a sexual activity group, age-class specific partner from the opposite gender. In generating the mixing matrix, we used 2 parameters to depict the degree of mixing between age and sexual activity groups. This strategy allowed us to represent a wide range of mixing patterns in the matrix, from fully assortative (as for persons with like persons when parameter is zero) to proportionate (random partners when parameter is 1) mixing (*1*,*2*,*8*,*9*). The baseline parameter values for the rate of sexual partner change, stratified by gender, sexual activity, and age, were calculated by using data from the National Health and Social Life Survey (*10*) and methods outlined in Garnett and Anderson (*2*) (Appendix Table 1).

Once HPV transmission occurs, susceptible persons enter the category of infected persons, *Y*. Persons leave this category when the infectious period for HPV ends and enter the category of recovered persons with a fixed duration of immunity, *Z*. In the base case, we assumed that duration of natural immunity is lifelong. Unvaccinated infected persons clear infection at a type-specific per capita rate. Persons in the immune (*Z*) category who are susceptible to only 1 type can be infected with that type and move to another infected/immune category, *U*.

A fraction of susceptible persons are vaccinated and move into the vaccination category *V*. The movement of those vaccinated through the model is similar to the movement of those unvaccinated, shown in Figure 1A. The remaining fraction of persons who are not vaccinated remains in the susceptible category *X*. The vaccine-induced immunity of those in the vaccinated category may wane over time. As a result, persons can eventually move to the susceptible category *S* at an age- and gender-dependent rate. We assumed that when a person loses vaccine-derived immunity, he or she becomes susceptible to infection with any of the types. In the base case, the duration of vaccine-derived immunity is assumed to be lifelong. Vaccinated persons can also expe-

Appendix Table 1. Baseline behavioral parameter values for the sexually active population*

Activity group	Proportion of population, %		Relative partner acquisition rate
	Male	Female	
1 (highest)	2.56	2.56	11.29
2	11.47	11.47	2.96
3 (lowest)	85.97	85.97	1.0
Age group, y	Relative partner acquisition rate	Overall mean partner acquisition rate	
12–14	0.11	0.1	
15–17	1.18	0.3	
18–19	2.42	1.3	
20–24	2.61		
25–29	2.55		
30–34	1.72		
35–39	1.65		
40–44	1.53		
45–49	1.38		
50–54	1.25		
55–59	1.00		
60–69	0.61	0.5	
≥70	0.44		

*Sources: Lauman et al. (*10*), Abma and Sonenstein (*11*).

Appendix Table 2. Baseline biologic parameter values for HPV disease categories*

Parameter	Base-case estimate	Source†
Progression in the presence of HPV 16/18 per year, %		
Normal to CIN 1	9.4	(RI)
Normal to CIN 1 to CIN 2	5.8	(*17*,RI)
Normal to CIN 1 to CIN 2 to CIN 3	3.5	(*17*,RI)
CIN 1 to CIN 2	13.6	(MRK)
CIN 2 to CIN 3 (severe dysplasia)	14.0	(*26*,*27*)
CIN 3 - severe dysplasia to CIN 3 - CIS 1	42.0	(*26*,*28*)
CIS 1 to CIS 2	5.0	
CIS 2 to LCC	18.0	
LCC to RCC	10.0	(*16*,*24*,*25*,*31*)
RCC to DCC	30.0	(*16*)
Progression in the presence of HPV 6/11 per year, %		
Normal to CIN 1	9.5	(RI)
Normal to CIN 1 to CIN 2	1.9	(RI)
Normal to CIN 1 to CIN 2 to CIN 3	0.0	(RI)
CIN 1 to CIN 2	0.0	(MRK)
Normal to genital warts	57	(*17*)
Mean duration of acute HPV infection, y		
HPV 16/18 infection	1.2	(RI)
HPV 6/11 infection	0.7	(RI)
Regression of HPV 16/18+ disease per year, %		
CIN 1 to normal/HPV	32.9	(MRK,*29*)
CIN 2 to normal/HPV	21.0	(*26*,*27*,*30*)
CIN 2 to CIN 1	13.3	(*27*)
CIN 3 (severe dysplasia) to normal/HPV	11.0	(*26*)
CIN 3 (severe dysplasia) to CIN 1	3.0	(*26*,*27*)
CIN 3 (severe dysplasia) to CIN 2	3.0	(*26*,*27*)
Regression of HPV 6/11+ disease per year, %		
CIN 1 to normal/HPV	55.2	(MRK)
Genital warts to normal/HPV	87.5	(*17*)
Age (y) and stage-specific cervical cancer mortality rates per year, 1997–2002, %		(*5*)
For LCC		
15–29	0.7	
30–39	0.6	
40–49	0.8	
50–59	1.9	
60–69	4.2	
≥70	11.6	
For RCC		
15–29	13.4	
30–39	8.9	
40–49	11.0	
50–59	10.1	
60–69	17.6	
≥70	28.6	
For DCC		
15–29	42.9	
30–39	41.0	
40–49	46.7	
50–59	52.7	
60–69	54.6	
≥70	70.3	

*HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; CIS, carcinoma in situ; LCC, localized cervical cancer; RCC, regional cervical cancer; DCC, distant cervical cancer.

†RI, R. Insinga, unpub. data; MRK, Merck, unpub. data.

rience a breakthrough infection and enter the category of infectious persons, *W*, at a per capita rate that depends on the degree of protection offered by the vaccine. Vaccinated persons can recover from an HPV infection at an age- and gender-specific rate by a factor that is different from the recovery rate for unvaccinated infected persons. Vaccinated persons then move to a category with fixed duration of immunity, *Q*. Persons in this category who are susceptible to 1 type can be infected with that type and move to another vaccinated infected/immune category, *P*.

No epidemiologic studies have estimated the probability of HPV infection transmission per partnership and by type. We assumed that this probability is higher for transmission from males to females (0.8) than that for transmission from females to males (0.7) (*12–15*). Using data on participants in the placebo arm of Merck's HPV vaccine clinical trials, we estimated mean duration of HPV infection before progression to CIN, or regression, at 1.2 years for HPV 16/18 and 0.7 years for HPV 6/11 (R. Insinga, unpub. data).

CIN, Cervical Cancer, and Genital Warts

CIN develops in infected girls and women at a specified rate and moves to the HPV disease categories of the model (Figure 1B). Several categories represent the true histologic health status of a woman: CIN grade 1 (CIN 1), CIN grade 2 (CIN 2), CIN grade 3 (CIN 3), localized cervical cancer (LCC), regional cervical cancer (RCC), distant cervical cancer (DCC), and cervical cancer survivors who are free from cancer. Women with CIN and cancer were further classified into undetected, detected, or treated categories. Two additional absorbing categories are for women who are no longer at risk for cervical cancer (*16*). These include the following: 1) women who have had a benign hysterectomy for reasons other than cervical cancer (at an age-specific rate) and 2) women treated and cured for cervical cancer. Finally, infection with the low-risk type can result in genital warts in females and males and move to the genital warts category, GW (*17*). We assumed women with benign hysterectomies can be infected and are at risk for genital warts (*18*). Women and men recovering from genital warts move to category *Z*.

We assumed all progression and regression rates to HPV and cancer states to be independent of age (*19–23*). Annual transition rates from HPV infection to clinically detectable CIN were calculated from studies by Winer et al. (*17*) and Insinga (R. Insinga, unpub. data). Several published reports were also used to estimate annual rates of CIN regression and progression to cervical cancer (*24–31*) (Merck, unpub. data). Incidence and regression rates for genital warts were obtained from Winer et al. (*17*) (Appendix Table 2). Hysterectomy rates; cervical cancer screening coverage, sensitivity, and specificity; and treatment efficacy were derived from several published studies (*32–40*) (Appendix Table 3).

Appendix Table 3. Hysterectomy, screening, and treatment parameters*

Parameter	Base-case estimate	Source
Hysterectomy rate, % per year		(*32*)
15–24 y	0.02	
25–29 y	0.26	
30–34 y	0.53	
35–39 y	0.89	
40–44 y	1.17	
45–54 y	0.99	
≥55 y	0.36	
Cervical cytology screening, excluding those with hysterectomy, % per year		(*33*)
10–14 y	0.6	
15–19 y	21.0	
20–24 y	44.8	
25–29 y	61.6	
30–34 y	54.9	
35–39 y	50.5	
40–44 y	48.1	
45–49 y	49.1	
50–54 y	51.1	
55–59 y	46.7	
60–64 y	42.5	
65–69 y	38.9	
70–74 y	29.6	
75–79 y	20.1	
80–84 y	11.1	
≥85	5.5	
Females never screened, %	5.0	
Liquid-based cytology specificity, %	94	(*34,35*)
Colposcopy sensitivity, %	96	(*36*)
Colposcopy specificity, %	48	(*36*)
GW patients seeking physician care, %	75	(*37*)
Symptom development, % per year		Assumed
Localized cervical cancer	4	
Regional cervical cancer	18	
Distant cervical cancer	90	
Eradication with treatment, %		
For CIN 1	96	(*38*)
For CIN 2	92	(*38*)
For CIN 3, CIS	92	(*38*)
For localized cervical cancer	92	(*39*)
For regional cervical cancer	55	(*39*)
For distant cervical cancer	17	(*39*)
Persistence of HPV after treatment for CIN or GW, %	34	(*40*)

*HPV, human papillomavirus; GW, genital warts; CIN, cervical intraepithelial neoplasia; CIS, carcinoma in situ.

Economic Parameters

All model costs were updated to 2005 US dollars by using the medical care component of the Consumer Price Index (*41*). The direct medical costs for screening and treatment for CIN, genital warts, and cervical cancer were based on administrative claims data and other sources (*42–44*). We measured the cost of cytology screening per unit time as the product of the cost per test, the test compliance rate, the frequency of administering the test per unit time, and the size of the unidentified population that is eligible for screening. We estimated the cost of following up on false-positive results of the cytology test as a function of the specificities of the cytology test and colposcopy procedure and the costs of colposcopy and biopsy. The cost of the HPV vaccine for 3 doses was assumed to be $360, which was consistent with HPV vaccination costs used in previous cost-effectiveness analy-

Appendix Table 4. Cost and quality-of-life parameters*

Parameter	Base-case estimate		Source
Costs of diagnosing and treating HPV disease			*(42–44)*
Genital warts	$489		
Liquid-based cytology screening	$99		
Colposcopy and biopsy	$318		
CIN 1	$1,554		
CIN 2/3, CIS	$3,483		
Localized cervical cancer	$26,470		
Regional cervical cancer	$28,330		
Distant cervical cancer	$45,376		
Quality-of-life weights (0–1 scale)			
CIN 1	0.91		*(47)*
CIN 2/3, CIS	0.87		*(47)*
Localized cervical cancer	0.76		*(47)*
Regional cervical cancer	0.67		*(47)*
Distant cervical cancer	0.48		*(46)*
Cervical cancer survivor	0.84		*(47,49,50)*
Genital warts	0.91		*(47)*
No condition	F	M	*(46)*
12–17 y	0.93	0.93	
18–34 y	0.91	0.92	
35–44 y	0.89	0.90	
45–54 y	0.86	0.87	
55–64 y	0.80	0.81	
65–74 y	0.78	0.76	
≥75 y	0.70	0.69	

*HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; CIS, carcinoma in situ; F, females; M, males.

ses (*7*). Productivity losses as a result of HPV disease or death were not included in the analyses (*45*).

Quality adjusted life years (QALYs) were measured by weighting survival time by the quality-of-life adjustment weights associated with each health state and integrating the sum of adjusted time in all these health states over the planning horizon. We measured survival time as the total number of years spent alive by the active population during a given period. The health utility values used to estimate QALYs were derived from various sources (*46–48*). Health utility values for diagnosed invasive cancer states were estimated by Myers et al. (*47*) at 0.76 for localized cancer and 0.67 for regional cancer; these values were derived from Gold et al. at 0.48 for distant cancer (*46*). We assumed that the quality of life for cervical cancer survivors after successful treatment would continue to be lower (0.76) than that of healthy women (*49*,*50*). Diagnosed and treated CIN 1 and CIN 2/3 states were assumed to have quality weights of 0.91 and 0.87, respectively (*47*,*48*). We assumed the quality weight for genital warts to be 0.91 (*47*) (Appendix Table 4).

Undiagnosed and asymptomatic HPV, CIN, and cancer states and successfully treated CIN states were assumed to have a quality-of-life weight similar to those of persons without these conditions. Gender- and age-specific quality weights for non-HPV disease states were also derived from Gold et al. (*46*). Time in these states was multiplied by the age- and gender-specific weights to reflect the variation of quality of life by age and gender groups. We assumed that quality of life did not vary by sexual activity groups. Finally, all costs and effects were discounted to present value at a rate of 3%.

Appendix References

1. Garnett GP, Anderson RM. Factors controlling the spread of HIV in heterosexual communities in developing countries: patterns of mixing between age and sexual activity classes. Philos Trans R Soc Lond B Biol Sci. 1993;342:137–59.
2. Garnett GP, Anderson RM. Balancing sexual partnerships in age and activity stratified model of HIV transmission in heterosexual populations. IMA J Math Appl Med Biol. 1994;11:161–92.
3. Hethcote H. The mathematics of infectious diseases. SIAM Review. 2000;42:599–653.
4. Kochanek KD, Murphy SL, Anderson RN, Scott C. Deaths: final data for 2002. Natl Vital Stat Rep 53. Hyattsville (MD): National Center for Health Statistics; 2004.
5. Surveillance, Epidemiology, and End Results (SEER) program. Public-use data (1973–2002), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch. Released 2005 Apr, based on the November 2004 submission [cited 2006 Mar 13]. Available from http://www.seer.cancer.gov
6. US Census Bureau. Census 2000 summary file 1. Washington: US Census Bureau; 2002.
7. Dasbach EJ, Elbasha EH, Insinga RP. Mathematical models for predicting the epidemiologic and economic impact of vaccination against human papillomavirus infection and disease. Epidemiol Rev. 2006;28:88–100.
8. Garnett GP, Hughes JP, Anderson RM, Stoner BP, Aral SO, Whittington WL, et al. The determination of the sexual mixing pattern of patients attending STD and other clinics in Seattle, USA, by contact tracing. Sex Transm Dis. 1996;23:248–57.
9. Garnett GP, Anderson RM. Contact tracing and the estimation of sexual mixing patterns: the epidemiology of gonococcal infections. Sex Transm Dis. 1993;20:181–91.
10. Lauman E, Gagnon J, Michael R, Michaels S. The social organization of sexuality. Chicago: University of Chicago Press; 1994.
11. Abma JC, Sonenstein FL. Sexual activity and contraceptive practices among teenagers in the United States, 1988 and 1995. National Center for Health Statistics. Vital Health Stat. 2001;23:1–79.
12. Hughes JP, Garnett GP, Koutsky L. The theoretical population level impact of a prophylactic human papillomavirus vaccine. Epidemiology. 2002;13: 631–9.
13. Oriel JD. Natural history of genital warts. Br J Vener Dis. 1971;47:1–13.
14. Frega A, Stentella P, Villani C, Ruzza D, Marcomin G, Rota F, et al. Correlation between cervical intraepithelial neoplasia and human papillomavirus male infections: a longitudinal study. Eur J Gynaecol Oncol. 1999;20:228–30.
15. Burchell AN, Richardson H, Mahmud SM, Trottier H, Tellier PP, Hanley J, et al. Modeling the sexual transmissibility of human papillomavirus infection using stochastic computer simulation and empirical data from a cohort study of young women in Montreal, Canada. Am J Epidemiol. 2006;163:534–43.
16. Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. Am J Epidemiol. 2000;151:1158–71.
17. Winer RL, Kiviat NB, Hughes JP, Adam DE, Lee S-K, Kuypers JM, et al. Development and duration of human papillomavirus lesions, after initial infection. J Infect Dis. 2005;191:731–8.
18. Castle PE, Schiffman M, Bratti MC, Hildesheim A, Herrero R, Hutchinson ML, et al. A population-based study of vaginal human papillomavirus infection in hysterectomized women. J Infect Dis. 2004;190:458–67.
19. Castle PE, Schiffman M, Herrero R, Hildesheim A, Rodriguez AC, Bratti MC, et al. A prospective study of age trends in cervical human papillomavirus acquisition and persistence in Guanacaste, Costa Rica. J Infect Dis. 2005;191:1808–16.
20. Syrjanen S, Shabalova I, Petrovichev N, Podistov J, Ivanchenko O, Zakharenko S, et al. Age-specific incidence and clearance of high-risk human papillomavirus infections in women in the former Soviet Union. Int J STD AIDS. 2005;16:217–23.
21. Dalstein V, Riethmuller D, Pretet JL, Le Bail Carval K, Sautiere JL, Carbillet J-P, et al. Persistence and load of high-risk HPV are predictors for development of high-grade cervical lesions: a longitudinal French cohort study. Int J Cancer. 2003;106:396–403.
22. Molano M, Van den Brule A, Plummer M, Weiderpass E, Posso H, Arslan A, et al. Determinants of clearance of human papillomavirus infections in Colombian women with normal cytology: a population-based, 5-year follow-up study. Am J Epidemiol. 2003;158:486–94.

23. Winer RL, Koutsky LA. Human papillomavirus through the ages. J Infect Dis. 2005;191:1787–9.
24. Sanders GD, Taira AV. Cost-effectiveness of a potential vaccine for human papillomavirus. Emerg Infect Dis. 2003;9:37–48.
25. Goldie SJ, Grima D, Kohli M, Wright TC, Weinstein MC, Franco E. A comprehensive natural history model of human papillomavirus (HPV) infection and cervical cancer: potential impact of and HPV 16/18 Vaccine. Int J Cancer. 2003;106:896–904.
26. Kataja V, Syrjanen K, Mantyjarvi R, Vayrynen M, Syrjanen S, Saarikoski S, et al. Prospective follow-up of cervical HPV infections: life table analysis of histopathological, cytological and colposcopic data. Eur J Epidemiol. 1989;5:1–7.
27. De Aloysio D, Miliffi L, Iannicelli T, Penacchioni P, Bottiglioni F. Intramuscular interferon-beta treatment of cervical intraepithelial neoplasia II associated with human papillomavirus infection. Acta Obstet Gynecol Scand. 1994;73:420–4.
28. Westergaard L, Norgaard M. Severe cervical dysplasia: control by biopsies or primary conization? A comparative study. Acta Obstet Gynecol Scand. 1981;60:549–54.
29. Sastre-Garau X, Cartier I, Jourdan-Da Silva N, De Cremoux P, Lepage V, Charron D, et al. Regression of low-grade cervical intraepithelial neoplasia in patients with HLA-DRB1*13 genotype. Obstet Gynecol. 2004;104:751–5.
30. Matsumoto K, Yasugi T, Oki A, Fujii T, Nagata C, Sekiya S, et al. IgG antibodies to HPV16, 52, 58 and 6 L1-capsids and spontaneous regression of cervical intraepithelial neoplasia. Cancer Lett. 2006;231:309–13.
31. Berkhof J, de Bruijne MC, Zielinski GD, Meijer CJ. Natural history and screening model for high-risk human papillomavirus infection, neoplasia and cervical cancer in the Netherlands. Int J Cancer. 2005;115:268–75.
32. Keshavarz H, Hillis SD, Kieke BA, Marchbanks PA. Hysterectomy surveillance—United States, 1994–1999. MMWR CDC Surveill Summ. 2002;51:1–8. Available from http://www.cdc.gov/mmwr/preview/mwrhtml/ss5105a1.htm
33. Insinga RP, Glass AG, Rush BB. Pap screening in a U.S. health plan. Cancer Epidemiol Biomarkers Prev. 2004;13:355–60.
34. Bigras G, de Marval F. The probability for a Pap test to be abnormal is directly proportional to HPV viral load: results from a Swiss study comparing HPV testing and liquid-based cytology to detect cervical cancer precursors in 13,842 women. Br J Cancer. 2005;93:575–81.
35. Coste J, Cochand-Priollet B, De Cremoux P, Le Gales C, Cartier I, Molinie V, et al. Cross sectional study of conventional cervical smear, monolayer cytology, and human papillomavirus DNA testing for cervical cancer screening. BMJ. 2003;326:733.
36. Mitchell MF, Schottenfeld D, Tortolero-Luna G, Cantor SB, Richards-Kortum R. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. Obstet Gynecol. 1998;91:626–31.
37. Chesson HW, Blandford JM, Gift TL, Tao G, Irwin KL. The estimated direct medical cost of sexually transmitted diseases among American youth, 2000. Perspect Sex Reprod Health. 2004;36:11–9.
38. Flannelly G, Langhan H, Jandial L, Mana E, Campbell M, Kitchener H. A study of treatment failures following large loop excision of the transformation zone for the treatment of cervical intraepithelial neoplasia. Br J Obstet Gynaecol. 1997;104:718–22.
39. Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, et al. SEER cancer statistics review, 1975–2002. Bethesda (MD): National Cancer Institute; 2005 [cited 2006 Mar 13]. Available from http://seer.cancer.gov/csr/1975_2002/
40. Cruickshank ME, Sharp L, Chambers G, Smart L, Murray G. Persistent infection with human papillomavirus following the successful treatment of high-grade cervical intraepithelial neoplasia. BJOG. 2002;109:579–81.
41. US Bureau of Labor Statistics. Statistical abstracts of the United States: consumer price index. Washington: National Center for Health Statistics; 2002.
42. Insinga RP, Dasbach EJ, Myers ER. The health and economic burden of genital warts in a set of private U.S. health plans. Clin Infect Dis. 2003;36:1397–403.
43. Medstat. MarketScan® database. Ann Arbor (MI): Thomson Medstat; 2001.
44. Kim JJ, Wright T, Goldie S. Cost-effectiveness of alternative triage strategies for atypical squamous cells of undetermined significance. JAMA. 2002;287:2382–90.
45. Gold MR, Siegel JE, Russell LB, Weinstein MC, editors. Cost-effectiveness in health and medicine. Report of the Panel on Cost-Effectiveness in Health and Medicine. New York: Oxford University Press; 1996.
46. Gold M, Franks P, McCoy K, Fryback D. Toward consistency in cost-utilities analysis: using national measures to create condition-specific values. Med Care. 1998;36:778–92.
47. Myers E, Green S, Lipkus I. Patient preferences for health states related to HPV infection: visual analogue scales vs. time trade-off elicitation. Proceedings of the 21st International Papillomavirus Conference. Abstract no. 390.2. Mexico City, Mexico. 2004.
48. Insinga RP, Glass AG, Myers ER, Rush BB. Abnormal outcomes following cervical cancer screening: event duration and health utility loss. Med Decis Making. 2006. In press.
49. Andersen B. Stress and quality of life following cervical cancer. J Natl Cancer Inst. 1996;21:65–70.
50. Wenzel L, DeAlba I, Habbal R, Kluhsman BC, Fairclough D, Krebs L, et al. Quality of life in long-term cervical cancer survivors. Gynecol Oncol. 2005;97:310–7.

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Appendix[1]

[1]Refer to the Appendix References, below, for citations in this Appendix.

Demographic Model

The demographic model stratifies the population by gender and 17 age groups (12–14, 15–17, 18–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, and ≥85 years). This age grouping permits age-specific inputs for patterns of sexual activity and cervical cancer screening and allows for age-specific outputs such as rates of cervical human papillomavirus (HPV) disease among girls and women, and genital warts among both males and females. Similar age groupings have been used by other sexually transmitted disease models (*1,2*). We further stratified each age group into 3 sexual activity groups (high, medium, low). We defined sexual activity according to the rates of sex partner change per year: low (0–1 per year), medium (2–4 per year), and high (≥5 per year). The number and the initial distribution of new entrants into the population by each gender were chosen to satisfy the Lotka characteristic equation with zero population growth (*3*). This allowed for variation in results across strategies to primarily be due to epidemiologic and program model features and not to changes in the demographic characteristics of the population over time (*3*).

The model starts with 12-year-olds entering the population at a gender-specific and sexual activity–specific rate, and transfers persons between successive age groups at an age- and gender-specific rate per year. The transfer rate depends on the rate of population growth, age- and gender-specific per capita mortality rate, and the number of years within an age group (*3*). We assumed equilibrium in the age distribution with zero population growth.

We set the population size in the model to 100,000 persons divided equally between females and males. Death rates for males and for females without cervical cancer were obtained from Vital Statistics data on gender- and age-specific mortality rates across all races for 2002 (*4*). Death rates among adolescent girls and women with cervical cancer were obtained from Surveillance Epidemiology and End Results (SEER)

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Program data for 1997–2002 (*5*). Other demographic data were obtained from US Vital Statistics and the 2000 Census (*4,6*).

Epidemiologic Model

The epidemiologic model simulates HPV infection and occurrence of HPV disease (cervical intraepithelial neoplasia [CIN], cervical cancer, and genital warts) in the population. The acquisition of infection and progression from infection to disease follow a similar natural history structure, as assumed in previous models for HPV 16 and 18 (*7*). Building on these previous models, we also incorporated HPV 6 and 11 infection and genital warts and modeled infection by using 3 groups of HPV types (HPV 16/18, HPV 6/11, or HPV 6/11/16/18).

To simulate the occurrence of CIN, genital warts, and cervical cancer among those infected with HPV, we divided the population into distinct epidemiologic categories, according to the population's susceptibility to infection or the population's status with respect to infection, disease, screening, and treatment. These categories were similar to what has previously been defined in other models (*7*). The following, along with Figure 1, describes the movement of the population through these categories.

HPV Infection: Acquisition and Transmission

The epidemiologic model begins with 12-year-olds entering into the susceptible category *X*. Susceptible persons acquire HPV infection with a given type (HPV 16/18 infected only, HPV 6/11 infected only, or HPV 6/11 and HPV 16/18 infected) at a rate dependent upon gender, sexual activity group, age, and time. The rate at which persons of a given gender, sexual activity group, and age class at a given time acquire infection with a certain type (per capita force of infection) depends on the number of sexual partnerships and how these persons form partnerships with persons of the opposite sex, the fraction of infected sex partners, and the transmission probability per partnership. The formation of sexual partnerships is governed by a conditional probability sexual mixing matrix. Each cell in the mixing matrix represents the probability of a person of a given gender, sexual activity group, and age class having a sexual activity group, age-class specific partner from the opposite gender. In generating the mixing matrix, we used 2 parameters to depict the degree of mixing between age and sexual activity groups. This strategy

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allowed us to represent a wide range of mixing patterns in the matrix, from fully assortative (as for persons with like persons when parameter is zero) to proportionate (random partners when parameter is 1) mixing (*1,2,8,9*). The baseline parameter values for the rate of sexual partner change, stratified by gender, sexual activity, and age, were calculated by using data from the National Health and Social Life Survey (*10*) and methods outlined in Garnett and Anderson (*2*) (Appendix Table 1).

Once HPV transmission occurs, susceptible persons enter the category of infected persons, *Y*. Persons leave this category when the infectious period for HPV ends and enter the category of recovered persons with a fixed duration of immunity, *Z*. In the base case, we assumed that duration of natural immunity is lifelong. Unvaccinated infected persons clear infection at a type-specific per capita rate. Persons in the immune (*Z*) category who are susceptible to only 1 type can be infected with that type and move to another infected/immune category, *U*.

A fraction of susceptible persons are vaccinated and move into the vaccination category *V*. The movement of those vaccinated through the model is similar to the movement of those unvaccinated, shown in Figure 1A. The remaining fraction of persons who are not vaccinated remains in the susceptible category *X*. The vaccine-induced immunity of those in the vaccinated category may wane over time. As a result, persons can eventually move to the susceptible category *S* at an age- and gender-dependent rate. We assumed that when a person loses vaccine-derived immunity, he or she becomes susceptible to infection with any of the types. In the base case, the duration of vaccine-derived immunity is assumed to be lifelong. Vaccinated persons can also experience a breakthrough infection and enter the category of infectious persons, *W,* at a per capita rate that depends on the degree of protection offered by the vaccine. Vaccinated persons can recover from an HPV infection at an age- and gender-specific rate by a factor that is different from the recovery rate for unvaccinated infected persons. Vaccinated persons then move to a category with fixed duration of immunity, *Q*. Persons in this category who are susceptible to 1 type can be infected with that type and move to another vaccinated infected/immune category, *P*.

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No epidemiologic studies have estimated the probability of HPV infection transmission per partnership and by type. We assumed that this probability is higher for transmission from males to females (0.8) than that for transmission from females to males (0.7) (*12–15*). Using data on participants in the placebo arm of Merck's HPV vaccine clinical trials, we estimated mean duration of HPV infection before progression to CIN, or regression, at 1.2 years for HPV 16/18 and 0.7 years for HPV 6/11 (R. Insinga, unpub. data).

CIN, Cervical Cancer, and Genital Warts

CIN develops in infected girls and women at a specified rate and moves to the HPV disease categories of the model (Figure 1B). Several categories represent the true histologic health status of a woman: CIN grade 1 (CIN 1), CIN grade 2 (CIN 2), CIN grade 3 (CIN 3), localized cervical cancer (LCC), regional cervical cancer (RCC), distant cervical cancer (DCC), and cervical cancer survivors who are free from cancer. Women with CIN and cancer were further classified into undetected, detected, or treated categories. Two additional absorbing categories are for women who are no longer at risk for cervical cancer (*16*). These include the following: 1) women who have had a benign hysterectomy for reasons other than cervical cancer (at an age-specific rate) and 2) women treated and cured for cervical cancer. Finally, infection with the low-risk type can result in genital warts in females and males and move to the genital warts category, *GW* (*17*). We assumed women with benign hysterectomies can be infected and are at risk for genital warts (*18*). Women and men recovering from genital warts move to category *Z*.

We assumed all progression and regression rates to HPV and cancer states to be independent of age (*19–23*). Annual transition rates from HPV infection to clinically detectable CIN were calculated from studies by Winer et al. (*17*) and Insinga (R. Insinga, unpub. data). Several published reports were also used to estimate annual rates of CIN regression and progression to cervical cancer (*24–31*) (Merck, unpub. data). Incidence and regression rates for genital warts were obtained from Winer et al. (*17*) (Appendix Table 2). Hysterectomy rates; cervical cancer screening coverage, sensitivity, and specificity; and treatment efficacy were derived from several published studies (*32–40*) (Appendix Table 3).

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Economic Parameters

All model costs were updated to 2005 US dollars by using the medical care component of the Consumer Price Index (*41*). The direct medical costs for screening and treatment for CIN, genital warts, and cervical cancer were based on administrative claims data and other sources (*42–44*). We measured the cost of cytology screening per unit time as the product of the cost per test, the test compliance rate, the frequency of administering the test per unit time, and the size of the unidentified population that is eligible for screening. We estimated the cost of following up on false-positive results of the cytology test as a function of the specificities of the cytology test and colposcopy procedure and the costs of colposcopy and biopsy. The cost of the HPV vaccine for 3 doses was assumed to be $360, which was consistent with HPV vaccination costs used in previous cost-effectiveness analyses (*7*). Productivity losses as a result of HPV disease or death were not included in the analyses (*45*).

Quality adjusted life years (QALYs) were measured by weighting survival time by the quality-of-life adjustment weights associated with each health state and integrating the sum of adjusted time in all these health states over the planning horizon. We measured survival time as the total number of years spent alive by the active population during a given period. The health utility values used to estimate QALYs were derived from various sources (*46–48*). Health utility values for diagnosed invasive cancer states were estimated by Myers et al. (*47*) at 0.76 for localized cancer and 0.67 for regional cancer; these values were derived from Gold et al. at 0.48 for distant cancer (*46*). We assumed that the quality of life for cervical cancer survivors after successful treatment would continue to be lower (0.76) than that of healthy women (*49,50*). Diagnosed and treated CIN 1 and CIN 2/3 states were assumed to have quality weights of 0.91 and 0.87, respectively (*47,48*). We assumed the quality weight for genital warts to be 0.91 (*47*) (Appendix Table 4).

Undiagnosed and asymptomatic HPV, CIN, and cancer states and successfully treated CIN states were assumed to have a quality-of-life weight similar to those of persons without these conditions. Gender- and *46*age-specific quality weights for non-HPV disease states were also derived from Gold et al. (). Time in these states was

multiplied by the age- and gender-specific weights to reflect the variation of quality of life by age and gender groups. We assumed that quality of life did not vary by sexual activity groups. Finally, all costs and effects were discounted to present value at a rate of 3%.

Appendix References

1. Garnett GP, Anderson RM. Factors controlling the spread of HIV in heterosexual communities in developing countries: patterns of mixing between age and sexual activity classes. Philos Trans R Soc Lond B Biol Sci. 1993;342:137–59.

2. Garnett GP, Anderson RM. Balancing sexual partnerships in age and activity stratified model of HIV transmission in heterosexual populations. IMA J Math Appl Med Biol. 1994;11:161–92.

3. Hethcote H. The mathematics of infectious diseases. SIAM Review. 2000;42:599–653.

4. Kochanek KD, Murphy SL, Anderson RN, Scott C. Deaths: final data for 2002. Natl Vital Stat Rep 53 (5). Hyattsville (MD): National Center for Health Statistics; 2004.

5. Surveillance, Epidemiology, and End Results (SEER) program. Public-use data (1973–2002), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch. Released 2005 Apr, based on the November 2004 submission. (cited 2006 Mar 13). Available from http://www.seer.cancer.gov

6. US Census Bureau. Census 2000 summary file 1. Washington: US Census Bureau; 2002.

7. Dasbach EJ, Elbasha EH, Insinga RP. Mathematical models for predicting the epidemiologic and economic impact of vaccination against human papillomavirus infection and disease. Epidemiol Rev. 2006;28:88–100.

8. Garnett GP, Hughes JP, Anderson RM, Stoner BP, Aral SO, Whittington WL, et al. The determination of the sexual mixing pattern of patients attending STD and other clinics in Seattle, USA, by contact tracing. Sex Transm Dis. 1996;23:248–57.

9. Garnett GP, Anderson RM. Contact tracing and the estimation of sexual mixing patterns: the epidemiology of gonococcal infections. Sex Transm Dis. 1993;20:181–91.

10. Lauman E, Gagnon J, Michael R, Michaels S. The social organization of sexuality. Chicago: University of Chicago Press; 1994.

11. Abma JC, Sonenstein FL. Sexual activity and contraceptive practices among teenagers in the United States, 1988 and 1995. National Center for Health Statistics. Vital Health Stat. 2001;23:1–79.

12. Hughes JP, Garnett GP, Koutsky L. The theoretical population level impact of a prophylactic human papillomavirus vaccine. Epidemiology. 2002;13:631–9.

13. Oriel JD. Natural history of genital warts. Br J Vener Dis. 1971;47:1–13.

14. Frega A, Stentella P, Villani C, Ruzza D, Marcomin G, Rota F, et al. Correlation between cervical intraepithelial neoplasia and human papillomavirus male infections: a longitudinal study. Eur J Gynaecol Oncol. 1999;20:228–30.

15. Burchell AN, Richardson H, Mahmud SM, Trottier H, Tellier PP, Hanley J, et al. Modeling the sexual transmissibility of human papillomavirus infection using stochastic computer simulation and empirical data from a cohort study of young women in Montreal, Canada. Am J Epidemiol. 2006;163:534–43.

16. Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. Am J Epidemiol. 2000;151:1158–71.

17. Winer RL, Kiviat NB, Hughes JP, Adam DE, Lee S-K, Kuypers JM, et al. Development and duration of human papillomavirus lesions, after initial infection. J Infect Dis. 2005;191:731–8.

18. Castle PE, Schiffman M, Bratti MC, Hildesheim A, Herrero R, Hutchinson ML, et al. A population-based study of vaginal human papillomavirus infection in hysterectomized women. J Infect Dis. 2004;190:458–67.

19. Castle PE, Schiffman M, Herrero R, Hildesheim A, Rodriguez AC, Bratti MC, et al. A prospective study of age trends in cervical human papillomavirus acquisition and persistence in Guanacaste, Costa Rica. J Infect Dis. 2005;191:1808–16.

20. Syrjanen S, Shabalova I, Petrovichev N, Podistov J, Ivanchenko O, Zakharenko S, et al. Age-specific incidence and clearance of high-risk human papillomavirus infections in women in the former Soviet Union. Int J STD AIDS. 2005;16:217–23.

21. Dalstein V, Riethmuller D, Pretet JL, Le Bail Carval K, Sautiere JL, Carbillet J-P, et al. Persistence and load of high-risk HPV are predictors for development of high-grade cervical lesions: a longitudinal French cohort study. Int J Cancer. 2003;106:396–403.

22. Molano M, Van den Brule A, Plummer M, Weiderpass E, Posso H, Arslan A, et al. Determinants of clearance of human papillomavirus infections in Colombian women with normal cytology: a population-based, 5-year follow-up study. Am J Epidemiol. 2003;158:486–94.

23. Winer RL, Koutsky LA. Human papillomavirus through the ages. J Infect Dis. 2005;191:1787–9.

24. Sanders GD, Taira AV. Cost-effectiveness of a potential vaccine for human papillomavirus. Emerg Infect Dis. 2003;9:37–48.

25. Goldie SJ, Grima D, Kohli M, Wright TC, Weinstein MC, Franco E. A comprehensive natural history model of human papillomavirus (HPV) infection and cervical cancer: potential impact of and HPV 16/18 Vaccine. Int J Cancer. 2003;106:896–904.

26. Kataja V, Syrjanen K, Mantyjarvi R, Vayrynen M, Syrjanen S, Saarikoski S, et al. Prospective follow-up of cervical HPV infections: life table analysis of histopathological, cytological and colposcopic data. Eur J Epidemiol. 1989;5:1–7.

27. De Aloysio D, Miliffi L, Iannicelli T, Penacchioni P, Bottiglioni F. Intramuscular interferon-beta treatment of cervical intraepithelial neoplasia II associated with human papillomavirus infection. Acta Obstet Gynecol Scand. 1994;73:420–4.

28. Westergaard L, Norgaard M. Severe cervical dysplasia: control by biopsies or primary conization? A comparative study. Acta Obstet Gynecol Scand. 1981;60:549–54.

29. Sastre-Garau X, Cartier I, Jourdan-Da Silva N, De Cremoux P, Lepage V, Charron D, et al. Regression of low-grade cervical intraepithelial neoplasia in patients with HLA-DRB1*13 genotype. Obstet Gynecol. 2004;104:751–5.

30. Matsumoto K, Yasugi T, Oki A, Fujii T, Nagata C, Sekiya S, et al. IgG antibodies to HPV16, 52, 58 and 6 L1-capsids and spontaneous regression of cervical intraepithelial neoplasia. Cancer Lett. 2006;231:309–13.

31. Berkhof J, de Bruijne MC, Zielinski GD, Meijer CJ. Natural history and screening model for high-risk human papillomavirus infection, neoplasia and cervical cancer in the Netherlands. Int J Cancer. 2005;115:268–75.

32. Keshavarz H, Hillis SD, Kieke BA, Marchbanks PA. Hysterectomy surveillance—United States, 1994–1999. MMWR CDC Surveill Summ. 2002;51:1–8. Available from http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5105a1.htm

33. Insinga RP, Glass AG, Rush BB. Pap screening in a U.S. health plan. Cancer Epidemiol Biomarkers Prev. 2004;13:355–60.

34. Bigras G, de Marval F. The probability for a Pap test to be abnormal is directly proportional to HPV viral load: results from a Swiss study comparing HPV testing and liquid-based cytology to detect cervical cancer precursors in 13,842 women. Br J Cancer. 2005;93:575–81.

35. Coste J, Cochand-Priollet B, De Cremoux P, Le Gales C, Cartier I, Molinie V, et al. Cross sectional study of conventional cervical smear, monolayer cytology, and human papillomavirus DNA testing for cervical cancer screening. BMJ. 2003;326:733.

36. Mitchell MF, Schottenfeld D, Tortolero-Luna G, Cantor SB, Richards-Kortum R. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. Obstet Gynecol. 1998;91:626–31.

37. Chesson HW, Blandford JM, Gift TL, Tao G, Irwin KL. The estimated direct medical cost of sexually transmitted diseases among American youth, 2000. Perspect Sex Reprod Health. 2004;36:11–9.

38. Flannelly G, Langhan H, Jandial L, Mana E, Campbell M, Kitchener H. A study of treatment failures following large loop excision of the transformation zone for the treatment of cervical intraepithelial neoplasia. Br J Obstet Gynaecol. 1997;104:718–22.

39. Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, et al. SEER cancer statistics review, 1975–2002. Bethesda (MD): National Cancer Institute; 2005. (cited 2006 Mar 13). Available from http://seer.cancer.gov/csr/1975_2002/

40. Cruickshank ME, Sharp L, Chambers G, Smart L, Murray G. Persistent infection with human papillomavirus following the successful treatment of high-grade cervical intraepithelial neoplasia. BJOG. 2002;109:579–81.

41. US Bureau of Labor Statistics. Statistical abstracts of the United States: consumer price index. Washington: National Center for Health Statistics; 2002.

42. Insinga RP, Dasbach EJ, Myers ER. The health and economic burden of genital warts in a set of private U.S. health plans. Clin Infect Dis. 2003;36:1397–403.

43. Medstat. MarketScan® database. Ann Arbor (MI): Thomson Medstat; 2001.

44. Kim JJ, Wright T, Goldie S. Cost-effectiveness of alternative triage strategies for atypical squamous cells of undetermined significance. JAMA. 2002;287:2382–90.

45. Gold MR, Siegel JE, Russell LB, Weinstein MC, editors. Cost-effectiveness in health and medicine. Report of the Panel on Cost-Effectiveness in Health and Medicine. New York: Oxford University Press; 1996.

46. Gold M, Franks P, McCoy K, Fryback D. Toward consistency in cost-utilities analysis: using national measures to create condition-specific values. Med Care. 1998;36:778–92.

47. Myers E, Green S, Lipkus I. Patient preferences for health states related to HPV infection: visual analogue scales vs. time trade-off elicitation. Proceedings of the 21st International Papillomavirus Conference. Abstract no. 390.2. Mexico City, Mexico. 2004.

48. Insinga RP, Glass AG, Myers ER, Rush BB. Abnormal outcomes following cervical cancer screening: event duration and health utility loss. Med Decis Making. 2006. In press.

49. Andersen B. Stress and quality of life following cervical cancer. J Natl Cancer Inst. 1996;21:65–70.

50. Wenzel L, DeAlba I, Habbal R, Kluhsman BC, Fairclough D, Krebs L, et al. Quality of life in long-term cervical cancer survivors. Gynecol Oncol. 2005;97:310–7.

Appendix Table 1. Baseline behavioral parameter values for the sexually active population*

	Proportion of population, %		
Activity group	Male	Female	Relative partner acquisition rate
1 (highest)	2.56	2.56	11.29
2	11.47	11.47	2.96
3 (lowest)	85.97	85.97	1.0
Age group, y	Relative partner acquisition rate	Overall mean partner acquisition rate	
12–14	0.11	0.1	
15–17	1.18	0.3	
18–19	2.42	1.3	
20–24	2.61		
25–29	2.55		
30–34	1.72		
35–39	1.65		
40–44	1.53		
45–49	1.38		
50–54	1.25		
55–59	1.00		
60–69	0.61	0.5	
≥70	0.44		

*Sources: Lauman et al. (*10*), Abma and Sonenstein (*11*).

Appendix Table 2. Baseline biologic parameter values for HPV disease categories*

Parameter	Base-case estimate	Source†

Progression in the presence of HPV 16/18 per year, %		
Normal to CIN 1	9.4	(RI)
Normal to CIN 1 to CIN 2	5.8	(*17*,RI)
Normal to CIN 1 to CIN 2 to CIN 3	3.5	(*17*,RI)
CIN 1 to CIN 2	13.6	(MRK)
CIN 2 to CIN 3 (severe dysplasia)	14.0	(*26,27*)
CIN 3 - severe dysplasia to CIN 3 - CIS 1	42.0	(*26,28*)
CIS 1 to CIS 2	5.0	
CIS 2 to LCC	18.0	
LCC to RCC	10.0	(*16,24,25,31*)
RCC to DCC	30.0	(*16*)
Progression in the presence of HPV 6/11 per year, %		
Normal to CIN 1	9.5	(RI)
Normal to CIN 1 to CIN 2	1.9	(RI)
Normal to CIN 1 to CIN 2 to CIN 3	0.0	(RI)
CIN 1 to CIN 2	0.0	(MRK)
Normal to genital warts	57	(*17*)
Mean duration of acute HPV infection, y		
HPV 16/18 infection	1.2	(RI)
HPV 6/11 infection	0.7	(RI)
Regression of HPV 16/18+ disease per year, %		
CIN 1 to normal/HPV	32.9	(MRK,*29*)
CIN 2 to normal/HPV	21.0	(*26,27,30*)
CIN 2 to CIN 1	13.3	(*27*)
CIN 3 (severe dysplasia) to normal/HPV	11.0	(*26*)
CIN 3 (severe dysplasia) to CIN 1	3.0	(*26,27*)
CIN 3 (severe dysplasia) to CIN 2	3.0	(*26,27*)
Regression of HPV 6/11+ disease per year, %		
CIN 1 to normal/HPV	55.2	(MRK)
Genital warts to normal/HPV	87.5	(*17*)
Age (y) and stage-specific cervical cancer mortality rates per year, 1997–2002, %		(*5*)
For LCC		
15–29	0.7	
30–39	0.6	
40–49	0.8	
50–59	1.9	
60–69	4.2	
≥70	11.6	
For RCC		
15–29	13.4	
30–39	8.9	
40–49	11.0	
50–59	10.1	
60–69	17.6	
≥70	28.6	
For DCC		
15–29	42.9	
30–39	41.0	
40–49	46.7	
50–59	52.7	
60–69	54.6	
≥70	70.3	

*HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; CIS, carcinoma in situ; LCC, localized cervical cancer; RCC, regional cervical cancer; DCC, distant cervical cancer.
†RI, R. Insinga, unpub. data; MRK, Merck, unpub. data.

Appendix Table 3. Hysterectomy, screening, and treatment parameters*

Parameter	Base-case	Source

Publisher: CDC; Journal: Emerging Infectious Diseases
Article Type: Research; Volume: 13; Issue: 1; Year: 2007; Article ID: 06-0438
DOI: 10.3201/eid1301.060438; TOC Head: Research

	estimate	
Hysterectomy rate, % per year		(*32*)
15–24 y	0.02	
25–29 y	0.26	
30–34 y	0.53	
35–39 y	0.89	
40–44 y	1.17	
45–54 y	0.99	
≥55 y	0.36	
Cervical cytology screening, excluding those with hysterectomy, % per year		(*33*)
10–14 y	0.6	
15–19 y	21.0	
20–24 y	44.8	
25–29 y	61.6	
30–34 y	54.9	
35–39 y	50.5	
40–44 y	48.1	
45–49 y	49.1	
50–54 y	51.1	
55–59 y	46.7	
60–64 y	42.5	
65–69 y	38.9	
70–74 y	29.6	
75–79 y	20.1	
80–84 y	11.1	
≥85	5.5	
Females never screened, %	5.0	
Liquid-based cytology specificity, %	94	(*34,35*)
Colposcopy sensitivity, %	96	(*36*)
Colposcopy specificity, %	48	(*36*)
GW patients seeking physician care, %	75	(*37*)
Symptom development, % per year		Assumed
Localized cervical cancer	4	
Regional cervical cancer	18	
Distant cervical cancer	90	
Eradication with treatment, %		
For CIN 1	96	(*38*)
For CIN 2	92	(*38*)
For CIN 3, CIS	92	(*38*)
For localized cervical cancer	92	(*39*)
For regional cervical cancer	55	(*39*)
For distant cervical cancer	17	(*39*)
Persistence of HPV after treatment for CIN or GW, %	34	(*40*)

*HPV, human papillomavirus; GW, genital warts; CIN, cervical intraepithelial neoplasia; CIS, carcinoma in situ.

Appendix Table 4. Cost and quality-of-life parameters*

Parameter	Base-case estimate	Source
Costs of diagnosing and treating HPV disease		*(42–44)*
Genital warts	$489	
Liquid-based cytology screening	$99	
Colposcopy and biopsy	$318	
CIN 1	$1,554	
CIN 2/3, CIS	$3,483	
Localized cervical cancer	$26,470	

Publisher: CDC; Journal: Emerging Infectious Diseases
Article Type: Research; Volume: 13; Issue: 1; Year: 2007; Article ID: 06-0438
DOI: 10.3201/eid1301.060438; TOC Head: Research

Regional cervical cancer	$28,330		
Distant cervical cancer	$45,376		
Quality-of-life weights (0–1 scale)			
CIN 1	0.91		*(47)*
CIN 2/3, CIS	0.87		*(47)*
Localized cervical cancer	0.76		*(47)*
Regional cervical cancer	0.67		*(47)*
Distant cervical cancer	0.48		*(46)*
Cervical cancer survivor	0.84		*(47,49,50)*
Genital warts	0.91		*(47)*
No condition	F	M	*(46)*
12–17 y	0.93	0.93	
18–34 y	0.91	0.92	
35–44 y	0.89	0.90	
45–54 y	0.86	0.87	
55–64 y	0.80	0.81	
65–74 y	0.78	0.76	
≥75 y	0.70	0.69	

*HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; CIS, carcinoma in situ; F, females; M, males.

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Supplementary Online Appendix

A Technical Report Accompanying Manuscript:

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1 Introduction

This technical report includes the mathematical model that was constructed to assess the impact of HPV vaccination strategies. It provides a detailed description of various model components as they relate to HPV infection, disease progression, vaccine characteristics, vaccination strategies, and the impact of HPV vaccination on epidemiologic and economic outcomes. The model allows for aggregating costs of vaccination, screening, and treatment of the population over time, compares them with total health outcomes as measured, for example, by quality adjusted life years (QALYs), and calculates incremental cost-effectiveness ratios for various vaccination strategies.

In constructing this model, we reviewed other relevant previous models and incorporated some of their structures and inputs. These included cervical cancer screening cohort models [17, 18, 21, 58, 61, 50], HPV vaccination cohort models [76, 71, 53, 31, 32], and HPV vaccination dynamic models [39, 28, 5, 19]. This model differs from its predecessors in several ways. First, the approach is more comprehensive in the sense that it incorporates the epidemiology of HPV infection, disease, and economics into a single dynamic model. Besides capturing the direct and indirect 'herd immunity' benefits and costs of vaccination for the population over time, the added advantage of this latter approach is its transparency, making critical review of the model and reproducibility of results [81] feasible without needing to review the actual source code used to generate the results. In particular, publication of the model includes the mathematical equations that summarize in their entirety the actual workings of the model. These equations can then be entered into any standard mathematical software package such as Mathematica® (Wolfram Research, Champaign, IL) or MatLab® (MathWorks, Natick, MA) to reproduce the results. Second, we also convened an expert panel that reviewed model assumptions and provided guidance on some aspects of the natural history of disease where there was little or no clinical evidence. Finally, key inputs in this model are based on data from recent studies that were not available when previous models were constructed.

For ease of exposition, the model is divided into two major components. The first part, which is presented in section 2, is a description of the demographic aspects of the model. This component of the model is intended to mimic the current age structure of the US population. Section 3 includes the second part which consists of the epidemiologic model that describes HPV transmission, and progression to cervical intraepithelial neoplasia (CIN), cervical cancer, and genital warts. Because females who undergo hysterectomies for benign conditions are no longer at risk of developing CIN and cervical cancer but can contribute to the transmission of HPV, another submodule for benign hysterectomy is created. Descriptions of the forces of infection, mixing preferences, and estimates of the epidemiologic model completes section 3. In sections 4 and 5, we describe how the epidemiologic and economic impact of screening and vaccination strategies are assessed.

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2 The demographic model

2.1 Demographic model structure

The demographic model is a modified version of the initial-boundary-value problem for age-dependent population growth described in more details in [36]. The population is divided into n age groups defined by the age intervals $[a_{i-1}, a_i]$, where $a_1 < a_2 < \ldots < a_n = \infty$ (all the symbols used to describe variables and parameters are defined in Table1 and 2). The number of individuals $N_i(t)$ at time t in the age interval $[a_{i-1}, a_i]$ is the integral of the age distribution function from a_{i-1} to a_i. Assuming that the population distribution has reached a steady state with exponential growth or decay of the form e^{qt}, Hethcote [36] derived a system of n ordinary differential equations (ODEs) for the sizes of the n age groups. The simple demographic model used here divides the population into 2 gender ($k = f, m$) groups, and 17 age ($i = 1, 2, \ldots 17$) groups (12–14, 15–17, 18–19, 20–24, 25–29, 30–34, 35–39,40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, and over 85). This age grouping is chosen to accurately account for patterns of HPV transmission among sexually active groups, cervical cancer screening patterns, and risk of cervical cancer development among females, and genital wart occurrence among both males and females. Similar age groupings have been used by other sexually transmitted diseases models [24, 25]. However, these models assumed an age of sexual debut of 15 years. By setting the age of sexual debut to 12 years, our model captures HPV transmission and disease that occurs before age 15. Recent data suggest age of first sexual intercourse is younger than 15 for some teenagers and adolescents. For example, according to data from the National Survey of Family Growth, 19% of female teenagers had had sex before age 15 in 1995, compared with 21% of male teenagers [1].

The sexually active population is further stratified into L sexual activity groups ($l = 1, \ldots, L$), defined according to the gender-, sexual activity-, and age-specific rate of sex partner change per unit time c_{kli}. The number of sexual activity groups considered here is 3 ($L = 3$). New additions to the sexually active population enter gender k, sexual activity l, and cervical screening category b ($b = 1, 2$) at rate of B_{klb}. Because males do not participate in cervical screening, throughout the model the subscript b does not apply to them. For example, $B_{mlb} = B_{ml}$. Individuals die of non-cervical cancer related causes at an age- and gender-specific per capita death rate μ_{ki} per year and females with cervical cancer (categories CC_s and DCC_s) also have an additional age- and stage-dependent mortality rate χ_{si} ($s = L, R, D$). It is assumed that being in any CIN or genital warts state does not pose an additional risk of death. Individuals are transferred between successive age groups at an age- and gender-specific per capita rate d_{ki} per year given by [36]

$$d_{ki} = \frac{\mu_{ki} + q}{\exp[band_i \times (\mu_{ki} + q)] - 1},$$

where $band_i$ is the number of years within age group i. The annual growth rate q of this demographic model should also satisfy a modified age-group form of

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the Lotka characteristic equations [36]

$$\begin{aligned} B_{ml} &= (d_{m1} + \mu_{m1} + q)N_{ml1}(0), \\ B_{flb} &= \varrho_b(d_{f1} + \mu_{f1} + q)N_{fl1}(0), \end{aligned}$$

where ϱ_b denotes the fraction of females entering cervical screening category b, with $\varrho_1 + \varrho_2 = 1$.

After taking into account cervical cancer-induced mortality and replacing fertility rates in Hethcote's model [36] by recruitment rates into the sexually active population B_{klb}, the demographic model is given by the following system of 102 ($= 17 \times 2 \times 3$) ODEs:

$$\begin{aligned} dN_{ml1}/dt &= B_{ml} - (\mu_{m1} + d_{m1})N_{ml1} \\ dN_{mli}/dt &= d_{mi-1}N_{mli-1} - (\mu_{mi} + d_{mi})N_{mli} \\ dN_{fl1}/dt &= \sum_{b=1}^{2} B_{flb} - \sum_{s} \chi_{s1}(DCC_{sl1} + \sum_{h=1}^{2}\sum_{b=1}^{2} CC^{h}_{sl1b}) - (\mu_{f1} + d_{f1})N_{fl1} \\ dN_{fli}/dt &= d_{fi-1}N_{fli-1} - \sum_{s} \chi_{si}(DCC_{sli} + \sum_{h=1}^{2}\sum_{b=1}^{2} CC^{h}_{slib}) - (\mu_{fi} + d_{fi})N_{fli}, \end{aligned}$$

$i \geq 2$, $s = L, R, D$, where $d_{k17} = 0$. All variables, parameters, and subscripts are defined in Tables 1 and 2 and the text.

2.2 Estimates of the demographic model parameters

Death rates for males and females without cervical cancer are obtained from Vital Statistics data on gender- and age-specific mortality rates, all races, 2002 [51]. Cancer mortality data are obtained from Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics age-specific mortality rates, 1997–2002 [75]. Because the U.S. population grew at a decennial rate of 13.2% between 1990 and 2000, the annual population growth rate was 1.23%. With recruitment rates into the sexually active population of 1.9% of the male active population and 1.7% of the female population, the largest annual growth rate q that satisfies the solution of the Lotka characteristic equation was 0.5%. Therefore, the annual growth rate q of this demographic model was set to zero, and B_{klb} was chosen to satisfy the Lotka characteristic equation. This will also ensure that variation in the results across strategies is mainly due to epidemiologic and program features rather than peculiar characteristics of the demographic model [36]. The sensitivity of the results to this assumption will be tested using an annual population growth rate of 1.23%.

The initial population size η is set to 100,000, divided equally between males and females. With the proportion of adults in sexually activity class l given by ω_l, the total number of individuals in sexual activity group l is given by

$$\sum_{i} N_{kli} = \frac{1}{2}\omega_l \eta$$

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Symbol	Description
subscripts	
k	gender (f = females, m = males)
i, j	age groups
l, m	sexual activity groups
h	group of HPV types (16/18 = 1, 6/11 = 2, joint = 12)
s	stage of cervical intraepithelial neoplasia (CIN) or cancer
b	cervical screening category (never =1, routine = 2)
variables	
λ^h_{kli}	force of infection with group type h
X_{klib}	susceptible to all types
Y^h_{klib}	infected with type h, susceptible to the other type
Z^h_{klib}	immune against type h, susceptible to the other type
U^h_{klib}	infected with type h, immune to the other type
V_{klib}	vaccinated against all types
S_{klib}	vaccinated with immunity waned
W^h_{klib}	vaccinated and infected with type h
Q^h_{klib}	vaccinated and immune to type h
P^h_{klib}	vaccinated infected with type h, immune to the other type
Ho^h_{li}	hysterectomy, vaccine, infection status o (e.g., $o = X$)
CIN^h_{slib}	undetected CIN, grade s, type h
CIS^h_{slib}	undetected carcinoma in situ (CIS), stage s, type h
$DCIN^h_{slib}$	detected CIN, grade s
$DCIS^h_{slib}$	detected CIS, stage s
$ICIN^h_{slib}$	treated CIN, grade s, infected type h
$ICIS^h_{slib}$	treated CIS, stage s, infected type h
$TCIN_{sli}$	treated CIN, grade s, immune
$TCIS_{sli}$	treated CIS, stage s, immune
CC^h_{slib}	undetected cervical cancer, stage s
DCC_{sli}	detected cervical cancer, stage s
SCC_{li}	cervical cancer survivor
GW^h_{slib}	undetected genital warts
DGW^h_{slib}	detected genital warts
N_{kli}	number of individuals

Table 1: Description of variables and subscripts

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Symbol	Description
demographic parameters	
B_{klb}	new entrants into the sexually active population
μ_{ki}	death rate
q	rate of population growth
d_{ki}	transfer rate between age groups
$band_i$	number of years within age group i
behavioral parameters	
c_{kli}	average rate of sexual partner change
ρ_{klmij}	probability of sexual mixing
$\varepsilon_1, \varepsilon_2$	mixing parameters between age and activity groups
ω_l	proportion of adults in sexual activity class l
ϱ_b	fraction of females recruits entering cervical screening category b
biological parameters	
$1/\sigma_{zki}$	average duration of immunity following natural infection
γ^h_{ki}	recovery from infection with HPV type h
$\tilde{\gamma}^h_{ki}$	probability of recovering from type h only, given coinfection
$\bar{\gamma}^h_{ki}$	probability of recovering from type h, given CIN regression
$\bar{\gamma}^h_{gki}$	probability of recovering from type h, given genital warts regression
θ^h_{ks}	progression from HPV infection to CIN states
θ^h_{cks}	progression from coinfection to CIN states
θ^h_{wks}	progression from breakthrough HPV infection to CIN states
θ^h_{wcks}	progression from breakthrough coinfection to CIN states
θ^h_{gk}	progression from HPV infection to genital warts
θ^h_{gwk}	progression from breakthrough HPV infection to genital warts
θ^h_{gs}	probability genital warts are asymptomatic and not treated
π^h_{is}	progression between CIN states or cancer
τ^h_{ks}	regression from CIN states to normal or HPV
τ^h_{ksg}	regression from CIN state s to CIN state g
τ^h_{gk}	regression from genital warts state to normal
β^h_k	transmission probability (from sex k' to sex k)
r^h_k	relative risk of transmission from vaccinated people
φ^h_k	relative risk of infection of a vaccinated person
α^h_k	vaccinated person relative rate of infection clearance
$1/\sigma_{ki}$	average duration of vaccine protection
χ_{si}	cervical cancer associated death
ϕ_{k0b}	percentage of 12-year olds vaccinated
ϕ_{kib}	percentage vaccinated in age group i
Δ_{ki}	rate of hysterectomy at age i
κ_{sib}	detection rate of CIN, stage s
θ^h_{rs}	recurrence of CIN stage s
Γ_s	cure rate of CIN
ψ_s	percentage of CIN stage s infected after treatment
υ_s	detection of cervical cancer, stage s
Ω_s	cure rate of cervical cancer, stage s

Table 2: Description of parameters

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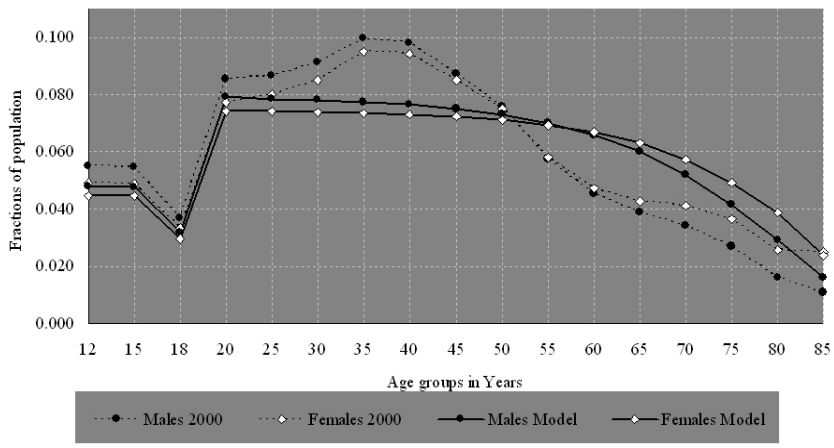

Figure 1: Age distribution for 2000 US population 12 years & above and model (0% annual growth).

By using $d_{ki-1}N_{kli-1} - (\mu_{ki} + d_{ki})N_{kli}$ with the above equation, we obtain the initial number of individuals in the youngest age group (12–14 years) of each gender and sexual activity category as

$$N_{kl1}(0) = \frac{1}{2}\omega_l \eta \left(1 + \sum_{i=2}^{17} \prod_{j=2}^{i} \frac{d_{kj-1}}{(d_{kj} + \mu_{kj})}\right)^{-1}.$$

The initial numbers of other age groups are given by

$$N_{kli}(0) = \frac{d_{ki-1}N_{kli-1}(0)}{d_{ki} + \mu_{ki}},$$

$l = 1, 2, 3$; $i = 2, 3, \ldots, 17$.

Note that the size of the male population in the model is always at a steady-state given by $\eta/2 = 50,000$. However, the size of the female population is not constant during the transient dynamics following vaccination because females are subject to additional cervical cancer-induced mortality.

The structure of the over 12-year old US population with 0% and 1.23% annual growth rates, together with data from the 2000 population census are plotted in Figures 1 and 2, respectively. The model fits well for early age groups, underestimates around age 40, and overestimates the number of people over age 40 years. It should be noted that the current model does not capture special characteristics of the US population such as the "Baby Boom" and migration.

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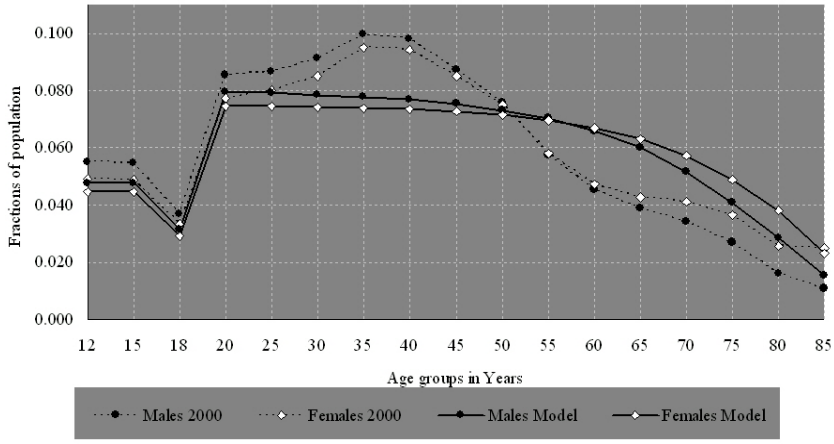

Figure 2: Age distribution for 2000 US population 12 years & above and model (1.23% annual growth).

3 The epidemiologic model

The epidemiologic model can be thought of as comprising three components: HPV transmission, cervical cancer development, and genital warts occurrence.

3.1 HPV transmission

To simplify the analysis, only three (types 16/18 = 1, types 6/11 = 2, and coinfection =12) HPV type groupings are modeled. The sexually active host population of size η at time t is divided into distinct epidemiologic classes, depending on the host's susceptibility to infection or the host's status with respect to infection, disease, screening, and treatment. The HPV component consists of 17 epidemiologic classes (X, V, Y, W, U, P, Z, Q), with each class further stratified by gender (2 groups), age (17 groups), and sexual activity (3 groups). The female population has two additional stratifications distinguishing females that are regularly screened from those who are never screened, and females who had hysterectomies from those with intact cervices. A schematical representation of the HPV transmission model is shown in Figures 3 and 4.

3.1.1 Susceptible individuals X

New additions to the sexually active population, at a rate of B_{klb}, enter into the uninfected (susceptible) category of gender k, sexual activity group l, and screening category b. A fraction of them is vaccinated at rate ϕ_{kl0b} and move to category V and the remaining fraction enter category X of susceptible individuals. The model also assumes that a proportion of individuals in other age

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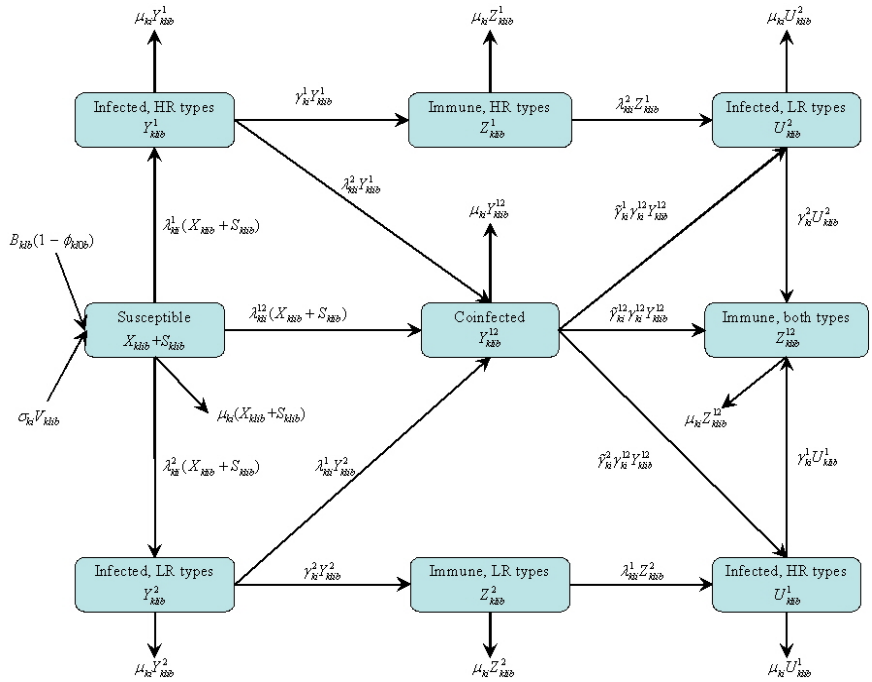

Figure 3: A simplified schematic presentation of the unvaccinated compartments of the HPV model. Individuals enter the population at rate B_{klb} and a fraction $1 - \phi_{kl0b}$ of them move into the unvaccinated susceptible (X) compartment. Individuals leave all compartments at rate μ_{ki}. A susceptible host may be infected by either or both HPV types. Susceptible individuals acquire type h infection at rate λ^h_{kli}. A host infected with type h can also be infected with the other type and move into compartment (Y^{12}). An infected individual clears infection with type h at rate γ^h_{ki}. Co-infected individuals clear infection with type h at rate $\tilde{\gamma}^h_{ki}\gamma^{12}_{ki}$.

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groups and epidemiologic classes is vaccinated at rate ϕ_{klib} and move into the vaccination classes V, W, P, or Q. It is assumed that the vaccine does not confer any therapeutic benefits to individuals already infected. Individuals in class X acquire HPV infection with type h at a gender, sexual activity group, age, and time dependent rate λ^h_{kli}, where $h = 1, 2, 12$. In this notation, λ^1_{kli} denotes infection with types in group 1 (HPV 16/18) and λ^{12}_{kli} infection with types in both groups (HPV 16/18 and HPV 6/11). The number of people in category X_{klib} is reduced by infection λ^h_{kli}, vaccination ϕ_{klib}, benign hysterectomy Δ_{ki}, death from other causes μ_{ki}, and aging d_{ki}. The ODEs for category X are

$$\begin{aligned}
dX_{kl1b}/dt &= B_{klb}(1-\phi_{kl0b}) + \sum_{h\in\{1,2,12\}} \sigma^h_{zk1} Z^h_{kl1b} \\
&\quad - \sum_{h\in\{1,2,12\}} (\lambda^h_{kl1} + \phi_{kl1b} + \Delta_{k1} + \mu_{k1} + d_{k1}) X_{kl1b}, \\
dX_{klib}/dt &= d_{ki-1} X_{kli-1b} + \sum_h \sigma^h_{zki} Z^h_{klib} \\
&\quad - \sum_{h\in\{1,2,12\}} (\lambda^h_{kli} + \phi_{klib} + \Delta_{ki} + \mu_{ki} + d_{ki}) X_{klib},
\end{aligned}$$

$i = 2, \ldots, 17$; $l = 1, 2, 3$; $k = f, m$; $b = 1, 2$.

3.1.2 Infected individuals Y

When transmission occurs, the unvaccinated X and vaccinated S susceptible individuals enter the Y class of infected individuals. Individuals enter class Y after they recover from genital warts at rate τ_{gk} but are still infected with probability $1 - \bar{\gamma}^h_{gki}$ Females enter class Y if their CIN spontaneously regress at rate τ_{fs} but are still infected with probability $1 - \bar{\gamma}^h_{ki}$. Individuals leave this class and enter the Z class of recovered people with immunity when the infectious period for HPV ends. Unvaccinated infected individuals in the Y class resolve infection at an age-, gender-, and type-specific per capita rate of γ^h_{ki}. Individuals develop CIN and genital warts at rate θ^h_{ks} and θ^h_{gk}, respectively. The ODEs for category Y^h are

$$\begin{aligned}
dY^h_{kl1b}/dt &= \lambda^h_{kl1}(X_{kl1b} + S_{kl1b}) + (1-\bar{\gamma}^h_{gk1})\tau^h_{gk}(GW^h_{kl1b} + DGW^h_{kl1b}) \\
&\quad + (1-\bar{\gamma}^h_{k1}) \sum_s \tau^h_{ks}(CIN^h_{sl1b} + DCIN^h_{sl1b}) \\
&\quad - (\lambda^{3-h}_{kl1} + \phi_{kl1b} + \gamma^h_{k1} + \sum_s \theta^h_{ks} + \theta^h_{gk} + \Delta_{k1} + \mu_{k1} + d_{k1}) Y^h_{kl1b}, \\
dY^h_{klib}/dt &= d_{ki-1} Y^h_{kli-1b} + \lambda^h_{kli}(X_{klib} + S_{klib}) + (1-\bar{\gamma}^h_{gki})\tau^h_{gk}(GW^h_{klib} + DGW^h_{klib}) \\
&\quad + (1-\bar{\gamma}^h_{ki}) \sum_s \tau^h_{ks}(CIN^h_{slib} + DCIN^h_{slib}) \\
&\quad - (\lambda^{3-h}_{kli} + \phi_{klib} + \gamma^h_{ki} + \sum_s \theta^h_{ks} + \theta^h_{gk} + \Delta_{ki} + \mu_{ki} + d_{ki}) Y^h_{klib}.
\end{aligned}$$

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The ODEs for coinfection are given by

$$\begin{aligned} dY^{12}_{kl1b}/dt &= \lambda^{12}_{kl1}(X_{kl1b}+S_{kl1b})+\sum_h \lambda^h_{kl1}Y^{3-h}_{kl1b}-(\phi_{kl1b}+\gamma^{12}_{k1} \\ &\quad +\sum_s \theta^{12}_{cks}+\theta^{12}_{gk}+\Delta_{k1}+\mu_{k1}+d_{k1})Y^{12}_{kl1b}, \\ dY^{12}_{klib}/dt &= d_{ki-1}Y^{12}_{kli-1b}+\sum_h \lambda^h_{kli}Y^{3-h}_{klib}-(\phi_{klib}+\gamma^{12}_{ki} \\ &\quad +\sum_s \theta^{12}_{cks}+\theta^{12}_{gk}+\Delta_{ki}+\mu_{ki}+d_{ki})Y^{12}_{klib}. \end{aligned}$$

3.1.3 Partially immune individuals Z

Individuals enter class Z when recovered from CIN or genital warts and having resolved infection. It is assumed that immunity derived from natural infection can be temporary, and individuals in the Z category can eventually move to the susceptible class X at rate σ^h_{zki}. Individuals in the Z class who are susceptible to one type can be infected with that type and move to class U. The ODEs for category Z^h are

$$\begin{aligned} dZ^h_{kl1b}/dt &= \gamma^h_{k1}Y^h_{kl1b}+\sum_{s=1}^{3}\{\bar{\gamma}^h_{k1}\tau^h_{ks}(CIN^h_{sl1b}+DCIN^h_{sl1b})+\gamma^h_{k1}ICIN^h_{sl1b}\} \\ &\quad +\sum_{s=1}^{2}\gamma^h_{k1}ICIS^h_{sl1b}+\bar{\gamma}^h_{gk1}\tau^h_{gk}(GW^h_{kl1b}+DGW^h_{kl1b}) \\ &\quad -(\lambda^{3-h}_{kl1}+\phi_{kl1b}+\Delta_{k1}+\sigma^h_{zk1}+\mu_{k1}+d_{k1})Z^h_{kl1b}, \\ dZ^h_{klib}/dt &= d_{ki-1}Z^h_{kli-1b}+\gamma^h_{ki}Y^h_{klib}+\sum_{s=1}^{3}\{\bar{\gamma}^h_{ki}\tau^h_{ks}(CIN^h_{slib}+DCIN^h_{slib}) \\ &\quad +\gamma^h_{ki}ICIN^h_{slib}\}+\sum_{s=1}^{2}\gamma^h_{ki}ICIS^h_{slib}+\bar{\gamma}^h_{gki}\tau^h_{gk}(GW^h_{klib}+DGW^h_{klib}) \\ &\quad -(\lambda^{3-h}_{kli}+\phi_{klib}+\Delta_{ki}+\sigma^h_{zki}+\mu_{ki}+d_{ki})Z^h_{klib}. \end{aligned}$$

The ODEs for the fully immune individuals Z^{12} are

$$\begin{aligned} dZ^{12}_{kl1b}/dt &= \tilde{\gamma}^{12}_{k1}\gamma^{12}_{k1}Y^{12}_{kl1b}+\sum_h \gamma^h_{k1}U^h_{kl1b} \\ &\quad -(\phi_{kl1b}+\Delta_{k1}+\sigma^{12}_{zk1}+\mu_{k1}+d_{k1})Z^{12}_{kl1b}, \\ dZ^{12}_{klib}/dt &= \tilde{\gamma}^{12}_{ki}\gamma^{12}_{ki}Y^{12}_{klib}+\sum_h \gamma^h_{ki}U^h_{klib}-(\phi_{klib}+\Delta_{ki}+\sigma^{12}_{zki}+\mu_{ki}+d_{ki})Z^{12}_{klib}. \end{aligned}$$

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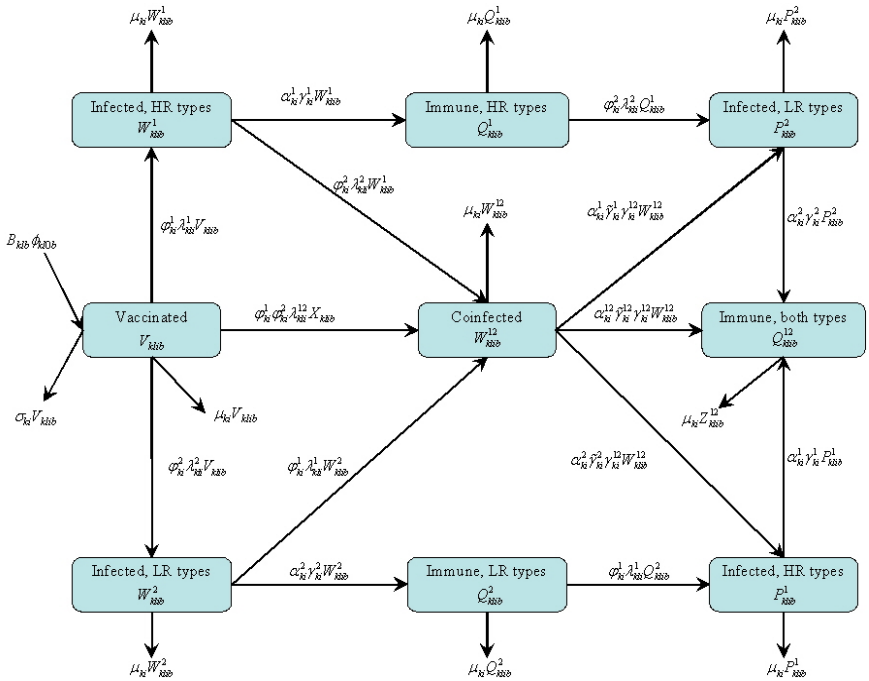

Figure 4: Schematic presentation of the vaccinated compartments of the HPV model. A fraction of the new susceptible recruits ϕ_{kl0b} are vaccinated and move into compartment V. The vaccine provides incomplete protection against the high-risk and low-risk types at rates $1-\varphi^1_{ki}$ and $1-\varphi^2_{ki}$, respectively. A vaccinated person moves into compartment W upon infection with any type. Upon clearance of infection at rate α^h_{ki} faster than natural infection, the person moves to compartment Q. The vaccine-induced immunity wanes at rate σ_{ki}.

3.1.4 Infected individuals with partial immunity U

The number of people in category U is reduced by vaccination ϕ_{klib}, resolution of infection γ^h_{ki}, and onset of disease. The ODEs for category U are

$$\begin{aligned} dU^h_{kl1b}/dt &= \lambda^h_{kl1} Z^{3-h}_{kl1b} + \tilde{\gamma}^{3-h}_{k1}\gamma^{12}_{k1} Y^{12}_{kl1b} \\ &\quad -(\phi_{kl1b} + \gamma^h_{k1} + \sum_s \theta^h_{ks} + \theta^h_{gk} + \Delta_{k1} + \mu_{k1} + d_{k1}) U^h_{kl1b}, \\ dU^h_{klib}/dt &= d_{ki-1} U^h_{kli-1b} + \lambda^h_{kli} Z^{3-h}_{klib} + \tilde{\gamma}^{3-h}_{ki}\gamma^{12}_{ki} Y^{12}_{klib} \\ &\quad -(\phi_{klib} + \gamma^h_{ki} + \sum_s \theta^h_{ks} + \theta^h_{gk} + \Delta_{ki} + \mu_{ki} + d_{ki}) U^h_{klib}. \end{aligned}$$

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3.1.5 Vaccinated individuals V

When 12-year olds are offered the vaccine, a fraction of them ϕ_{kl0} are vaccinated and move into the vaccination class V. Also, individuals in class X are vaccinated at rate ϕ_{kl1b} and enter category V. The vaccine-induced immunity of those in the vaccinated class V wanes, so that people eventually move to the susceptible class S at an age- and gender-dependent rate σ_{ki}. It is assumed that when an individual loses vaccine-derived immunity, the individual becomes susceptible to infection with any of the types. Vaccinated individuals can also experience a break-through infection and enter the class W of infective people at per capita rate $\varphi_k^h \lambda_{kli}^h$. The ODEs for category V are

$$\begin{aligned} dV_{kl1b}/dt &= B_{klb}\phi_{kl0b} + \phi_{kl1b}X_{kl1b} - (\sum_h \varphi_k^h \lambda_{kl1}^h + \sigma_{k1} + \Delta_{k1} + \mu_{k1} + d_{k1})V_{kl1b}, \\ dV_{klib}/dt &= d_{ki-1}V_{kli-1b} + \phi_{klib}X_{klib} - (\sum_h \varphi_k^h \lambda_{kli}^h + \sigma_{ki} + \Delta_{ki} + \mu_{ki} + d_{ki})V_{klib}. \end{aligned}$$

3.1.6 Vaccinated individuals with waned immunity S

Individuals in this class can get infected at the same rate as those in the susceptible class X. The ODEs for class S are

$$\begin{aligned} dS_{kl1b}/dt &= \sigma_{k1}V_{kl1b} - (\sum_h \lambda_{kl1}^h + \Delta_{k1} + \mu_{k1} + d_{k1})S_{kl1b}, \\ dS_{klib}/dt &= d_{ki-1}S_{kli-1b} + \sigma_{ki}V_{klib} - (\sum_h \lambda_{kli}^h + \Delta_{ki} + \mu_{ki} + d_{ki})S_{klib}. \end{aligned}$$

3.1.7 Infectious vaccinated individuals W

Individuals infected with one type and susceptible to the other move category W when vaccinated. Vaccinated individuals are infected at an age- and gender-specific rate φ_k^h times slower, and recover from infection at a rate α_{ki}^h faster than unvaccinated infected individuals and move to class Q. They also progress to disease at a different rate (θ_{wks}^h or θ_{gkw}^h) compared with that of infected unvaccinated individuals. The ODEs for category W are

$$\begin{aligned} dW_{kl1b}^h/dt &= \varphi_k^h \lambda_{kl1}^h V_{kl1b} + \phi_{kl1b}Y_{kl1b}^h - (\varphi_k^{3-h}\lambda_{kl1}^{3-h} + \alpha_{k1}^h\gamma_{k1}^h \\ &\quad + \sum_s \theta_{wks}^h + \theta_{gkw}^h + \Delta_{k1} + \mu_{k1} + d_{k1})W_{kl1b}^h, \\ dW_{klib}^h/dt &= d_{ki-1}W_{kli-1b}^h + \varphi_k^h \lambda_{kli}^h V_{klib} + \phi_{klib}Y_{klib}^h - (\varphi_k^{3-h}\lambda_{kli}^{3-h} \\ &\quad + \alpha_{ki}^h\gamma_{ki}^h + \sum_s \theta_{wks}^h + \theta_{gkw}^h + \Delta_{ki} + \mu_{ki} + d_{ki})W_{klib}^h. \end{aligned}$$

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The ODEs for coinfection W^{12} are

$$\begin{aligned} dW^{12}_{kl1b}/dt &= \varphi^1_k\varphi^2_k\lambda^{12}_{kl1}V_{kl1b} + \sum_h \varphi^h_k\lambda^h_{kl1}W^{3-h}_{kl1b} + \phi_{kl1b}Y^{12}_{kl1b} - (\alpha^{12}_{k1}\gamma^{12}_{k1} \\ &\quad + \sum_s \theta^{12}_{wcks} + \theta^{12}_{kgw} + \Delta_{k1} + \mu_{k1} + d_{k1})W^{12}_{kl1b}, \\ dW^{12}_{klib}/dt &= d_{ki-1}W^{12}_{kli-1b} + \varphi^1_k\varphi^2_k\lambda^{12}_{kli}V_{klib} + \sum_h \varphi^h_k\lambda^h_{kli}W^{3-h}_{klib} + \phi_{klib}Y^{12}_{klib} \\ &\quad -(\alpha^{12}_{ki}\gamma^{12}_{ki} + \sum_s \theta^{12}_{wcks} + \theta^{12}_{gwk} + \Delta_{ki} + \mu_{ki} + d_{ki})W^{12}_{klib}. \end{aligned}$$

3.1.8 Vaccinated, partially immune individuals Q

Infected vaccinated individuals (category W) recovering from infection and individuals with natural immunity to one type (category Z) receiving the vaccine move to category Q. Individuals in this class who are susceptible to one type can be infected with that type and move to class P. The ODEs for category Q are

$$\begin{aligned} dQ^h_{kl1b}/dt &= \alpha^h_{k1}\gamma^h_{k1}W^h_{kl1b} + \phi_{kl1b}Z^h_{kl1b} - (\varphi^{3-h}_k\lambda^{3-h}_{kl1} + \Delta_{k1} + \mu_{k1} + d_{k1})Q^h_{kl1b}, \\ dQ^h_{klib}/dt &= d_{ki-1}Q^h_{kli-1b} + \alpha^h_{ki}\gamma^h_{ki}W^h_{klib} + \phi_{klib}Z^h_{klib} \\ &\quad -(\varphi^{3-h}_k\lambda^{3-h}_{kli} + \Delta_{ki} + \mu_{ki} + d_{ki})Q^h_{klib}. \end{aligned}$$

The ODEs for Q^{12} are

$$\begin{aligned} dQ^{12}_{kl1b}/dt &= \alpha^{12}_{k1}\tilde{\gamma}^{12}_{k1}\gamma^{12}_{k1}W^{12}_{kl1b} + \sum_h \gamma^h_{k1}P^h_{kl1b} + \phi_{kl1b}Z^{12}_{kl1b} \\ &\quad -(\Delta_{k1} + \mu_{k1} + d_{k1})Q^{12}_{klib}, \\ dQ^{12}_{klib}/dt &= d_{ki-1}Q^{12}_{kli-1b} + \alpha^{12}_{ki}\tilde{\gamma}^{12}_{ki}\gamma^{12}_{ki}W^{12}_{klib} + \sum_h \gamma^h_{ki}P^h_{klib} + \phi_{klib}Z^{12}_{klib} \\ &\quad -(\Delta_{ki} + \mu_{ki} + d_{ki})Q^{12}_{klib}. \end{aligned}$$

3.1.9 Vaccinated, infected individuals with partial immunity P

Coinfected vaccinated individuals recovering from one infection (category W^{12}), vaccinated individuals (category Q) getiing infected, and individuals infected with one type (category Z) receiving the vaccine move to category P. The ODEs for category P are

$$\begin{aligned} dP^h_{kl1b}/dt &= \varphi^h_k\lambda^h_{kl1}Q^{3-h}_{kl1b} + \alpha^{3-h}_{k1}\tilde{\gamma}^{3-h}_{k1}\gamma^{12}_{k1}W^{12}_{kl1b} + \phi_{kl1b}U^h_{kl1b} \\ &\quad -(\alpha^h_{k1}\gamma^h_{k1} + \sum_s \theta^h_{wks} + \theta^h_{gwk} + \Delta_{k1} + \mu_{k1} + d_{k1})P^h_{kl1b}, \\ dP^h_{klib}/dt &= d_{ki-1}P^h_{kli-1b} + \varphi^h_k\lambda^h_{kli}Q^{3-h}_{klib} + \alpha^{3-h}_{ki}\tilde{\gamma}^{3-h}_{ki}\gamma^{12}_{ki}W^{12}_{klib} + \phi_{klib}U^h_{klib} \\ &\quad -(\alpha^h_{ki}\gamma^h_{ki} + \sum_s \theta^h_{wks} + \theta^h_{gwk} + \Delta_{ki} + \mu_{ki} + d_{ki})P^h_{klib}. \end{aligned}$$

Note that for males, $\Delta_{mi} = \theta^h_{wms} = \tau^h_{ms} = \theta^h_{ms} = \theta^h_{cms} = 0$.

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3.2 Cervical intraepithelial neoplasia

Infected females (whether vaccinated or not) can develop CIN and move to the CIN segment of the model. There are several states that represent the true histological health status of a female: infected with a normal cervix, CIN grade 1 (CIN 1), CIN grade 2 (CIN 2), and CIN grade 3 (CIN 3). Females in the CIN and cancer stages are further classified into unknown, detected, or treated classes. There are also two additional absorbing states where only females who are no longer at risk of developing cervical cancer enter. These are benign hysterectomy for reasons other than cervical cancer (at an age-specific rate Δ_{fi}) and treated and cured CIN at stage-specific rate $(1-\psi_s)\Gamma_s$. Females in these two states are considered to be at no risk of developing cervical cancer [61]. However, females with hysterectomies for benign conditions can be infected and are at risk of developing genital warts [9]. Further, to take into account the fact that treatment of CIN does not completely eliminate the virus, another category of women with treated CIN who remain infected after treatment ($ICIN$) was created. Females enter this category from the detected state at rate $\psi_s\Gamma_s$ and stay there until their CIN recurs at rate θ^h_{rs} or they clear infection.

An infected female with a normal cervix can only directly progress to CIN^h_s (at rate θ^h_{fs} if unvaccinated or θ^h_{wfs} if vaccinated), die due to causes other than cervical cancer, or remain infected without progressing to CIN (Figure 5). The respective progression rates given coinfection are θ^h_{cfs} and θ^h_{cwfs}. For the base case, it is assumed that cases with coinfection progress to CIN according to the rate of high-risk HPV types. That is, $\theta^1_{cfs} = \theta^1_{fs}$, $\theta^2_{cfs} = 0$, $\theta^1_{cwfs} = \theta^1_{wfs}$, and $\theta^2_{cwfs} = 0$. It is assumed that infected females classified as CIN can progress only to higher CIN states (CIN1 to CIN2, CIN2 to CIN3), or cancer (CIN3 to cervical carcinoma in situ, CIS) at rate π^h_{si}, regress to normal at rate τ^h_s or CIN state g at rate τ^h_{sg}, die from other causes, be detected at rate κ_{sib} and be treated and cured at rate Γ_s, or remain in that CIN state. Coinfection of females in CIN and cervical cancer states is not modeled. It is assumed that regression from CIN states does not necessarily imply recovery from HPV infection. A female whose CIN regresses to normal but is still infected moves to the infected category Y^h_{fi} at an age- and stage-specific rate $\tau^h_s(1-\bar{\gamma}^h_{fi})$ regardless of her vaccination status. Only mutual regression from both HPV and CIN confers immunity against that type. Females regressing from CIN, whose HPV infection clears, move into class Z at an age- and state-specific rate $\bar{\gamma}^h_{fi}\tau^h_s$ $(s = 1, 2, 3)$.

The cervical neoplasia segment includes several epidemiologic classes (CIN_s, $DCIN_s$, $TCIN_s$, $ICIN_s$; $s = 1, 2, 3$), with each class further subdivided into age ($= 17$), sexual activity ($= 3$), and screening ($= 2$) groups.

3.2.1 Undetected CIN CIN_s

The number of females with undetected CIN increases as infected females develop disease or fail treatment. Screening κ_{sib}, spontaneous regression τ^h_{fs}, and progression to higher disease grades π^h_{si} reduce the number of females in this

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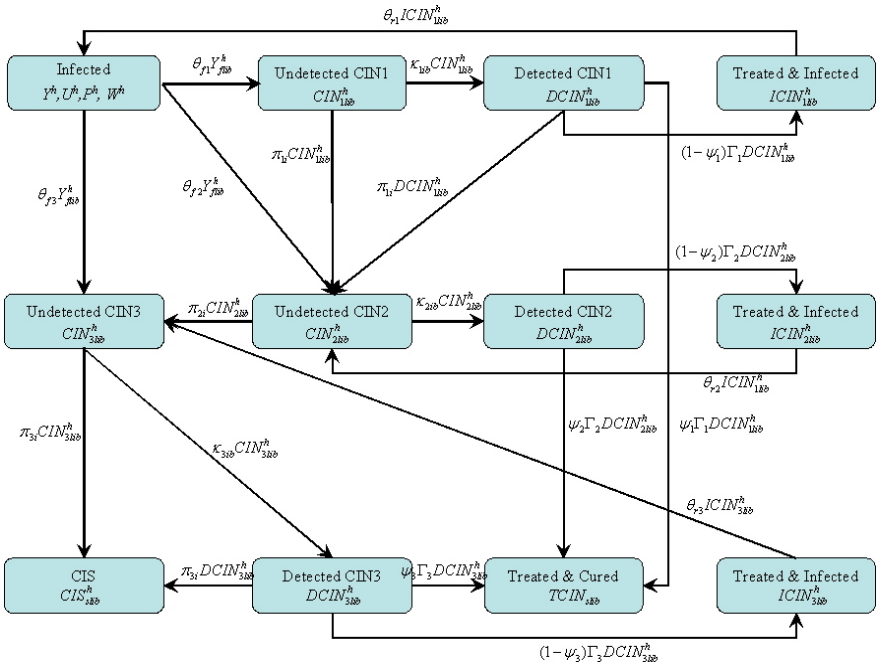

Figure 5: A simplified schematic presentation of the cervical intraepithelial neoplasia (CIN) model. Females can develop cervical intraepithelial neoplasia (CIN) and progress though several histological states: infected with a normal cervix, CIN 1, CIN 2, CIN 3, and cervical carcinoma in situ (CIS). Females with CIN can regress to normal with or without infection.

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category. Equations for undetected CIN are

$$\begin{aligned}
dCIN^h_{1l1b}/dt &= \theta^h_{f1}(Y^h_{fl1b}+U^h_{fl1b})+\theta^h_{cf1}Y^{12}_{fl1b}+\theta^h_{wf1}(W^h_{fl1b}+P^h_{fl1b}) \\
&\quad +\theta^h_{wcf1}W^{12}_{fl1b}+\theta^h_{r1}ICIN^h_{1l1b}+\tau^h_{f21}CIN^h_{2l1b}+\tau^h_{f31}CIN^h_{3l1b} \\
&\quad -(\tau^h_{f1}+\pi^h_{11}+\Delta_{f1}+\kappa_{11b}+\mu_{f1}+d_{f1})CIN^h_{1l1b}, \\
dCIN^h_{1lib}/dt &= d_{fi-1}CIN^h_{1li-1b}+\theta^h_{f1}(Y^h_{flib}+U^h_{flib})+\theta^h_{cf1}Y^{12}_{flib} \\
&\quad +\theta^h_{wfi}(W^h_{flib}+P^h_{flib})+\theta^h_{wcfi}W^{12}_{flib}+\theta_{rs}ICIN^h_{1lib} \\
&\quad +\tau^h_{f21}CIN^h_{2lib}+\tau^h_{f31}CIN^h_{3lib} \\
&\quad -(\tau^h_{f1}+\pi^h_{1i}+\Delta_{fi}+\kappa_{1ib}+\mu_{fi}+d_{fi})CIN^h_{1lib},
\end{aligned}$$

$$\begin{aligned}
dCIN^h_{sl1b}/dt &= \theta^h_{fs}(Y^h_{fl1b}+U^h_{fl1b})+\theta^h_{cfs}Y^{12}_{fl1}+\theta^h_{wfs}(W^h_{fl1b}+P^h_{fl1b}) \\
&\quad +\theta^h_{wcfs}W^{12}_{fl1b}+\theta^h_{rs}ICIN^h_{1l1b} \\
&\quad +\pi^h_{s-11}(CIN^h_{s-1l1b}+DCIN^h_{s-1l1b}) \\
&\quad +\tau^h_{fs+1s}CIN^h_{s+1l1b}-(\tau^h_{fs}+\tau^h_{fss-1}+\tau^h_{fss-2}+\pi^h_{s1}+\Delta_{f1} \\
&\quad +\kappa_{s1b}+\mu_{f1}+d_{f1})CIN^h_{sl1b},
\end{aligned}$$

$$\begin{aligned}
dCIN^h_{slib}/dt &= d_{fi-1}CIN^h_{sli-1b}+\theta^h_{fs}(Y^h_{flib}+U^h_{flib})+\theta^h_{cfs}Y^{12}_{flib} \\
&\quad +\theta^h_{wfs}(W^h_{flib}+P^h_{flib})+\theta^h_{wcfi}W^{12}_{flib}+\theta^h_{rs}ICIN^h_{1lib} \\
&\quad +\pi^h_{s-1i}(CIN^h_{s-1lib}+DCIN^h_{s-1lib})+\tau^h_{fs+1s}CIN^h_{s+1lib} \\
&\quad -(\tau^h_{fs}+\tau^h_{fss-1}+\tau^h_{fss-2}+\pi^h_{si}+\Delta_{fi} \\
&\quad +\kappa_{sib}+\mu_{fi}+d_{fi})CIN^h_{slib},
\end{aligned}$$

where $s=2,3$, and $\tau^h_{f43}=\tau^h_{f20}=0$.

3.2.2 Detected CIN $DCIN_s$

Detection of CIN occurs only as result of screening at rate κ_{sib}. This rate depends on screening coverage and the characteristics of the screening and diagnostic tests. If it does not regress at rate τ^h_{fs} or is treated at rate Γ_s, CIN can progress to a higher grade at rate π^h_{si}. Equations for detected CIN are

$$\begin{aligned}
dDCIN^h_{sl1b}/dt &= \kappa_{s1b}CIN^h_{sl1b}-(\tau^h_{fs}+\pi^h_{s1}+\Delta_{f1}+\Gamma_s+\mu_{f1}+d_{f1})DCIN^h_{sl1b}, \\
dDCIN^h_{slib}/dt &= d_{fi-1}DCIN^h_{sli-1b}+\kappa_{sib}CIN^h_{slib} \\
&\quad -(\tau^h_{fs}+\pi^h_{si}+\Delta_{fi}+\Gamma_s+\mu_{fi}+d_{fi})DCIN^h_{slib},
\end{aligned}$$

where $s=1,2,3$.

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3.2.3 Treated CIN $TCIN_s$

It is assumed that treatment does not completely eliminate infection. A fraction of treated females ψ_s will remain infectious after treatment and move to the category treated but infectious $ICIN_s$. Equations for treated CIN are

$$\begin{aligned} dTCIN_{sl1}/dt &= (1-\psi_s)\Gamma_s \sum_h \sum_b DCIN^h_{sl1b} - (\Delta_{f1} + \mu_{f1} + d_{f1})TCIN_{sl1}, \\ dTCIN_{sli}/dt &= d_{fi-1}TCIN_{li-1} + (1-\psi_s)\Gamma_s \sum_h \sum_b DCIN^h_{slib} \\ &\quad -(\Delta_{fi} + \mu_{fi} + d_{fi})TCIN_{sli}, \end{aligned}$$

where $s = 1, 2, 3$.

3.2.4 Treated CIN but infectious $ICIN_s$

CIN for females in this category can recur at rate θ_{rs} and move to category CIN_s. Infection can also resolve and individuals enter category Z^h. Equations for treated but infectious CIN are

$$\begin{aligned} dICIN^h_{sl1b}/dt &= \psi_s\Gamma_s DCIN^h_{sl1b} - (\gamma^h_{f1} + \theta^h_{rs} + \Delta_1 + \mu_{f1} + d_{f1})ICIN^h_{sl1b}, \\ dICIN^h_{slib}/dt &= d_{fi-1}ICIN^h_{sli-1b} + \psi_s\Gamma_s DCIN^h_{slib} \\ &\quad -(\gamma^h_{fi} + \theta^h_{rs} + \Delta_i + \mu_{fi} + d_{fi})ICIN^h_{slib}, \end{aligned}$$

where $s = 1, 2, 3$.

3.3 Cervical carcinoma in situ

It is assumed that females classified as CIN can progress to carcinoma in situ (CIS). Because females spend, on average, a long time in CIS, two CIS states are modeled (CIS 1 and CIS 2). It is assumed that regression from CIS states is not possible. CIS is further divided into several epidemiologic classes (CIS_s, $DCIS_s$, $TCIS_s$, $ICIS_s$; $s = 1, 2$), with each class further subdivided into age ($= 17$), sexual activity ($= 3$), and screening ($= 2$) groups.

3.3.1 Undetected CIS CIS_s

The number of females with undetected CIS increases as they progress from CIN 3 (severe dysplasia) or fail treatment. Screening κ_{3+sib} and progression to higher disease grades π^h_{3+si} reduce the number of females in this category, $s = 1, 2$. Equations for undetected CIS are

$$\begin{aligned} dCIS^h_{1l1b}/dt &= \theta^h_{r4}ICIS^h_{1l1b} + \pi^h_{31}(CIN^h_{3l1b} + DCIN^h_{3l1b}) \\ &\quad -(\pi^h_{41} + \Delta_{f1} + \kappa_{41b} + \mu_{f1} + d_{f1})CIS^h_{1l1b}, \\ dCIS^h_{1lib}/dt &= d_{fi-1}CIS^h_{1li-1b} + \theta^h_{r4}ICIS^h_{1lib} + \pi^h_{3i}(CIN^h_{3lib} + DCIN^h_{3lib}) \\ &\quad -(\pi^h_{4i} + \Delta_{fi} + \kappa_{4ib} + \mu_{fi} + d_{fi})CIN^h_{1lib}, \end{aligned}$$

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$$
\begin{aligned}
dCIS^h_{2l1b}/dt &= \theta^h_{r5} ICIS^h_{2l1b} + \pi^h_{41}(CIS^h_{1l1b} + DCIS^h_{1l1b}) \\
&\quad -(\pi^h_{51} + \Delta_{f1} + \kappa_{51b} + \mu_{f1} + d_{f1}) CIS^h_{2l1b}, \\
dCIS^h_{2lib}/dt &= d_{fi-1} CIS^h_{2li-1b} + \theta^h_{r5} ICIS^h_{2lib} + \pi^h_{4i}(CIS^h_{2lib} + DCIS^h_{2lib}) \\
&\quad -(\pi^h_{51} + \Delta_{f1} + \kappa_{51b} + \mu_{f1} + d_{f1}) CIS^h_{2l1b}.
\end{aligned}
$$

3.3.2 Detected CIS $DCIS_s$

Detection of CIS occurs only as result of screening at rate κ_{3+sib}. If it is not treated and cured at rate Γ_{3+s}, CIS can progress to a higher grade π^h_{3+si} or cancer. Equations for detected CIS are

$$
\begin{aligned}
dDCIS^h_{sl1b}/dt &= \kappa_{3+s1b} CIS^h_{sl1b} - (\pi^h_{3+s1} + \Delta_{f1} + \Gamma_{3+s} + \mu_{f1} + d_{f1}) DCIS^h_{sl1b}, \\
dDCIS^h_{slib}/dt &= d_{fi-1} DCIS^h_{sli-1b} + \kappa_{3+sib} CIS^h_{slib} \\
&\quad -(\pi^h_{3+si} + \Delta_{fi} + \Gamma_{3+s} + \mu_{fi} + d_{fi}) DCIS^h_{slib},
\end{aligned}
$$

where $s = 1, 2$.

3.3.3 Treated CIS $TCIS_s$

It is assumed that treatment does not completely eliminate infection. A fraction of treated females ψ_{3+s} will remain infectious after treatment and move to the category treated but infectious $ICIS_s$. Equations for treated CIS are

$$
\begin{aligned}
dTCIS_{sl1}/dt &= (1 - \psi_{3+s}) \Gamma_{3+s} \sum_h \sum_b DCIS^h_{sl1b} - (\Delta_{f1} + \mu_{f1} + d_{f1}) TCIS_{sl1}, \\
dTCIS_{sli}/dt &= d_{fi-1} TCIS_{li-1} + (1 - \psi_{3+s}) \Gamma_{3+s} \sum_h \sum_b DCIS^h_{slib} \\
&\quad -(\Delta_{fi} + \mu_{fi} + d_{fi}) TCIS_{sli},
\end{aligned}
$$

where $s = 1, 2$.

3.3.4 Treated CIS but infectious $ICIS_s$

It is assumed that CIS recurs at rate θ^h_{r3+s} and women with recuring CIS move to category CIS_s. Infection can also resolve and individuals enter category Z^h. Equations for treated but infectious CIS are

$$
\begin{aligned}
dICIS^h_{sl1b}/dt &= \psi_{3+s} \Gamma_{3+s} DCIS^h_{sl1b} - (\gamma^h_{f1} + \theta^h_{r3+s} + \Delta_1 + \mu_{f1} + d_{f1}) ICIS^h_{sl1b}, \\
dICIS^h_{slib}/dt &= d_{fi-1} ICIS^h_{sli-1b} + \psi_{3+s} \Gamma_{3+s} DCIN^h_{slib} \\
&\quad -(\gamma^h_{fi} + \theta^h_{r3+s} + \Delta_i + \mu_{fi} + d_{fi}) ICIS^h_{slib},
\end{aligned}
$$

where $s = 1, 2$.

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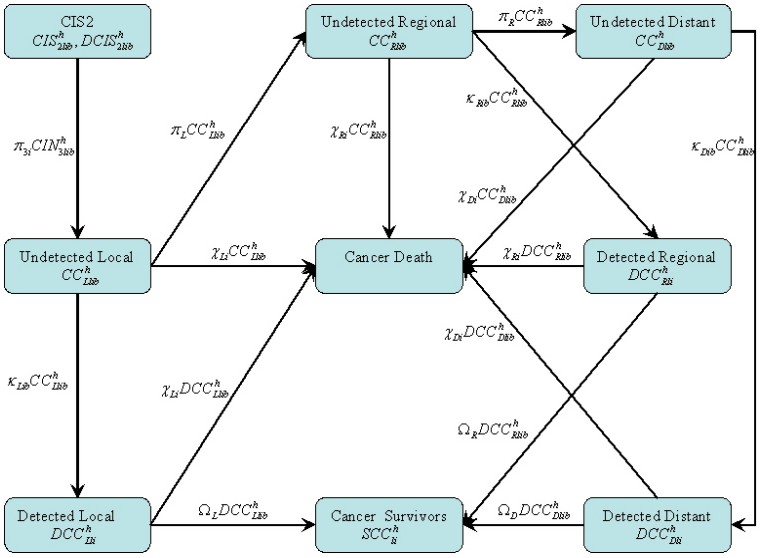

Figure 6: Schematic presentation of the cervical cancer (CC) model. Females can develop cervical cancer from carcinoma in situ stage 2 (CIS2) and progress though several cancer stages: early invasive local cervical cancer, regional late invasive cervical cancer, and distant late invasive cervical cancer. If detected, cancer cases are treated. After successful treatment, those cases move to the cancer survivors compartment. Cancer cases die at rate χ_{si}.

3.4 Cervical cancer

There are several states that represent the health status of a female with cervical cancer: localized cervical cancer (LCC), regional cervical cancer (RCC), distant cervical cancer (DCC), and cancer survivors who are free from cancer (Figure 6). Females in cancer stages are further classified into unknown, detected, or treated classes. A female with an invasive cancer can progress only to the next higher cancer state CC^h_s (LCC to RCC, RCC to DCC) at rate π_{si} $(s = L, R)$, her cervical cancer is detected at rate υ_{sib} and successfully treated and move to the cancer survivors state at rate Ω_s, die from cancer at rate χ_{si}, or stay in that undetected cancer state. Regression from invasive cancer to normal is not allowed. It is assumed that females who were successfully treated for invasive cancer are no longer infectious.

3.4.1 Undetected cervical cancer CC_s

CIS 2 cases that are not detected and treated can progress to localized cervical cancer at rate π^h_{5i}. Undetected cancer cases, if undetected at rate υ_{sib}, can progress to more advanced stages at rate π_s, $s = L, R$. Cervical cancer has an

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additional mortality rate χ_{si}. Equations for undetected CC are

$$\begin{aligned}
dCC^h_{Ll1b}/dt &= \pi^h_{51}(CIS^h_{2l1b} + DCIS^h_{2l1b}) - (\pi_L + \upsilon_{L1b} + \chi_{L1} + \mu_{f1} + d_{f1})CC^h_{Ll1b}, \\
dCC^h_{Llib}/dt &= d_{fi-1}CC^h_{Lli-1b} + \pi^h_{5i}(CIS^h_{5lib} + DCIS^h_{5lib}) \\
&\quad -(\pi_L + \upsilon_{Lib} + \chi_{Li} + \mu_{fi} + d_{fi})CC^h_{Llib}, \\
dCC^h_{Rl1b}/dt &= \pi_L CC^h_{Ll1b} - (\pi_R + \upsilon_{R1b} + \chi_{R1} + \mu_{f1} + d_{f1})CC^h_{Rl1b}, \\
dCC^h_{Rlib}/dt &= d_{fi-1}CC^h_{Rli-1b} + \pi_L CC^h_{Llib} - (\pi_D + \upsilon_{Rib} + \chi_{Ri} + \mu_{fi} + d_{fi})CC^h_{Rlib}, \\
dCC^h_{Dl1b}/dt &= \pi_R CC^h_{Rl1b} - (\upsilon_{D1b} + \chi_{D1} + \mu_{f1} + d_{f1})CC^h_{Dl1b}, \\
dCC^h_{Dlib}/dt &= \pi_R CC^h_{Rlib} + d_{fi-1}CC^h_{Dli-1b} - (\upsilon_{Dib} + \chi_{Di} + \mu_{fi} + d_{fi})CC^h_{Dlib},
\end{aligned}$$

where $i \geq 2$.

3.4.2 Detected cervical cancer DCC_s

Detected cancer cases are treated and cured at rate Ω_s and move to the cancer survivors category SCC. Equations for detected CC are

$$\begin{aligned}
dDCC_{sl1}/dt &= \sum_h \sum_b \upsilon_{s1b} CC^h_{sl1b} - (\Omega_s + \chi_{s1} + \mu_{f1} + d_{f1})DCC_{sl1}, \\
dDCC_{sli}/dt &= d_{fi-1}DCC_{sli-1} + \sum_h \sum_b \upsilon_{sib} CC^h_{slib} - (\Omega_s + \chi_{si} + \mu_{fi} + d_{fi})DCC_{sli},
\end{aligned}$$

where $s = L, R, D$.

3.4.3 Cervical cancer survivors SCC

Equations for cancer survivors are

$$\begin{aligned}
dSCC_{l1}/dt &= \sum_s \Omega_s DCC_{sl1} - (\mu_{f1} + d_{f1})SCC_{l1}, \\
dSCC_{li}/dt &= d_{fi-1}SCC_{li-1} + \sum_s \Omega_s DCC_{sli} - (\mu_{fi} + d_{fi})SCC_{li}.
\end{aligned}$$

3.5 Genital warts GW

Individuals (whether vaccinated or not) infected with HPV 6/11 can develop genital warts at rate θ^2_{gwk} and move to the genital warts class GW. Of those, a proportion θ_{gs} will remain asymptomatic and will not be treated whereas the rest will be recognized and treated. Individuals recovering from genital warts at rate τ^2_{kg} move to class Z. It is assumed that only infection with HPV 6/11 can cause genital warts whereas infection with HPV 16/18 does not lead to genital

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warts [84]. The asymptomatic genital warts class consists of the following ODEs

$$\begin{aligned} dGW^2_{kl1b}/dt &= \theta_{gs}(\theta^2_{gk}(Y^2_{kl1b}+U^2_{kl1b})+\theta^{12}_{gk}Y^{12}_{kl1b}+\theta^2_{gwk}(W^2_{kl1b}+P^2_{kl1b}) \\ &\quad +\theta^{12}_{gwk}W^{12}_{kl1b})-(\tau^2_{gk}+\Delta_{k1}+\mu_{k1}+d_{k1})GW^2_{kl1b}, \\ dGW^2_{klib}/dt &= d_{ki-1}GW^2_{kli-1b}+\theta_{gs}(\theta^2_{gk}(Y^2_{klib}+U^2_{klib})+\theta^{12}_{gk}Y^{12}_{klib} \\ &\quad +\theta^2_{gwk}(W^2_{klib}+P^2_{klib})+\theta^{12}_{gwk}W^{12}_{klib}) \\ &\quad -(\tau^2_{gk}+\Delta_{ki}+\mu_{ki}+d_{ki})GW^2_{klib}. \end{aligned}$$

The symptomatic genital warts class consists of the following ODEs

$$\begin{aligned} dDGW^2_{kl1b}/dt &= (1-\theta_{gs})(\theta^2_{gk}(Y^2_{kl1b}+U^2_{kl1b})+\theta^{12}_{gk}Y^{12}_{kl1b} \\ &\quad +\theta^2_{gwk}(W^2_{kl1b}+P^2_{kl1b})+\theta^{12}_{gwk}W^{12}_{kl1b}) \\ &\quad -(\tau^2_{gk}+\Delta_{k1}+\mu_{k1}+d_{k1})DGW^2_{kl1b}, \\ dDGW^2_{klib}/dt &= d_{ki-1}GW^2_{kli-1b}+(1-\theta_{gs})(\theta^2_{gk}(Y^2_{klib}+U^2_{klib}) \\ &\quad +\theta^{12}_{gk}Y^{12}_{klib}+\theta^2_{gwk}(W^2_{klib}+P^2_{klib})+\theta^{12}_{gwk}W^{12}_{klib}) \\ &\quad -(\tau^2_{gk}+\Delta_{ki}+\mu_{ki}+d_{ki})DGW^2_{klib}. \end{aligned}$$

3.6 Hysterectomies for benign conditions

Females who undergo hysterectomies for benign conditions move to the H compartment and stay there at no risk of developing CIN or cervical cancer. However, females in this compartment can be infected, can transmit infection, and can develop genital warts. There are several epidemiologic classes within the H compartment ($HX, HV, HS, HY, HW, HU, HP, HZ, HQ, HGW$), with each class further stratified by age (=17) and sexual activity (=3) groups.

3.6.1 Susceptible individuals HX

The ODEs for category HX are

$$\begin{aligned} dHX_{fl1}/dt &= \Delta_{f1}\sum_b X_{fl1b}+\sum_h \sigma^h_{zf1}HZ^h_{fl1b}-(\sum_h \lambda^h_{fl1}+\mu_{f1}+d_{f1})HX_{fl1}, \\ dHX_{fli}/dt &= d_{fi-1}HX_{fli-1}+\Delta_{fi}\sum_b X_{flib}+\sum_h \sigma^h_{zfi}HZ^h_{flib} \\ &\quad -(\sum_h \lambda^h_{fli}+\mu_{fi}+d_{fi})HX_{fli}, \end{aligned}$$

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3.6.2 Infected individuals HY

The ODEs for category HY are

$$\begin{aligned}
dHY^h_{fl1}/dt &= \lambda^h_{fl1}(HX_{fl1}+HS_{fl1})-(\lambda^{3-h}_{fl1}+\gamma^h_{f1}+\theta^h_{gf}+\mu_{f1}+d_{f1})HY^h_{fl1}\\
&\quad +\Delta_{f1}(\sum_b Y^h_{fl1b}+\sum_s(CIN^h_{sl1b}+DCIN^h_{sl1b}+ICIN^h_{sl1b})),\\
dHY^h_{fli}/dt &= d_{fi-1}HY^h_{fli-1}+\lambda^h_{fli}(HX_{fli}+HS_{fli})\\
&\quad -(\lambda^{3-h}_{fli}+\gamma^h_{fi}+\theta^h_{gf}+\mu_{fi}+d_{fi})HY^h_{fli}\\
&\quad +\Delta_{fi}(\sum_b Y^h_{flib}+\sum_s(CIN^h_{slib}+DCIN^h_{slib}+ICIN^h_{slib})).
\end{aligned}$$

The ODEs for HY^{12} are

$$\begin{aligned}
dHY^{12}_{fl1}/dt &= \lambda^{12}_{fl1}(HX_{fl1}+HS_{fl1})+\sum_h \lambda^h_{fl1}HY^{3-h}_{fl1}+\Delta_{f1}\sum_b Y^{12}_{fl1b}\\
&\quad -(\gamma^{12}_{f1}+\theta^{12}_{gf}+\mu_{f1}+d_{f1})HY^{12}_{fl1},\\
dHY^{12}_{fli}/dt &= d_{fi-1}HY^{12}_{fli-1}+\lambda^{12}_{fli}(HX_{fli}+HS_{fli})+\sum_h \lambda^h_{fli}HY^{3-h}_{fli}\\
&\quad +\Delta_{fi}\sum_b Y^{12}_{flib}-(\gamma^{12}_{fi}+\theta^{12}_{gf}+\mu_{fi}+d_{fi})HY^{12}_{fli}.
\end{aligned}$$

3.6.3 Partially immune individuals HZ

The ODEs for category HZ are

$$\begin{aligned}
dHZ^h_{fl1}/dt &= \gamma^h_{f1}HY^h_{fl1}+\Delta_{f1}\sum_b Z^h_{fl1b}+\tau^h_{gf}(HGW^h_{fl1}+DHGW^h_{fl1})\\
&\quad -(\lambda^{3-h}_{fl1}+\sigma^h_{zf1}+\mu_{f1}+d_{f1})HZ^h_{fl1},\\
dHZ^h_{fli}/dt &= d_{fi-1}HZ^h_{fli-1}+\gamma^h_{fi}HY^h_{fli}+\Delta_{fi}\sum_b Z^h_{flib}\\
&\quad +\tau^h_{gf}(HGW^h_{fli}+DHGW^h_{fli})-(\lambda^{3-h}_{fli}+\sigma^h_{zfi}+\mu_{fi}+d_{fi})HZ^h_{fli}.
\end{aligned}$$

The ODEs for HZ^{12} are

$$\begin{aligned}
dHZ^{12}_{fl1}/dt &= \tilde{\gamma}^{12}_{f1}\gamma^{12}_{f1}HY^{12}_{fl1}+\sum_h \gamma^h_{f1}HU^h_{fl1}+\Delta_{f1}(\sum_b Z^{12}_{fl1b}+\sum_s TCIN_{sl1})\\
&\quad -(\sigma^{12}_{zf1}+\mu_{f1}+d_{f1})HZ^{12}_{fl1},\\
dHZ^{12}_{fli}/dt &= d_{fi-1}HZ^{12}_{fli-1}+\tilde{\gamma}^{12}_{fi}\gamma^{12}_{fi}HY^{12}_{fli}+\sum_h \gamma^h_{fi}U^h_{flib}\\
&\quad +\Delta_{fi}(\sum_b Z^{12}_{flib}+\sum_s TCIN_{sli})-(\sigma^h_{zfi}+\mu_{fi}+d_{fi})HZ^{12}_{fli}.
\end{aligned}$$

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3.6.4 Infected individuals with partial immunity HU

The ODEs for category HU are

$$\begin{aligned} dHU^h_{fl1}/dt &= \lambda^h_{fl1} HZ^{3-h}_{fl1} + \tilde{\gamma}^{3-h}_{f1}\gamma^{12}_{f1} HY^{12}_{fl1} + \Delta_{f1}\sum_b U^h_{fl1b} \\ &\quad -(\gamma^h_{f1} + \theta^h_{gf} + \mu_{f1} + d_{f1}) HU^h_{fl1}, \\ dHU^h_{fli}/dt &= d_{fi-1} HU^h_{fli-1} + \lambda^h_{fli} HZ^{3-h}_{fli} + \tilde{\gamma}^{3-h}_{fi}\gamma^{12}_{fi} HY^{12}_{fli} \\ &\quad +\Delta_{fi}\sum_b U^h_{flib} - (\gamma^h_{fi} + \theta^h_{gf} + \mu_{fi} + d_{fi}) HU^h_{fli}. \end{aligned}$$

3.6.5 Vaccinated individuals HV

The ODEs for category HV are

$$\begin{aligned} dHV_{fl1}/dt &= \Delta_{f1}\sum_b V^h_{fl1b} - (\sum_h \varphi^h_f \lambda^h_{fl1} + \sigma_{f1} + \mu_{f1} + d_{f1}) HV_{fl1}, \\ dHV_{fli}/dt &= d_{fi-1} HV_{fli-1} + \Delta_{fi}\sum_b V^h_{flib} - (\sum_h \varphi^h_f \lambda^h_{fli} + \sigma_{fi} + \mu_{fi} + d_{fi}) HV_{fli}. \end{aligned}$$

3.6.6 Vaccinated individuals with waned immunity HS

The ODEs for classes HS are

$$\begin{aligned} dHS_{fl1}/dt &= \sigma_{f1} HV_{fl1} + \Delta_{f1}\sum_b S_{fl1b} - (\sum_h \lambda^h_{fl1} + \Delta_{f1} + \mu_{f1} + d_{f1}) HS_{fl1}, \\ dHS_{fli}/dt &= d_{fi-1} HS_{fli-1} + \sigma_{fi} HV_{fli} + \Delta_{fi}\sum_b S_{flib} - (\sum_h \lambda^h_{fli} + \mu_{fi} + d_{fi}) HS_{fli}. \end{aligned}$$

3.6.7 Infectious vaccinated individuals HW

The ODEs for category HW are

$$\begin{aligned} dHW^h_{fl1}/dt &= \varphi^h_f \lambda^h_{fl1} HV_{fl1} + \Delta_{f1}\sum_b W^h_{fl1b} \\ &\quad -(\varphi^{3-h}_f \lambda^{3-h}_{fl1} + \alpha^h_{f1}\gamma^h_{f1} + \theta^h_{gfw} + \mu_{f1} + d_{f1}) HW^h_{fl1}, \\ dHW^h_{fli}/dt &= d_{fi-1} HW^h_{fli-1} + \varphi^h_f \lambda^h_{fli} HV_{fli} + \Delta_{fi}\sum_b W^h_{flib} \\ &\quad -(\varphi^{3-h}_f \lambda^{3-h}_{fli} + \alpha^h_{fi}\gamma^h_{fi} + \theta^h_{gfw} + \mu_{fi} + d_{fi}) HW^h_{fli}, \end{aligned}$$

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The ODEs for HW^{12} are

$$\begin{aligned} dHW^{12}_{fl1}/dt &= \varphi^1_f\varphi^2_f\lambda^{12}_{fl1}HV_{fl1} + \sum_h \varphi^h_f\lambda^h_{fl1}HW^{3-h}_{fl1} + \Delta_{f1}\sum_b W^{12}_{fl1b} \\ &\quad -(\alpha^{12}_{f1}\gamma^{12}_{f1} + \theta^{12}_{gwf} + \mu_{f1} + d_{f1})HW^{12}_{fl1}, \\ dHW^{12}_{fli}/dt &= d_{fi-1}HW^{12}_{fli-1} + \varphi^1_f\varphi^2_f\lambda^{12}_{fli}HV_{fli} + \sum_h \varphi^h_f\lambda^h_{fli}HW^{3-h}_{fli} \\ &\quad +\Delta_{fi}\sum_b W^{12}_{flib} - (\alpha^{12}_{fi}\gamma^{12}_{fi} + \theta^{12}_{gwf} + \mu_{fi} + d_{fi})HW^{12}_{fli}. \end{aligned}$$

3.6.8 Vaccinated, partially immune individuals HQ

The ODEs for category HQ are

$$\begin{aligned} dHQ^h_{fl1}/dt &= \alpha^h_{f1}\gamma^h_{f1}HW^h_{fl1} + \Delta_{f1}\sum_b Q^h_{fl1b} \\ &\quad -(\varphi^{3-h}_f\lambda^{3-h}_{fl1} + \mu_{f1} + d_{f1})HQ^h_{fl1}, \\ dHQ^h_{fli}/dt &= d_{fi-1}HQ^h_{fli-1} + \alpha^h_{fi}\gamma^h_{fi}HW^h_{fli} + \Delta_{fi}\sum_b Q^h_{flib} \\ &\quad -(\varphi^{3-h}_f\lambda^{3-h}_{fli} + \mu_{fi} + d_{fi})HQ^h_{fli}, \end{aligned}$$

The ODEs for HQ^{12} are

$$\begin{aligned} dHQ^{12}_{fl1}/dt &= \alpha^{12}_{f1}\tilde{\gamma}^{12}_{f1}\gamma^{12}_{f1}HW^{12}_{fl1} + \sum_h \gamma^h_{f1}HP^h_{fl1} + \Delta_{f1}\sum_b Q^{12}_{fl1b} \\ &\quad -(\mu_{f1} + d_{f1})HQ^{12}_{fli}, \\ dHQ^{12}_{fli}/dt &= d_{fi-1}HQ^{12}_{fli-1} + \alpha^{12}_{fi}\tilde{\gamma}^{12}_{fi}\gamma^{12}_{fi}HW^{12}_{fli} + \sum_h \gamma^h_{fi}HP^h_{fli} + \Delta_{fi}\sum_b Q^{12}_{flib} \\ &\quad -(\mu_{fi} + d_{fi})HQ^{12}_{fli}. \end{aligned}$$

3.6.9 Vaccinated, infected individuals with partial immunity HP

The ODEs for category HP are

$$\begin{aligned} dHP^h_{fl1}/dt &= \varphi^h_f\lambda^h_{fl1}HQ^{3-h}_{fl1} + \alpha^{3-h}_{f1}\tilde{\gamma}^{3-h}_{f1}HW^{12}_{fl1} \\ &\quad +\Delta_{f1}\sum_b P^h_{fl1b} - (\alpha^h_{f1}\gamma^h_{f1} + \theta^h_{gwf} + \mu_{f1} + d_{f1})HP^h_{fl1}, \\ dHP^h_{fli}/dt &= d_{fi-1}HP^h_{fli-1} + \varphi^h_f\lambda^h_{fli}HQ^{3-h}_{fli} + \alpha^{3-h}_{fi}\tilde{\gamma}^{3-h}_{fi}HW^{12}_{fli} \\ &\quad +\Delta_{fi}\sum_b P^h_{flib} - (\alpha^h_{fi}\gamma^h_{fi} + \theta^h_{gwf} + \mu_{fi} + d_{fi})HP^h_{flib}. \end{aligned}$$

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3.6.10 Genital warts GW

The genital warts class consists of the following differential equations

$$\begin{aligned}
dHGW^2_{kl1b}/dt &= \theta_{gs}(\theta^2_{gk}(HY^2_{kl1b}+HU^2_{kl1b})+\theta^{12}_{gk}HY^{12}_{kl1b} \\
&\quad +\theta^2_{gwk}(HW^2_{kl1b}+HP^2_{kl1b})+\theta^{12}_{gwk}HW^{12}_{kl1b})+\Delta_{k1}GW^2_{klib} \\
&\quad -(\tau^2_{gk}+\mu_{k1}+d_{k1})HGW^2_{kl1b}, \\
dHGW^2_{klib}/dt &= d_{ki-1}HGW^2_{kli-1b}+\theta_{gs}(\theta^2_{gk}(HY^2_{klib}+HU^2_{klib})+\theta^{12}_{gk}HY^{12}_{klib} \\
&\quad +\theta^2_{gwk}(HW^2_{klib}+HP^2_{klib})+\theta^{12}_{gwk}HW^{12}_{klib})+\Delta_{ki}GW^2_{klib} \\
&\quad -(\tau^2_{gk}+\mu_{ki}+d_{ki})HGW^2_{kl1b},
\end{aligned}$$

$$\begin{aligned}
dDHGW^2_{kl1b}/dt &= (1-\theta_{gs})(\theta^2_{gk}(HY^2_{kl1b}+HU^2_{kl1b})+\theta^{12}_{gk}HY^{12}_{kl1b} \\
&\quad +\theta^2_{gwk}(HW^2_{kl1b}+HP^2_{kl1b})+\theta^{12}_{gwk}HW^{12}_{kl1b})+\Delta_{k1}HGW^2_{kl1b} \\
&\quad -(\tau^2_{gk}+\mu_{k1}+d_{k1})DHGW^2_{kl1b}, \\
dDHGW^2_{klib}/dt &= d_{ki-1}HGW^2_{kli-1b}+(1-\theta_{gs})(\theta^2_{gk}(HY^2_{klib}+HU^2_{klib}) \\
&\quad +\theta^{12}_{gk}HY^{12}_{klib}+\theta^2_{gwk}(HW^2_{klib}+HP^2_{klib})+\theta^{12}_{gwk}HW^{12}_{klib}) \\
&\quad +\Delta_{ki}HGW^2_{klib}-(\tau^2_{gk}+\mu_{ki}+d_{ki})DGW^2_{klib}.
\end{aligned}$$

3.7 Forces of HPV infection λ

The rate at which susceptible individuals acquire infection with type h (per capita force of infection) λ^h_{kli} is gender, sexual activity, age, and time dependent. The rate λ^h_{kli} at which individuals of gender k, sexual activity group l, age class i, at time t acquire infection with type h depends on the number of gender partnerships and the way they form partnerships with individuals of the opposite gender k', the fraction of infected sex partners, and the transmission probability β^h_k per partnership. The force of HPV infection λ^h_{kli} is given by

$$\begin{aligned}
\lambda^h_{mli} &= \beta^h_m\sum_{j=1}^{17}\sum_{a=1}^{3}c_{mlaij}\rho_{mlaij}\Bigg(\sum_{b=1}^{2}[r_f(W^h_{fajb}+P^h_{fajb}+W^{12}_{fajb})+Y^h_{fajb} \\
&\quad +Y^{12}_{fajb}+U^h_{fajb}+\sum\nolimits_s^3\left(CIN^h_{sajb}+DCIN^h_{sajb}+ICIN^h_{sajb}\right)+GW^h_{fajb} \\
&\quad +DGW^h_{fajb}+\sum_s^{L,R,D}CC^h_{sajb}]+\sum\nolimits_s^2\left(CIS^h_{sajb}+DCIS^h_{sajb}+ICIS^h_{sajb}\right)] \\
&\quad +r_f(HP^h_{faj}+HW^h_{faj}+HW^{12}_{faj})+HU^h_{faj}+HY^{12}_{faj} \\
&\quad +HGW^h_{faj}+DHGW^h_{faj}\Big)/N_{faj}, \\
\lambda^h_{fli} &= \beta^h_f\sum_{j=1}^{17}\sum_{a=1}^{3}c_{flaij}\rho_{flaij}\left(Y^h_{maj}+U^h_{maj}+Y^{12}_{maj}+GW^h_{maj}+DGW^h_{maj}\right. \\
&\quad \left.+r_m\left(W^h_{maj}+W^{12}_{maj}+P^h_{maj}\right)\right)/N_{maj},
\end{aligned}$$

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$h = 1, 2$. Coinfection occurs at rate

$$\begin{aligned}
\lambda^{12}_{mli} &= \beta^1_m \beta^2_m \sum_{j=1}^{17} \sum_{a=1}^{3} c_{mlaij} \rho_{mlaij} \times \\
&\left(HY^{12}_{faj} + r_f HW^{12}_{faj} + \sum_{b=1}^{2} (Y^{12}_{fajb} + r_f W^{12}_{fajb}) \right) / N_{faj}, \\
\lambda^{12}_{fli} &= \beta^1_f \beta^2_f \sum_{j=1}^{17} \sum_{a=1}^{3} c_{flaij} \rho_{flaij} \left(Y^{12}_{maj} + r_m W^{12}_{maj} \right) / N_{maj}.
\end{aligned}$$

3.8 Mixing preferences

3.8.1 Mixing matrix ρ

The way sex partnerships are formed is governed by the conditional probability matrix ρ. Thus, ρ_{klmij} is the probability of someone of gender k, sexual activity group l, age class i having a partner from the opposite gender from sexual activity group m and age class j. This depends on the proportion of sex partners from the opposite gender from sexual activity group m and age class j, $c_{k'mj} N_{k'mj}(0)$, in the total sexually active population. In generating the mixing matrix ρ, the parameters ϵ_1 and ϵ_2 are used to depict the degree of assortative mixing between age and sexual activity groups, respectively. Thus, mixing is fully assortative (ρ is the identity matrix $\rho_{klmij} = \delta_{lm}\delta_{ij}$, where δ_{ij} is the Kronecker delta) if $\epsilon_1 = \epsilon_2 = 0$ and proportionate when $\epsilon_1 = \epsilon_2 = 1$ [24, 25, 26, 27]. The mixing matrix ρ_{klmij} is given by

$$\begin{aligned}
\rho_{klmij} &= \left((1-\epsilon_1)\delta_{ij} + \epsilon_1 \frac{\sum_{s=1}^{3} c_{k'sj} N_{k'sj}(0)}{\sum_{u=1}^{17} \sum_{a=1}^{3} c_{k'au} N_{k'au}(0)} \right) \times \\
&\left((1-\epsilon_2)\delta_{lm} + \epsilon_2 \frac{\sum_{u=1}^{17} c_{k'mu} N_{k'mu}(0)}{\sum_{u=1}^{17} \sum_{a=1}^{3} c_{k'au} N_{k'au}(0)} \right).
\end{aligned}$$

The model should satisfy the constraints balancing the supply of and demand for sexual partnerships: $c_{klmij}\rho_{klmij}N_{kli} = c_{k'mlji}\rho_{k'mlji}N_{k'mj}$. This is accomplished by specifying the mean rates of sex partner change as functions of the initial imbalance in the supply and demand of sex partnerships. Thus,

$$c_{klmij} = c_{kli} B^{0.5}_{lmij},$$

where

$$B_{lmij} = \frac{c_{k'mj}\rho_{k'mlji}N_{k'mj}(0)}{c_{kli}\rho_{klmij}N_{kli}(0)}.$$

The differential effects of cervical cancer-induced mortality are also likely to cause an imbalance between the demand for and supply of sex partnerships. There are few options for rectifying this. One option is to let the rates of sex

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partner change and mixing pattern of one gender vary over time so as to satisfy the above constraints. Another option is to fix the mixing patterns of both sexes and to let their rates of sex partner change vary over time so as to balance the supply of and demand for sex partnerships [25]. However, this latter option requires adding additional differential equations that may considerably increase the size of the model. Because of this additional complexity only the former option is tried. Thus,

$$c_{k'mlji}(t) = \frac{c_{klmij}\rho_{klmij}N_{kli}(t)}{\rho_{k'mlji}N_{k'mj}(t)}.$$

In the sensitivity analysis, the gender that will be chosen first will be varied to test the robustness of the results.

3.8.2 Estimates of the mixing matrix

Even though the crucial role of the mixing matrix in the spread of many sexually transmitted infections has been repeatedly emphasized before [24, 25, 26, 27], there are no adequate data to generate such a matrix. The current analysis follows previous work in this area by examining the range of patterns that are likely to arise in practice. This range is governed by the parameters ϵ_1 and ϵ_2 whose respective values are set to 0.6 and 0.7 in the baseline analysis and varied over a wide range in the sensitivity analysis. These estimates are obtained from the National Health and Social Life Survey (NHSLS) [55, 63, 64]. Higher values for ϵ_2 are reported for high-risk populations. For example, Garnett et al [26] estimated a value of 0.9 using data from a sample of patients with STD seen at the Harborview Medical Center. The baseline parameter values for the rate of sex partner change, stratified by gender, sexual activity, and age, are calculated from Table 3 using data from the NHSLS and the procedure outlined in Garnett and Anderson [24, 25]. Briefly, this procedure can be described as follows. Let the relative partner acquisition rate of sexual activity group l relative to the lowest group be pc_l. Similarly, define the relative partner acquisition rate of age group i relative to the lowest group as pa_i. Therefore, the rate of sex partner change for people in age group 18–59 is

$$c_{kli} = \frac{pc_l pa_i \bar{c}_3 \sum_{l=1}^{3}\sum_{j=3}^{11} N_{klj}(0)}{\sum_{l=1}^{3}\sum_{j=3}^{11} N_{klj}(0) pc_l pa_j},$$

where $\bar{c}_3$ is the weighted mean rate of sex partner change rate. The rates of sex partner change for the individuals in the age groups 12–14, 15–17, and over 60 years are calculated in a similar fashion. For individuals in the sexually active age groups 18–59, a value for $\bar{c}_3$ of 1.3 new partners per year was used in the analysis [55]. A value for $\bar{c}_1$of 0.1 and $\bar{c}_2$ of 0.3 new partners per year was used for individuals in age groups 12–14, and 15–17, respectively [1]. It is assumed

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Activity group	Proportion of population, %		Relative partner acquisition rate (RPAR), pc_l	Reference
	males, ω_m	females, ω_f		
1 (highest)	2.56	2.56	11.29	[55]
2	11.47	11.47	2.96	
3 (lowest)	85.97	85.97	1	
Age group	**RPAR, pa_i**	**Mean partner acquisition rate, $\bar{c}_j$**		
12–14	0.11		0.1	[1]
15–17	1.18		0.3	[1]
18–19	2.42		1.3	[55]
20–24	2.61			
25–29	2.55			
30–34	1.72			
35–39	1.65			
40–44	1.53			
45–49	1.38			
50–54	1.25			
55–59	1.00			
$60-69$	0.61		0.5	assumed
≥ 70	0.44			
	males	females		
Population size, N_k	50,000	50,000		

Table 3: Baseline behavioral parameter values for the sexually active population

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that for individuals 60 years and older $\bar{c}_4$ is 0.5. Other values were used in the sensitivity analysis.

3.9 Balancing population

To close the model, the total number of people in each gender category k, $(k = f, m)$, age group i (i = 1, 2, …,17) and sexual activity group l (l = 1, 2, 3) must be equal to the sum of individuals in each epidemiologic class in the respective gender, age, and sexual activity groups. That is,

$$\begin{aligned} N_{mli} &= \sum_{h=1}^{2} \left(Y^h_{mli} + Z^h_{mli} + U^h_{mli} + W^h_{mli} + Q^h_{mli} + P^h_{mli} + GW^h_{mli}\right) \\ &\quad + X_{mli} + V_{mli} + S_{mli} + Y^{12}_{mli} + Z^{12}_{mli} + W^{12}_{mli} + Q^{12}_{mli}, \end{aligned}$$

For females this requires

$$\begin{aligned} N_{fli} &= \sum_{b=1}^{2} \Bigg(\sum_{h=1}^{2} [Y^h_{flib} + Z^h_{flib} + U^h_{flib} + W^h_{flib} + Q^h_{flib} + P^h_{flib} + GW^h_{flib} \\ &\quad + \sum_{s=1}^{3} (CIN^h_{slib} + DCIN^h_{slib} + ICIN^h_{slib}) + \sum_{s=1}^{2} (CIS^h_{slib} + DCIS^h_{slib} \\ &\quad + ICIS^h_{slib}) + \sum_{s}^{L,R,D} CC^h_{slib}] + X_{flib} + V_{flib} + S_{flib} + Y^{12}_{flib} \\ &\quad + Z^{12}_{flib} + W^{12}_{flib} + Q^{12}_{flib}\Big) + \sum_{s=1}^{3} TCIN_{sli} + \sum_{s=1}^{2} TCIS_{sli} \sum_{s}^{L,R,D} DCC_{sli} \\ &\quad + \sum_{h=1}^{2} \left(HY^h_{fli} + HZ^h_{fli} + HU^h_{fli} + HW^h_{fli} + HQ^h_{fli} + HP^h_{fli} + HGW^h_{fli}\right) \\ &\quad + HX_{fli} + HV_{fli} + HS_{fli} + HY^{12}_{fli} + HZ^{12}_{fli} + HQ^{12}_{fli} + HW^{12}_{fli} + SCC_{li}. \end{aligned}$$

As evident from the system of equations described above, the demographic model, the HPV model, the cancer model, and the genital warts model are fully integrated, and can only be solved together. The total number of differential equations in the entire model is 7191.

3.10 Estimates of epidemiologic parameters

A comprehensive search of the literature was conducted in order to obtain baseline values for the natural history and clinical parameters.

3.10.1 Estimates of natural history parameters

The values of natural history parameters are reported in Tables 4–5. The way these estimates were derived is explained elsewhere [46].

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Parameter	Estimate	Reference
mean duration of acute HPV infection , years		[29]
HPV 16/18, $1/(\gamma^1_{ki} + \sum_s \theta^1_{ks})$	1.2	
HPV 6/11, $1/(\gamma^2_{ki} + \theta^2_{kg} + \sum_s \theta^2_{ks})$	0.7	
progression in the presence of HPV 16/18 per year, %		
Normal to CIN1, θ^1_{k1}	9.4	[38]
Normal to CIN2, θ^1_{k2}	5.8	[84]
Normal to CIN3, θ^1_{k3}	5.3	[84]
CIN1 to CIN2, π^1_{1i}	13.6	[42]
CIN2 to CIN3, π^1_{2i}	14	[48, 16]
CIN3 to CIS1, π^1_{3i}	42	[48, 80]
CIS1 to CIS2, π^1_{4i}	5	
CIS2 to LCC, π^1_{5i}	18	
LCC to RCC, π^1_{Li}	10	[32, 71, 61]
RCC to DCC, π^1_{Ri}	30	[61]
progression in the presence of HPV 6/11 HPV per year, %		
Normal to CIN1, θ^2_{k1}	9.5	[43]
Normal to CIN2, θ^2_{k2}	1.9	[43, 3, 20, 40, 68]
CIN1 to CIN2, π^2_{1i}	0	[43, 3, 20, 40, 68]
Normal to genital warts, θ^2_{kg}	57	[84]
regression in the presence of HPV 16/18 per year, %		
CIN1 to normal/HPV, τ^1_{f1}	32.9	[43, 72]
CIN2 to normal/HPV, τ^1_{f2}	31	[48, 16, 57]
CIN2 to CIN1, τ^1_{f21}	13.3	[16]
CIN3 to normal/HPV, τ^1_{f3}	11	[48]
CIN3 to CIN1, τ^1_{f31}	3	[48, 16]
CIN3 to CIN2, τ^1_{f32}	3	[48, 16]
regression in the presence of HPV 6/11 HPV per year, %		
CIN1, τ^2_{f1}	55.2	[43]
genital warts, τ^2_{gk}	87.5	[84]
hysterectomy rate, Δ_i, %		[49]
15–24 years	0.02	
25–29 years	0.26	
30–34 years	0.53	
35–39 years	0.89	
40–44 years	1.17	
45–54 years	0.99	
$\geq$ 55 years	0.36	

Table 4: Baseline biological parameter values for the HPV and disease compartments and hysterectomy

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Parameter	Estimate	Reference
age-specific cervical cancer mortality rates, % per year		[75]
for LCC, χ_L		
15–29 years	0.7	
30–39 years	0.6	
40–49 years	0.8	
50–59 years	1.9	
60–69 years	4.2	
$\geq$ 70 years	11.6	
for RCC, χ_R		
15–29 years	13.4	
30–39 years	8.9	
40–49 years	11.0	
50–59 years	10.1	
60–69 years	17.6	
$\geq$ 70 years	28.6	
for DCC, χ_D		
15–29 years	42.9	
30–39 years	41.0	
40–49 years	46.7	
50–59 years	52.7	
60–69 years	54.6	
$\geq$ 70 years	70.3	

Table 5: Annual age-specific cervical cancer mortality rates, 1997–2002

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3.10.2 Estimates of other clinical parameters

The values of screening, diagnosis, and treatment parameters are reported in Tables 6.

3.10.3 Estimates of vaccine parameters

The efficacy of the vaccine against incident infection (HPV 6/11 or 16/18) was assumed to be 90%. It was also assumed that infected vaccinated individuals do not progress to disease [52, 78]. We assumed the vaccine does not affect the natural course of disease. The duration of immunity conferred by vaccination is currently unknown. We assumed the duration of protection of HPV vaccination to be lifelong for the base case as was done in previous models [32] and examined a duration of 10 years in sensitivity analyses. Given HPV vaccination coverage is unknown, we assumed that 70% of adolescents will receive a 3-dose vaccine before they turn 12 similar to the coverage rates used in previous models [71, 32]. Coverage was also assumed to increase linearly from 0% up to 70% during the first five years of the program and remain at 70% thereafter. We assumed that vaccine coverage for the catch-up program would increase linearly from 0% up to 50% during the first 5 years and then drop to 0% after 5 years.

4 Epidemiologic impact of screening and vaccination strategies

To assess the epidemiologic impact of each vaccination strategy several intermediate and two final outcome measures of effectiveness were chosen. Examples of some of the intermediate outcome are shown in Figures **??**–**??** and discussed below.

4.1 Years of life

The first final outcome measure is the total number of years spent alive by the active population. Thus, the discounted total number of years of life achieved using strategy a is given by

$$YL_a = \int_0^T \left(\sum_{k \in \{f,m\}} \sum_{l=1}^{3} \sum_{i=1}^{17} N_{kli} \right) e^{-\xi t} dt$$

where N_{kli} is the size of the population of gender k, in sexual activity group l, and in age group i; ξ is the discount rate; and T is the planning horizon.

4.2 Quality-adjusted life years

The second final measure of effectiveness assigns quality of life weights to each health state and integrates the sum of all these quality-adjusted health states

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Parameter	Estimate	Reference
Routine cervical screening, $cover_i$, % per year		[44]
10–14 years	0.6	
15–19 years	21.0	
20–24 years	44.8	
25–29 years	61.6	
30–34 years	54.9	
35–39 years	50.5	
40–44 years	48.1	
45–49 years	49.1	
50–54 years	51.1	
55–59 years	46.7	
60–64 years	42.5	
65–69 years	38.9	
70–74 years	29.6	
75-79 years	20.1	
80-84 years	11.1	
85+	5.5	
Females never screened, ϱ_1	5	
Liquid-based cytology sensitivity, $papsn_s$, %		
for CIN1	28	[7]
for $\geq$ CIN2/3	59	[7]
Liquid-based cytology specificity, $papsp$, %	94	[7, 14]
Colposcopy sensitivity, $colpsn$, %	96	[60]
Colposcopy specificity, $colpsp$, %	48	[60]
Genital wart patients seeking physician care, $1 - \theta_{gs}$, %	75	[12]
Symptoms recognition, %		
LCC, $recog_L$	3.8	
RCC, $recog_R$	18	
DCC, $recog_d$	90	
Cure rate with treatment per year, %		
for CIN1, $cure_1$	96	[22]
for CIN2, Γ_2	92	[22]
for CIN3, Γ_3	92	[22]
for LCC, Ω_L	92	[69]
for RCC, Ω_R	53	[69]
for DCC, Ω_D	17	
Persistence of HPV after treatment for CIN, %	34	[15]

Table 6: Cervical cytology screening and colposcopy characteristics and rates of cure and symptom recognition

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over the planning horizon $(0, T)$. Let $qcin_s$, $qcis_s$, qcc_s, $qccs$, qgw_k, and q_{ki} denote the quality of life weights for an individual in the detected health state CIN stage s, CIS stage s, cervical cancer stage s, genital warts, and normal of gender k at age i; respectively. The discounted total number of quality-adjusted life years using strategy a over the planning horizon $(0, T)$ is given by

$$
\begin{aligned}
QALY_a = \int_0^T e^{-\xi t} \Bigg\{ & \sum_{l=1}^{3} \sum_{i=1}^{17} q_{mi} \left(N_{mli} - (1 - qgw_m) DGW^2_{mli} \right) \\
& + q_{fi} \Bigg[N_{fli} - (1 - qgw_f)(DHGW^2_{fli} + \sum_{b=1}^{2} DGW^2_{flib}) - (1 - qccs) SCC_{li} \\
& - \sum_{h=1}^{2} \left(\sum_{s=1}^{3} (1 - qcin_s) \sum_{b=1}^{2} DCIN^h_{slib} + \sum_{s=1}^{2} (1 - qcis_s) \sum_{b=1}^{2} DCIS^h_{slib} \right) \\
& - \left(\sum_{s=L,R,D} (1 - qcc_s) DCC_{sli} \right) \Bigg] \Bigg\} dt.
\end{aligned}
$$

Note that the quality-adjusted years of life for females are reduced by time spent in diagnosed genital warts, CIN, and cancer states $DCIN_s$, DCC_s, DGW, and SCC. Males' quality of life deteriorates by spending time with detected genital warts. The probability of genital warts being recognized and treated is assumed to be 75%. It is assumed here that if a persons's health condition is not detected, the quality of life of that person will be the same as that of a person without the condition. This assumption biases the results against the vaccine. In the sensitivity analysis, the magnitude of the quality of life improvements for persons with undetected conditions prevented by the vaccine will be quantified.

4.3 Estimates of quality of life weights

Women diagnosed with CIN1 and CIN2/3 were assumed to have quality weight of 0.91 and 0.87, respectively [62, 54]. The quality weight for genital warts is assumed to be 0.91 [62]. Females with local and regional cancer are assumed to have a quality of life weight of 0.76 and 0.67, respectively [62]. A quality weight for invasive distant cancer of 0.48 was derived from Gold et al [30] using the 25th percentiles of female genital cancer weights. It is assumed that the quality of life for cervical cancer survivors after successful treatment will continue to be lower (at 0.76) than that of healthy females [4, 83]. Undiagnosed HPV, genital warts, CIN, and cervical cancer states and successfully treated CIN states are assumed to have a quality of life weight similar to those of individuals without HPV disease. Gender- and age-specific quality weights for other health states were derived from Gold [30]. Similar values were reported from the Beaver Dam Health Outcomes study [23]. CIN and cancer health states were multiplied by the age- and gender-specific weights to reflect the variation in quality of life by age and gender groups.

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Condition	Estimate		Reference
	females	males	
genital warts, qgw_k	0.91	0.91	[62]
CIN1, $qcin_1$	0.91		[62]
CIN2, $qcin_2$	0.87		[62]
CIN3, $qcin_3$	0.87		[62]
CIS, $qcis_s$	0.87		[62]
EICC, qcc_L	0.76		[62]
RLICC, qcc_R	0.67		[62]
DLICC, qcc_D	0.48		[30]
Cancer survivors, $qccs$	0.76		[83]
No condition, q_{ki}			
12–17 years	0.93	0.93	[30]
18–34 years	0.91	0.92	[30]
35–44 years	0.89	0.90	[30]
45–54 years	0.86	0.87	[30]
55–64 years	0.80	0.81	[30]
65–74 years	0.78	0.76	[30]
$\geq$ 75 years	0.70	0.69	[30]

Table 7: Quality of life weights

5 Economic consequences of screening and vaccination strategies

The total costs of each strategy includes costs of cytology screening per unit time, cost of vaccination, lifetime cost of treating detected genital warts, CIN and invasive cancer cases, and the cost of following false positive results of screening.

5.1 Screening costs

The cost of cytology screening per unit time is the product of the cost per test scn, the test compliance rate $cover_{ib}$ given the frequency of administering the test per unit time (e.g., every year), and the size of the population eligible for screening $\sum_l \sum_i \{\sum_b (X_{flib}+V_{flib}+S_{flib}+Y^{12}_{flib}+Z^{12}_{flib}+W^{12}_{flib}+Q^{12}_{flib}+\sum_h [Y^h_{flib}+Z^h_{flib}+U^h_{flib}+W^h_{flib}+Q^h_{flib}+P^h_{flib}+GW^h_{flib}+\sum_s CIN^h_{slib}+\sum_s CIS^h_{slib}+\sum_s CC^h_{slib}]$. For simplicity, it is assumed that females in the hysterectomy class are not screened. However, this may not be the case as suggested by recent studies [70]. The cost of following false positive results of the cytology test is the product of the cost of colposcopy $colp$ of those females who do not have a $repeat$ cytology test, one minus cytology specificity $papsp$ and the size of the screened population that is truly negative $\sum_l \sum_i \{\sum_b (X_{flib}+V_{flib}+S_{flib}+Y^{12}_{flib}+Z^{12}_{flib}+W^{12}_{flib}+Q^{12}_{flib}+\sum_h [Y^h_{flib}+Z^h_{flib}+U^h_{flib}+W^h_{flib}+Q^h_{flib}+P^h_{flib}+GW^h_{flib}]$. Since

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colposcopy is not 100% specific, to this it should be added the cost of a false positive colposcopy result. This, in turn, equals the product of the cost of biopsy *biopsy*, one minus colposcopy specificity *colsp* and the size of the screened population that has false cytology results. We also assumed that females in categories $TCIN_s, ICIN_s$, $ICIN_s$, and SCC receive annual Pap tests, some of which will be false positives resulting in additional colposcopies and biopsies. Total screening costs associated with strategy a at time t are

$$
\begin{aligned}
&Screen_a(t) = \\
&scn \times \{\sum_l \sum_i (\sum_b cover_{ib} \times (X_{flib} + V_{flib} + S_{flib} + Y^{12}_{flib} + Z^{12}_{flib} + W^{12}_{flib} \\
&+Q^{12}_{flib} + \sum_h [Y^h_{flib} + Z^h_{flib} + U^h_{flib} + W^h_{flib} + Q^h_{flib} + P^h_{flib} + GW^h_{flib} \\
&+ \sum_s CIN^h_{slib} + \sum_s CIS^h_{slib} + \sum_s CC^h_{slib})]\} + \\
&(1 - papsp) \times [repeat \times scn + (1 - repeat)(colp + biopsy \times (1 - colpsp))] \\
&\times\{\sum_l \sum_i [\sum_b cover_{ib} \times (X_{flib} + V_{flib} + S_{flib} + Y^{12}_{flib} + Z^{12}_{flib} + W^{12}_{flib} \\
&+Q^{12}_{flib} + \sum_h [Y^h_{flib} + Z^h_{flib} + U^h_{flib} + W^h_{flib} + GW^h_{flib} + Q^h_{flib} + P^h_{flib})]\} \\
&+\{scn + (1 - papsp) \times [colp + biopsy \times (1 - colpsp)]\} \\
&\times\{\sum_l \sum_i [SCC_{li} + \sum_s TCIN_{sli} + \sum_h \sum_b (\sum_s ICIN^h_{slib} + \sum_s ICIS^h_{slib})]\}.
\end{aligned}
$$

5.2 Treatment costs

Treatment costs of genital warts, CIN, and cancer cases are the product of the number of cases detected and treated and the cost of treatment. Cases of genital warts occur at rate $(1-\theta_{gs}) \sum_k \{\theta^2_{gk}[HY^2_{kli} + HU^2_{kli} + \sum_b (Y^2_{klib} + U^h_{klib})] + \theta^{12}_{gk}(HY^{12}_{kli} + \sum_b Y^{12}_{klib}) + \theta^2_{gwk}[HW^2_{kli} + HP^2_{kli} + \sum_b (W^2_{klib} + P^h_{klib})] + \theta^{12}_{gwk}(HW^{12}_{kli} + \sum_b W^{12}_{klib})\}$ at a cost of cgw_k per case. Because it is assumed that the rate of treatment for diagnosed CIN is Γ_s and all cancer cases are treated, the number of cases treated at time t is the total number of treated CIN and cancer detected $\sum_h \sum_l \sum_i \sum_b [\sum_s \Gamma_s DCIN^h_{slib} + \sum_s \Gamma_{3+s} DCIS^h_{slib} + \sum_s \upsilon_{sib} CC^h_{slib})]$. The cost of treating CIN and cancer at stage s is denoted by $ctcin_s$ and $ctcc_s$, respectively.

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Thus, total treatment costs at time t if strategy a is adopted is:

$$
\begin{aligned}
&Treat_a(t) = \\
&\sum_l \sum_i \sum_k cgw_k(1-\theta_{gs})\{\theta^2_{gk}[HY^2_{kli} + HU^2_{kli} + \sum_b (Y^2_{klib} + U^2_{klib})] \\
&+\theta^{12}_{gk}(HY^{12}_{kli} + \sum_b Y^{12}_{klib}) + \theta^2_{gwk}[HW^2_{kli} + HP^2_{kli} \\
&+ \sum_b (W^2_{klib} + P^2_{klib})] + \theta^{12}_{gwk}(HW^{12}_{kli} + \sum_b W^{12}_{klib})\} + \sum_h \sum_l \sum_i \sum_b \\
&\left(\sum_s ctcin_s(\Gamma_s DCIN^h_{slib} + \Gamma_{3+s} DCIS^h_{slib}) + \sum_s (ctcc_s \times \upsilon_{sib} CC^h_{slib}) \right).
\end{aligned}
$$

5.3 Vaccination costs

Total vaccination costs at time t include the cost of the vaccine and the number of people vaccinated $\sum_k \sum_l \sum_b \{B_{klb}\phi_{kl0b} + \sum_i \phi_{klib}[Y^{12}_{klib} + Z^{12}_{klib} + \sum_h (X^h_{klib} + Y^h_{klib} + Z^h_{klib} + U^h_{klib} + GW^h_{klib} + \sum_s (CIN^h_{slib} + CIS^h_{slib} + CC^h_{slib}))]\}$. Thus, total vaccination costs at time t associated with strategy a are:

$$
\begin{aligned}
Vaccinate_a(t) \quad = \quad & vaccine \times \sum_l \sum_k \sum_b \{B_{klb}\phi_{kl0b} + \sum_i \phi_{klib}[Y^{12}_{klib} + Z^{12}_{klib} \\
& + \sum_h (X^h_{klib} + Y^h_{klib} + Z^h_{klib} + U^h_{klib} + GW^h_{klib} \\
& + \sum_s (CIN^h_{slib} + CIS^h_{slib} + CC^h_{slib}))]\}.
\end{aligned}
$$

5.4 Total costs

Discounted total cost over the planning horizon $(0, T)$ of following strategy a is

$$
Cost_a = \int_0^T [Screen_a(t) + Treat_a(t) + Vaccinate_a(t)]\, e^{-\xi t} dt.
$$

5.5 Estimates of costs

Direct medical costs for screening and diagnosis were estimated from the 2001 Medstat Marketscan® commercial insurance database [56] and updated to 2005 dollar values by using the medical care component of the U.S. consumer price index [77]. The direct medical costs in 2005 of liquid-based cytology were estimated at $99. The cost of colposcopy was $165 and colposcopy with cervical biopsy at the same visit was $318. The direct medical costs of treatment of CIN and cervical cancer were based on the results of Kim et al [50] and updated to 2005 dollar values [77]. The costs of CIN 1 were $1554, CIN 2/3 $3483, local invasive cervical cancer $26,470, regional invasive cervical cancer $28,330, and

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Condition	Estimate females	males	Reference
cytology test, *scn*	\$99		[56]
colposcopy, *colp*	\$165		[56]
colposcopy and biopsy, *biopsy*	\$318		[56]
genital warts, cgw_k	\$489	\$489	[41]
CIN1, $ctcin_1$	\$1554		[50]
CIN2, $ctcin_2$	\$3483		[50]
CIN3/CIS, $ctcin_3$	\$3483		[50]
EICC, $ctcc_L$	\$26,470		[50]
RLICC, $ctcc_R$	\$28,330		[50]
DLICC, $ctcc_D$	\$45,376		[50]

Table 8: Cost of screening, diagnosis, and treatment

local invasive cervical cancer \$45,376. Treatment of genital warts is assumed to cost \$489 in 2005 dollars [41].

5.6 Cost-effectiveness ratio

To compare mutually exclusive vaccination strategies a and a', we calculate the incremental cost-effectiveness ratio [82]

$$\frac{Cost_a - Cost_{a'}}{QALY_a - QALY_{a'}}.$$

6 Analysis using the model

6.1 Simulations with the baseline estimates of the parameters

Mathematica® (Wolfram Research, Champaign, IL) version 5.2 was used to generate numerical solutions of the model. The NDSolve subroutine in Mathematica is a general numerical differential equations solver. Since the model consists of non-stiff ODEs, the Explicit Runge Kutta methods, with adaptive embedded pairs of 2(1) through 9(8), provide accurate and less expensive solutions [85]. Other methods such as the Predictor-Corrector Adams method, with orders 1 through 12, produced the same results, but took longer to compute the solution.

The following strategy for simulations was followed. First, the baseline parameter estimates were used to solve the model for the pre-vaccination steady-state values of the variables. Second, the pre-vaccination data were used as initial values for the vaccination model and the model was solved for the entire time path of the variables until the system approached the steady state (approximately 100 years). The solution approximates the potential impact of various HPV

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vaccination programs, including routine vaccination of 12-years old individuals. Finally, once the solution is obtained the results can be presented for various outcomes in many different formats.

6.2 Model validation

The validity of a complex model like this cannot be established directly. Instead, its face validity may be judged by how reasonable model assumptions are [34, 81]. In the process of building this model, we comprehensively reviewed previous relevant models and consulted experts on the natural history of HPV infection and HPV-related diseases. A comprehensive review of the literature was conducted to identify studies to inform model inputs. To facilitate independent review of the model and the ability to replicate its results, all model equations and inputs are made available. All model equations and inputs are programmed in Mathematica^{TM} (Wolfram Research, Champaign, IL). A series of tests were performed to debug and establish the technical accuracy of the Mathematica programs. For example, the sum of the number of individuals of a given gender, age, and sexual activity group in each compartment is verified to be equal to the total number of people N_{kli} at each point in time (see section 3.9 on balancing population). Finally, the predictive validity of the model was evaluated by looking at age-specific HPV prevalence, CIN, genital warts, and cervical cancer incidence rates predicted by the model and comparing them with those reported in the literature [29, 47, 73, 74, 75, 41, 45]. The model predictions were well within the range of values found in the literature. For example, the predicted HPV 16/18 attributable cervical cancer incidence curve in the absence of screening had a shape and magnitude at peak (55.9 per 100,000 women years for age 50–54) similar to that estimated for unscreened populations [33, 58].

References

[1] Abma, J.C., Sonenstein, F.L., 2001. Sexual activity and contraceptive practices among teenagers in the United States, 1988 and 1995. National Center for Health Statistics. Vital Health Stat. 23(21), 1–79.

[2] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 1995. IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 64. Human papillomaviruses. Lyons, France: International Agency for Research on Cancer.

[3] Aoyama, C., Peters, J., Senadheera, S., et al., 1998. Uterine cervical dysplasia and cancer: identification of c-myc status by quantitative polymerase chain reaction. Diagn. Mol. Pathol. 7, 324–330.

[4] Andersen, B., 1996. Stress and quality of life following cervical cancer. J. Natl. Cancer Inst. 21, 65–70.

This material, provided by the authors as a supplement to Model for Assessing Human Papillomavirus Vaccination Strategies, is not part of Emerging Infectious Diseases contents.

[5] Barnabas, R. V., Garnett, G. P., 2004. The potential public health impact of vaccines against human papillomavirus. The Clinical Handbook of Human Papillomavirus. W. Prendiville and P. Davies. Lancaster, UK, Parthenon Publishing/Parthenon Medical Communications.

[6] Barnabas, R.V., Laukkanen, P., Koskela, P., et al., 2006. Epidemiology of HPV 16 and cervical cancer in Finland and the potential impact of vaccination: mathematical modelling analyses. PLOS Medicine 3, 1–9. (www.plosmedicine.org).

[7] Bigras, G., de Marval, F., 2005. The probability for a Pap test to be abnormal is directly proportional to HPV viral load: results from a Swiss study comparing HPV testing and liquid-based cytology to detect cervical cancer precursors in 13,842 women. Br. J. Cancer 93, 575–581.

[8] Bosch, F.X., de Sanjose, S., 2003. Chapter 1: Human papillomavirus and cervical cancer-burden and assessment of causality. J. Natl. Cancer Inst. Monogr. 31, 3–13.

[9] Castle, P.E., Schiffman, M., Bratti, M.C., Hildesheim, A., Herrero, R., et al., 2004. A population-based study of vaginal human papillomavirus infection in hysterectomized women. J. Infect. Dis. 190, 458–67.

[10] Center on the Evaluation of Value and Risk in Health. The cost-effectiveness analysis registry [Internet]. (Boston), Tufts-New England Medical Center, ICRHPS. Available from: <http://www.tufts-nemc.org/cearegistry/> (Accessed March 13, 2006).

[11] Centers for Disease Control and Prevention, 2004. Prevention of genital human papillomavirus infection. Report to Congress, Washington DC, January.

[12] Chesson, H.W., Blandford, J.M., Gift, T.L., et al., 2004. The estimated direct medical cost of sexually transmitted diseases among American youth, 2000. Perspect. Sex. Reprod. Health 36, 11–19.

[13] Costa, S., De Simone, P., Venturoli, S., Cricca, M., Zerbini, M.L., et al., 2003. Factors predicting human papillomavirus clearance in cervical intraepithelial neoplasia lesions treated by conization. Gynecol. Oncol. 90, 358–65.

[14] Coste, J., Cochand-Priollet, B., De Cremoux, P., et al., 2003. Cross sectional study of conventional cervical smear, monolayer cytology, and human papillomavirus DNA testing for cervical cancer screening. BMJ 326, 733.

[15] Cruickshank, M.E., Sharp, L., Chambers, G., et al., 2002. Persistent infection with human papillomavirus following the successful treatment of high grade cervical intraepithelial neoplasia. BJOG 109, 579–581.

This material, provided by the authors as a supplement to Model for Assessing Human Papillomavirus Vaccination Strategies, is not part of Emerging Infectious Diseases contents.

[16] De Aloysio, D., Miliffi, L., Iannicelli, T., et al., 1994. Intramuscular interferon-beta treatment of cervical intraepithelial neoplasia II associated with human papillomavirus infection. Acta. Obstet. Gynecol. Scand. 73, 420–424.

[17] Eddy, D.M., 1980. Screening for cancer: theory, analysis, and design. Prentice-Hall, Englewood Cliffs, New Jersey.

[18] Eddy, D.M., 1990 Screening for cervical cancer. Ann. Intern. Med. 113, 214–226.

[19] Elbasha, E.H., Galvani, A.P., 2005. Vaccination against multiple HPV types. Math. Biosci. 197, 88–117.

[20] Evans, M.F., Mount, S.L., Beatty, B.G., et al., 2002. Biotinyl-tyramide-based in situ hybridization signal patterns distinguish human papillomavirus type and grade of cervical intraepithelial neoplasia. Mod. Pathol. 15, 1339–1347.

[21] Fahs, M.C., Mandelblatt, J., Schechter, C., Muller, C., 1992. Cost effectiveness of cervical cancer screening for the elderly. Ann. Intern. Med. 117, 520–527.

[22] Flannelly, G., Langhan, H., Jandial, L., Mana, E., Campbell, M., Kitchener, H., 1997. A study of treatment failures following large loop excision of the transformation zone for the treatment of cervical intraepithelial neoplasia. Br. J. Obstet. Gynaecol. 104, 718–22.

[23] Fryback, D., Dasbach, E., Klein, R., et al., 1993. Initial catalog of health-state quality factors. Med. Decis. Making 13, 89–102.

[24] Garnet, G.P., Anderson, R.M., 1993. Factors controlling the spread of HIV in heterosexual communities in developing countries: patterns of mixing between age and sexual activity classes. Phil. Trans. R. Soc. Lond. B. 342, 137–159.

[25] Garnett, G.P., Anderson, R.M., 1994. Balancing sexual partnerships in age and activity stratified model of HIV transmission in heterosexual populations. IMA J. Math. Appl. Med. Biol. 11, 161–192.

[26] Garnett, G.P., Hughes, J.P., Anderson, R.M., Stoner, B.P., Aral, S.O., Whittington, W.L., Handsfield, H.H., Holmes, K.K., 1996. The determination of the sexual mixing pattern of patients attending STD and other clinics in Seattle, USA, by contact tracing. Sex. Transm. Dis. 23, 248–257.

[27] Garnett, G.P., Anderson, R.M., 1993. Contact tracing and the estimation of sexual mixing patterns: The epidemiology of gonoccal infections. Sex. Transm. Dis. 20,181–191.

This material, provided by the authors as a supplement to Model for Assessing Human Papillomavirus Vaccination Strategies, is not part of Emerging Infectious Diseases contents.

[28] Garnett, G.P., Waddell, H., 2000. Public health paradoxes and the epidemiological impact of an HPV vaccine. J. Clinical Virology 19, 101–111.

[29] Giuliano, A.R., Harris, R., Sedjo, R.L., et al., 2002. Incidence, prevalence, and clearance of type-specific human papillomavirus infections: The Young Women's Health Study. J. Infect. Dis. 186, 462–469.

[30] Gold, M., Franks, P., McCoy, K., Fryback, D., 1998. Toward consistency in cost-utilities analysis. Med. care 36, 778–792.

[31] Goldie, S.J., Grima, D., Kohli, M., Wright, T.C., Weinstein, M.C., Franco, E., 2003. A comprehensive natural history model of human papillomavirus (HPV) infection and cervical cancer: Potential impact of and HPV 16/18 Vaccine. Int. J. Cancer 106, 896–904.

[32] Goldie, S.J., Kohli, M., Grima, D., Weinstein, M.C., Wright, T.C., Bosch, F.X., Franco, E., 2004. Projected Clinical Benefits and Cost-Effectiveness of a Human Papllomavirus 16/18 Vaccine. J. Natl. Cancer Inst. 96, 604–615.

[33] Gustafsson, L., Ponten, J., Bergstrom, R., Adami, H.O., 1997. International incidence rates of invasive cervical cancer before cytological screening. Int. J. Cancer 71, 159–65.

[34] Hammerschmidt, T., Goertz, A., Wagenpfeil, S., et al., 2003. Validation of Health Economic Models. The Example of EVITA. Value Health 6, 551–559.

[35] Harper, D., Franco, E., Wheeler, C., Ferris, D., Jenkins, D., et al., 2004. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet 364, 1757–1765.

[36] Hethcote, H., 1997. An age-structured model of pertussis transmission. Math. Biosci. 145, 89–136.

[37] Ho, G.Y.F., Burk, R.D., Klein, S., et al., 1995. Persistent genital human papillomavirus infection as a risk factor for persistent cervical dysplasia. J. Natl. Cancer Inst. 87, 1365–1371.

[38] Hoyer, H., Scheungraber, C., Kuehne-Heid, R., et al., 2005. Cumulative 5-year diagnoses of CIN2, CIN3 or cervical cancer after concurrent high-risk HPV and cytology testing in a primary screening setting. Int. J. Cancer 116, 136–143.

[39] Hughes, J.P., Garnett, G.P., Koutsky, L.A., 2002. The theoretical population level impact of a prophylactic human papilloma virus vaccine. Epidemiology 13, 631–639.

This material, provided by the authors as a supplement to Model for Assessing Human Papillomavirus Vaccination Strategies, is not part of Emerging Infectious Diseases contents.

[40] Isacson, C., Kessis, T.D., Hedrick, L., et al., 1996. Both cell proliferation and apoptosis increase with lesion grade in cervical neoplasia but do not correlate with human papillomavirus type. Cancer Res. 56, 669–674.

[41] Insinga, R.P., Dasbach, E.J., Myers, E.R., 2003. The health and economic burden of genital warts in a set of private U.S. Health Plans. Clin. Infect. Dis. 36, 1397–1403.

[42] Insinga, R.P., 2006. The natural history of low-grade cervical intraepithelial neoplasia. Manuscript in preparation.

[43] Insinga, R.P., 2006. The natural history of cervical HPV 6/11 infection. 2006. Manuscript in preparation.

[44] Insinga, R.P., Glass, A.G., Rush, B.B., 2004. Pap screening in a U.S. health plan. Cancer Epidemiol. Biomarkers Prev. 13, 355–360.

[45] Insinga, R.P., Glass, A.G., Rush, B.B., 2004. Diagnoses and outcomes in cervical cancer screening: a population-based study. Am. J. Obstet. Gynecol. 191, 105–113.

[46] Insinga, R.P., Dasbach, E.J., Elbasha, E.H., 2006. Epidemiologic natural history and clinical outcomes of human papillomavirus (HPV) disease: a critical review of the literature in the development of an HPV dynamic transmission model. Manuscript in preparation.

[47] Jacobs, M.V., Walboomers, J.M., Snijders, P.J., Voorhorst, F.J., Verheijen, R.H., Fransen-Daalmeijer, N., Meijer, C.J., 2000. Distribution of 37 mucosotropic HPV types in women with cytologically normal cervical smears: the age-related patterns for high-risk and low-risk types. Int. J. Cancer 87, 221–227.

[48] Kataja, V., Syrjanen, K., Mantyjarvi, R., et al., 1989. Prospective follow-up of cervical HPV infections: life table analysis of histopathological, cytological and colposcopic data. Eur. J. Epidemiol. 5, 1–7.

[49] Keshavarz, H., Hillis, S.D., Kieke, B.A., et al., 2002. Hysterectomy surveillance-United States, 1994-1999. MMWR CDC Surveill. Summ. 51, 1–8.

[50] Kim, J., Wright, T., Goldie, S., 2002. Cost-effectiveness of alternative triage strategies for atypical squamous cells of undetermined significance. JAMA 287, 2382–90.

[51] Kochanek, K.D., Murphy, S.L., Anderson, R.N., Scott, C., 2004. Deaths: Final data for 2002. Natl. Vital. Stat. Rep. 53.

[52] Koutsky, L. A., Ault, K. A., Wheeler, C. M., Brown, D. R., Barr, E., et al., 2002. A controlled trial of a human papillomavirus type 16 vaccine. N. Engl. J. Med. 347, 1645–1651.

This material, provided by the authors as a supplement to Model for Assessing Human Papillomavirus Vaccination Strategies, is not part of Emerging Infectious Diseases contents.

[53] Kulasingam, S.L., Myers, E.R., 2003. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. JAMA 290, 781–789.

[54] Kulasingam, S., Harper, D., Tosteson, A., Myers, E., 2002. Impact of quality-of-life assumptions on cost-effectiveness of cervical cancer screening. 20th International Papillomavirus Conference, Paris, France, October (abstract 121).

[55] Lauman, E., Gagnon, J., Michael, R., Michaels, S., 1994. The social organization of sexuality. University of Chicago Press, Chicago, IL.

[56] Medstat, 2001. MarketScan® database, Thomson Medstat. Ann Arbor, MI.

[57] Matsumoto, K., Yasugi, T., Oki, A., et al., 2006. IgG antibodies to HPV16, 52, 58 and 6 L1-capsids and spontaneous regression of cervical intraepithelial neoplasia. Cancer Lett. 231, 309–313.

[58] McCrory, D., Mather, D., Bastain, L., Datta, S., Hasselblad, V., Hickey, J., Myers, E., Nanda, K., 1999. Evaluation of cervical cytology. Evidence Report/Technology Assessment No.5 (Prepared by Duke University under Contract No. 290-97-0014). AHCPR Publication No. 99-E010. Rockville, MD, Agency for Health Care Policy and Research, February. Available: http://www.ahrq.gov/clinic/epcsums/ cervsumm.htm.

[59] McIntyre, J.A., Leeson, P.A., 2006. Gardasil™: anti-papillomavirus vaccine. Drugs Future 3, 97–100.

[60] Mitchell, M.F., Schottenfeld, D., Tortolero Luna, G., Cantor, S.B., Richards Kortum, R., 1998. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta analysis. Obstet. Gynecol. 91, 626–31.

[61] Myers, E., McCrory, D., Nanda, K., Bastian, L., Matchar, D., 2000. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. Am. J. Epidemiol. 151, 1158–71.

[62] Myers, E., Green, S., Lipkus, I., 2004. Pateint preferences for health states related to HPV infection: visual analogue scales vs. time trade-off elicitation. Proceedings of the 21st International Papillomavirus Conference, 390.2, Mexico City, Mexico.

[63] Michael, R., Gagnon, J., Lauman, E., Kolata, G., 1994. Sex in America. Little, Brown & Co, Inc., New York, NY.

[64] Michael, R., Wadsworth, J., Feinleib, J., Johnson, A., Lauman, E., Wellings, K., 1998. Private sexual behavior, public opinion, and public health policy related to sexualy transmitted diseases: a US-British comparison. Am. J. Public Health 88, 749–754.

This material, provided by the authors as a supplement to Model for Assessing Human Papillomavirus Vaccination Strategies, is not part of Emerging Infectious Diseases contents.

[65] Nobbenhuis, M.A., Walboomers, J.M., Helmerhorst, T.J., et al., 1999. Relation of human papillomavirus status to cervical lesions and consequences for cervical-cancer screening: a prospective study. Lancet 354, 20–25.

[66] Parkin, D.M., Bray, F., Ferlay, J., Pisani, P., 2005. Global cancer statistics. CA Cancer J. Clin. 55, 74–108.

[67] Peyton, C., Gravitt, P., Hunt, W., Hundley, R., Zhao, M., Apple, R.J., Wheeler, C.M., 2001. Determinants of genital human papillomavirus detection in a U.S. population. J. Infect. Dis. 183, 1554–1564.

[68] Quade, B.J., Park, J.J., Crum, C.P., et al., 1998. In vivo cyclin E expression as a marker for early cervical neoplasia. Mod Pathol 11, 1238–1246.

[69] Ries, L., Eisner, M., Kosary, C., et al., 2005. SEER cancer statistics review, 1975–2002. Bethesda, MD, National Cancer Institute, http://seer.cancer.gov/csr/1975_2002/.

[70] Saint, M., Gildengorin, G., Sawaya, G. F., 2005. Current cervical neoplasia screening practices of obstetrician/gynecologists in the US. Am. J. Obstet. Gynecol. 192, 414–21.

[71] Sanders, G.D., Taira, A.V., 2003. Cost Effectiveness of a Potential Vaccine for Human Papillomavirus. Emerg. Infect. Dis. 9, 37–48.

[72] Sastre-Garau, X., Cartier, I., Jourdan-Da Silva, N., et al., 2004. Regression of low-grade cervical intraepithelial neoplasia in patients with HLA-DRB1*13 genotype. Obstet. Gynecol. 104, 751–755.

[73] Sellors, J., Mahony, J., Kaczorowski, J., Lytwyn, A., Bangura, H., Lorincz, A., et al., 2000. Prevalence and predictors of human papillomavirus infection in women in Ontario, Canada. CMAJ 163, 503–508.

[74] Sellors, J., Kaczorowski, T., Kaczorowski, J., Mahony, J., Lytwyn, A., Chong, S., et al., 2002. Prevalence of infection with carcinogenic human papillomavirus among older women. CMAJ 167, 871–872.

[75] Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Survival - SEER 9 Regs Public-Use, Nov 2004 Sub (1973–2002), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission.

[76] Stratton, K., Durch, J., Lawerence, R., eds., 2000. Committee to Study Priorities for Vaccine Development. Institute of Medicine. Vaccines for the 21st century: A tool for decisionmaking. Appendix 11. Human Papillomavirus pp 213–222. Washington DC: National Academy Press, http://www.iom.edu/report.asp?id=5648.

This material, provided by the authors as a supplement to Model for Assessing Human Papillomavirus Vaccination Strategies, is not part of Emerging Infectious Diseases contents.

[77] US Bureau of Labor Statistics, 2002. Statistical abstracts of the United States: Consumer price index. National Center for Health Statistics, Washington, DC.

[78] Villa, L.L., Costa, R.L.R., Petta, C.A., Andrade, R.P., Ault, K. A., et al., 2005. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-conrolled multicentre phase II efficacy trial. Lancet Oncol. 6, 271–78.

[79] Wallin, K.-L., Wiklund, F., Ångström, T., et al.,1999. Type-specific persistence of human papillomavirus DNA before the development of invasive cervical cancer. N. Engl. J. Med. 341, 1633–1638.

[80] Westergaard, L., Norgaard, M., 1981. Severe cervical dysplasia. Control by biopsies or primary conization? A comparative study. Acta Obstet. Gynecol. Scand. 60, 549–554.

[81] Weinstein, M.C., O'Brien, B., Hornberger, J., Jackson, J., Johannesson, M., McCabe, C., Luce, B.R., 2003. Principles of good decision analytic modeling. Value Health 6, 9–17.

[82] Weinstein, M., 1996. From cost-effectiveness ratios to resource allocation: Where to draw the line? In Valuing health care: costs, benefits, and effectiveness of pharmaceuticals and other medical technologies. ed., F Sloan, pp. 77–97. New York: Cambridge University Press.

[83] Wenzel, L., DeAlba, I., Habbal, R., Kluhsman, B.C., Fairclough, D., et al., 2005. Quality of life in long-term cervical cancer survivors. Gynecol. Oncol. 97, 310–7.

[84] Winer, R.L., Kiviat, N.B., Hughes, J.P., Adam, D.E., Lee, S.K., et al., 2005. Development and duration of human papillomavirus lesions, after initial infection. J. Infect. Dis. 191, 731–8.

[85] Wolfram, S., 2005. The Mathematica book, 5th ed. Wolfram Media, Wolfram Research, Inc., Champaign, IL, USA.