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ORIGINAL ARTICLE

A Multi-Type HPV Transmission Model

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Abstract A prophylactic quadrivalent (types 6/11/16/18) vaccine against oncogenic and warts-causing genital Human papillomavirus (HPV) types was approved by the US Food and Drug Administration in 2006. This paper presents a nonlinear, deterministic, age-structured, mathematical model of the transmission dynamics of HPV and disease occurrence in a US population stratified by gender and sexual activity group. The model can assess both the epidemiologic consequences and cost effectiveness of alternative vaccination strategies in a setting of organized cervical cancer screening in the United States. Inputs for the model were obtained from public data sources, published literature, and analyses of clinical trial data. The results suggest that a prophylactic quadrivalent HPV vaccine can: (i) substantially reduce the incidence of disease, (ii) increase survival among females, (iii) improve quality of life for both males and females, (iv) be cost-effective when administered to females age 12–24 years, and (v) be cost-effective when implemented as a strategy that combines vaccination of both females and males before age 12 vaccination with a 12 to 24 years of age catch-up vaccination program.

Keywords Human papillomavirus · Cervical intraepithelial neoplasia · Uterine cervical neoplasms · Condylomata acuminata · Vaccines · Theoretical models · Nonlinear dynamics · Herd immunity · Disease transmission · Cost-effectiveness analysis

1. Introduction

Infection with the nonenveloped, encapsulated, double-stranded DNA human papillomavirus (HPV) is the most commonly occurring type of infection among sexually active men and women. There are approximately 20 million current infections and 5.5 million new infections occurring every year in the US (Centers for Disease Control and Prevention, 2004). The lifetime risk of a sexually active woman being infected with HPV is close to 70% (Bosch and de Sanjose, 2003). HPV is enormously diverse, with over 100 HPV types having been identified to date. Of those, more than 40 genotypes infect the anogenital tract. Several studies have documented the role

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of infection in the etiologies of cervical intraepithelial neoplasia (CIN), cervical cancer, and other genital lesions and cancers (Ho et al., 1995; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 1995; Nobbenhuis et al., 1999; Wallin et al., 1999). The high-risk HPV types 16 and 18 cause approximately 70% of cervical cancers, whereas types 6 and 11 result in about 90% of genital warts. Despite the success of medical advances in controlling some of these diseases, HPV continues to cause significant morbidity and mortality. For example, cervical cancer is currently 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 (Parkin et al., 2005).

Prophylactic HPV vaccines hold promise for controlling the spread of HPV and HPV-related diseases. Recently, a number of randomized clinical trials have demonstrated that administration of a three-dose regimen of an HPV virus-like-particle prophylactic vaccine is highly efficacious against HPV infection and HPV-related disease (Koutsky et al., 2002; Harper et al., 2004; Villa et al., 2005). Following the success of these studies, GARDASIL® [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine], the first prophylactic HPV vaccine, was approved by the US Food and Drug Administration (FDA) in 2006. GARDASIL® is approved for use in 9- to 26-year old girls and women. The Centers for Disease Control and Prevention (CDC)'s Advisory Committee for Immunization Practices (ACIP) recommended that girls and women 11–26 years old be vaccinated with GARDASIL® to prevent cervical cancer, precancerous and low-grade lesions, and genital warts caused by HPV types 6, 11, 16, and 18. With the introduction of such a vaccine, policy makers and other public health officials will need information on its epidemiologic and economic consequences in order to formulate appropriate HPV vaccination guidelines (McIntyre and Leeson, 2006).

In a previous paper (Elbasha et al., 2007), we used a mathematical model to assess both the epidemiologic consequences and cost effectiveness of alternative strategies of administering a prophylactic quadrivalent (types 6/11/16/18) HPV vaccine in a setting of organized cervical cancer screening in the United States. This paper provides a detailed description of various components of the model as they relate to HPV infection, disease progression, cervical cancer screening, treatment, 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. By making available the mathematical equations and parameters that entirely summarize the actual workings of the model, critical review of the model and reproducibility of results are made feasible without needing to review the actual source code used to generate the results (Weinstein et al., 2003). These 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. There are examples of previous modeling efforts that followed this approach (e.g., Hethcote, 1997; Schuette and Hethcote, 1999). In addition to serving as a technical background document to the paper by Elbasha et al. (2007), this paper also presents new results on the impact of vaccination as well as provides the results of additional sensitivity analyses on assumptions regarding sexual behavior and mixing among different population groups.

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 (Eddy, 1980, 1990; Fahs et al., 1992; McCrory et al., 1999; Myers et al., 2000; Kim et al., 2002), HPV vaccination cohort models (Stratton et al., 2000; Sanders and Taira, 2003; Kulasingam and Myers, 2003; Goldie et al., 2003, 2004), and HPV vaccination dynamic models (Hughes et al., 2002; Garnett and Waddell, 2000; Barnabas and Garnett, 2004; Elbasha and Galvani, 2005). This model differs from its predecessors in several ways. First, the approach is comprehensive in the sense that it incorporates the epidemiology of HPV infection, disease, and economics into a single dynamic model. This allows capturing the direct and indirect "herd immunity" benefits and costs of vaccination for the population over time in one model (Edmunds et al., 1999; Brisson and Edmunds, 2003). Second, we also convened an expert panel that reviewed model assumptions and provided guidance on some aspects of the natural 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 these 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 CIN, cervical cancer, and genital warts. Because women who undergo hysterectomies for benign conditions are no longer at risk of developing CIN and cervical cancer but can contribute in 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 is assessed. A description of how the simulation and validation is performed, some results using the baseline parameter set, and sensitivity analysis are provided in Section 6. Summary and conclusions are included in Section 7.

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 (Hethcote, 1997). The population is divided into in n age groups defined by the age intervals $[a_{i-1}, a_i]$, where $a_1 < a_2 < \cdots < a_n = \infty$. 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 (1997) 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, 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 women and genital

warts occurrence among both men and women. Similar age groupings have been used by other sexually transmitted diseases models (Garnett and Anderson, 1993a, 1994). By setting the age of sexual debut to 12 years, the model captures HPV transmission and disease that occur before age 15. Recent data suggest age of first sexual intercourse is younger than 15 for some teenagers and adolescents. 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 (Abma and Sonenstein, 2001).

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 sexual partner change per unit time c_{kli}. The number of sexual activity groups considered here are 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 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 naturally at an age- and gender-specific per capita death rate μ_{ki} per year and women 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. The transfer rate d_{ki} is given by Hethcote (1997)

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

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 the Lotka characteristic equations (Hethcote, 1997)

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

where ϱ_b denotes the fraction of females entering cervical screening category b ($\varrho_1 + \varrho_2 = 1$) and N_{kli} denote the number of individuals of gender k in age group i and sexual activity group l.

After taking into account cervical cancer-induced mortality and replacing fertility rates in Hethcote's model (Hethcote, 1997) with gender-specific recruitment rates into sexual activity class l, the demographic model is given by the following system of 102 ($= 17 \times 2 \times 3$) ODEs:

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

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

Table 1 Description of variables and subscripts

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 group 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 against the other type
V_{klib}	Vaccinated against all types
S_{klib}	Vaccinated whose immunity waned
W^h_{klib}	Vaccinated but infected with type h
Q^h_{klib}	Vaccinated and immune against type h
P^h_{klib}	Vaccinated infected with type h, immune against 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 with type h
$ICIS^h_{slib}$	Treated CIS, stage s, infected with type h
$TCIN_{sli}$	Treated CIN, grade s, immune against all types
$TCIS_{sli}$	Treated CIS, stage s, immune against all types
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

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 (Kochanek et al., 2004). Cancer mortality data are obtained from SEER Cancer Statistics age-specific mortality rates, 1997–2002 (Surveillance, Epidemiology, and End Results (SEER) Program, 2004). Because the US population grew at a decennial rate of 13.2% between 1990 and

Table 2 Description of parameters

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 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 new entrants in cervical screening category b
Biological parameters	
$1/\sigma^h_{zki}$	Average duration of immunity from natural infection
γ^h_{ki}	Rate of recovery from HPV infection with type h
$\bar{\gamma}^h_{ki}$	Probability of recovering from type h only, given coinfection
$\bar{\gamma}^h_{ki}$	Probability of recovering from type h only, given CIN regression
$\bar{\gamma}^h_{gki}$	Probability of recovering from type h only, given genital warts regression
θ^h_{ks}	Rate of progression from HPV infection to CIN states
θ^h_{cks}	Rate of progression from coinfection to CIN states
θ^h_{wks}	Rate of progression from breakthrough HPV infection to CIN states
θ^h_{wcks}	Rate of progression from breakthrough coinfection to CIN states
θ^h_{gk}	Rate of progression from HPV infection to genital warts
θ^h_{gwk}	Rate of progression from breakthrough HPV infection to genital warts
θ^h_{gs}	Probability genital warts are asymptomatic and not treated
π^h_{is}	Rate of progression between CIN states or cancer
τ^h_{ks}	Rate of regression from CIN stage s to normal or HPV
τ^h_{ksg}	Rate of regression from CIN stage s to CIN stage g
τ^h_{gk}	Rate of 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 with type h of a vaccinated person
α^h_k	Vaccinated person relative rate of infection with type h clearance
$1/\sigma_{ki}$	Average duration of vaccine protection
χ_{si}	Rate of cervical cancer associated death
ϕ_{k0b}	Percentage of 12 years old 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 rate of CIN stage s
Γ_s	Cure rate of CIN
ψ_s	Percentage of CIN stage s infected after treatment
υ_s	Rate of detection of cervical cancer, stage s
Ω_s	Cure rate of cervical cancer, stage s

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 (Hethcote, 1997). 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 individuals in sexually activity class l given by ω_l, the total number of individuals in sexual activity group l is given by

$$\sum_{i}^{17} N_{kli} = \frac{1}{2}\omega_l \eta.$$

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

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

The initial numbers of other age groups are given by

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

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

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 cancer-induced mortality.

The structure of the over 12 years age US population with 0% and 1.23% annual growth rate together with data from the 2000 population census are plotted in Figs. 1 and 2, respectively. The model fits well for early age groups, underestimate around age 40, and overestimate 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 "baby boom" and immigration.

3. The epidemiologic model

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

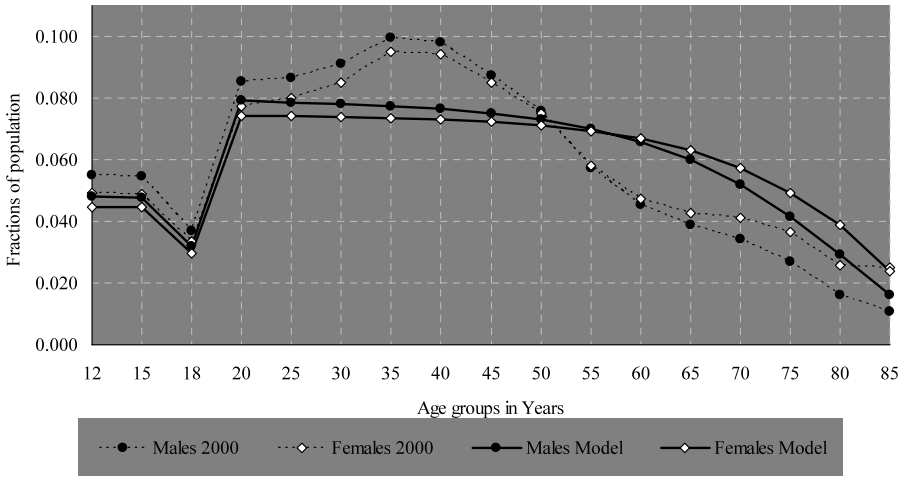

Fig. 1 Age distribution for 2000 US population 12 years and above and model (0% annual growth).

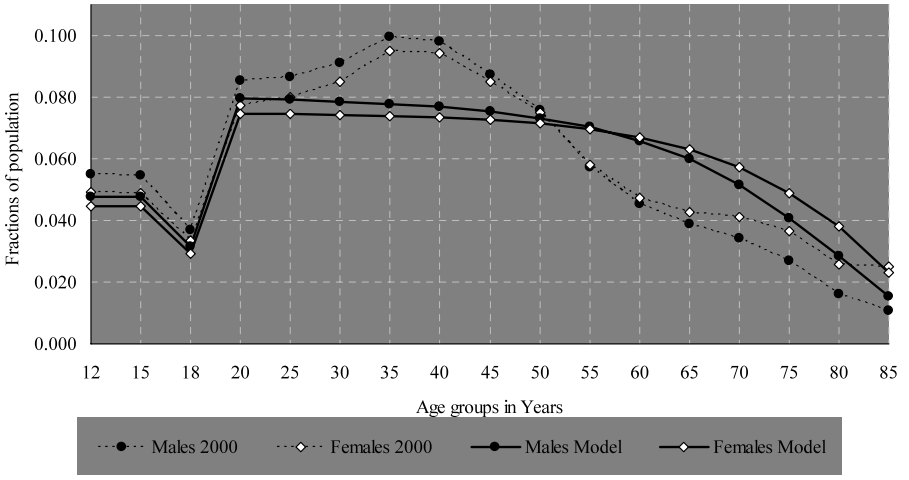

Fig. 2 Age distribution for 2000 US population 12 years and above and model (1.23% annual growth).

3.1. HPV transmission

To simplify the analysis, only three (types $16/18 = 1$, types $6/11 = 2$, and coinfection $=$ 12) HPV types groupings are modeled. The sexually active host population of size η at time t is divided into distinct epidemiologic classes, depending on host's susceptibility to infection or host's status with respect to infection, disease, screening, and treatment. The HPV transmission 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 women who had hysterectomies from those with intact cervices. A schematic representation of the HPV transmission model is shown in Figs. 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 l, and screening category b. A fraction ϕ_{kl0b} of them is vaccinated and move to category V and the remaining fraction enter category X of susceptible individuals. The model also assumes that a proportion ϕ_{klib} of individuals in other age groups and epidemiologic classes is vaccinated 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}, and death from other causes μ_{ki}. Individuals are transferred between age groups at rate d_{ki}. The ODEs for category X are

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

$i = 2, \ldots, 17; l = 1, 2, 3; k = f, m; b = 1, 2; h \in \{1, 2, 12\}$.

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

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

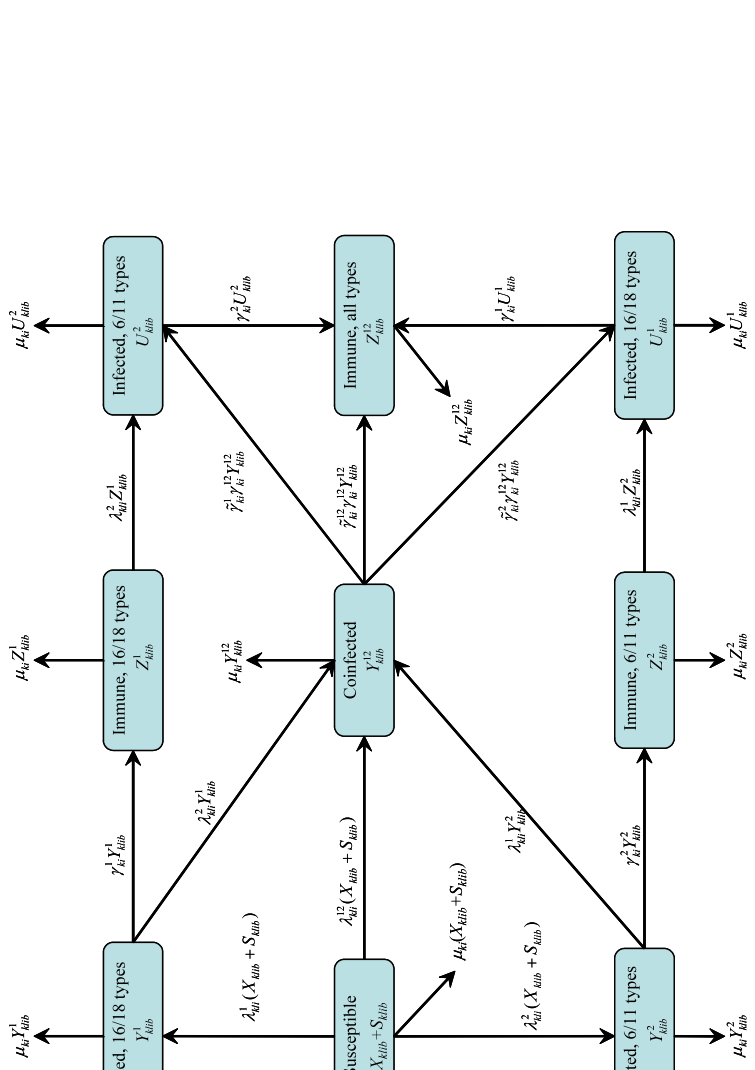

Fig. 3 A simplified schematical presentation of the unvaccinated compartments of the HPV model. Individuals enter the population into the susceptible (X) compartment at rate B_{klb} and leave all compartments at rate μ_{kj}. A susceptible host may be infected with either or both HPV types. Susceptible individuals acquire type h infection at rate λ_{kli}^h. 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_{ki}^h. Co-infected individuals clear infection with type h at rate $\tilde{\gamma}_{ki}^h \gamma_{ki}^{12}$.

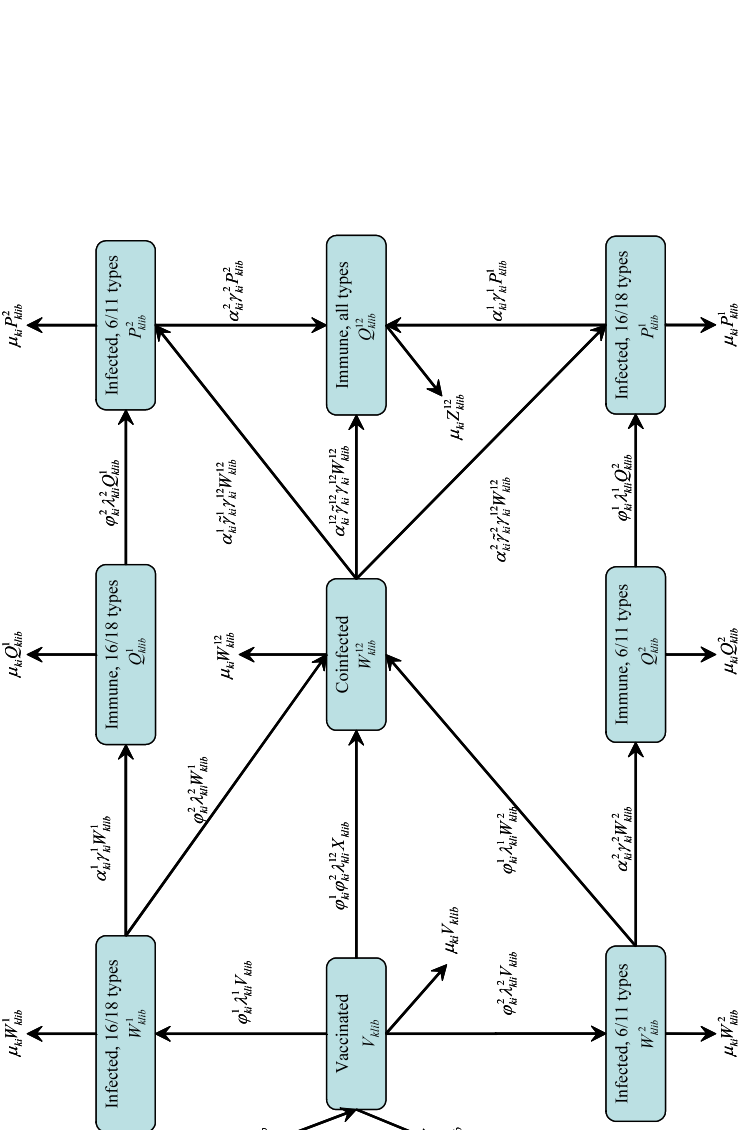

Fig. 4 Schematic presentation of the vaccinated compartments of the HPV model. A fraction of the new susceptible recruits ϕ_{k10b} are vaccinated and move into compartment V. The vaccine provides incomplete protection against the types 16/18 and 6/11 at rates $1-\varphi_{ki}^{1}$ and φ_{ki}^{2}, respectively. A vaccinated person moves into compartment W upon infection with any type. Upon clearance of infection at rate α_{ki}^{h} faster than natural infection, the person moves to compartment Q. The vaccine-induced immunity wanes at rate σ_{ki}.

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

The ODEs for coinfection are given by

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

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 eventually move to the susceptible class X at rate σ^h_{zki}. In the absence of conclusive evidence on whether natural immunity can wane or not, our model includes both the situation where type-specific immunity is long lasting ($\sigma^h_{zki} = 0$) as well as the situation where immunity is temporary ($\sigma^h_{zki} > 0$). 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

$$
\begin{aligned}
dZ^h_{kl1b}/dt &= \gamma^h_{k1}Y^h_{kl1b} + \sum_{s=1}^{3}\bigl\{\bar{\gamma}^h_{k1}\tau^h_{ks}\bigl(CIN^h_{sl1b} + DCIN^h_{sl1b}\bigr) + \gamma^h_{k1}ICIN^h_{sl1b}\bigr\} \\
&\quad + \sum_{s=1}^{2}\gamma^h_{k1}ICIS^h_{sl1b} + \bar{\gamma}^h_{gk1}\tau^h_{gk}\bigl(GW^h_{kl1b} + DGW^h_{kl1b}\bigr) \\
&\quad - \bigl(\lambda^{3-h}_{kl1} + \phi_{kl1b} + \Delta_{k1} + \sigma^h_{zk1} + \mu_{k1} + d_{k1}\bigr)Z^h_{kl1b}, \\
dZ^h_{klib}/dt &= d_{ki-1}Z^h_{kli-1b} + \gamma^h_{ki}Y^h_{klib} + \sum_s\bigl\{\bar{\gamma}^h_{ki}\tau^h_{ks}\bigl(CIN^h_{slib} + DCIN^h_{slib}\bigr) \\
&\quad + \gamma^h_{ki}ICIN^h_{slib}\bigr\} + \sum_{s=1}^{2}\gamma^h_{ki}ICIS^h_{slib} + \bar{\gamma}^h_{gki}\tau^h_{gk}\bigl(GW^h_{klib} + DGW^h_{klib}\bigr) \\
&\quad - \bigl(\lambda^{3-h}_{kli} + \phi_{klib} + \Delta_{ki} + \sigma^h_{zki} + \mu_{ki} + d_{ki}\bigr)Z^h_{klib}.
\end{aligned}
\tag{4}
$$

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

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

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 CIN or genital warts. The ODEs for category U are

$$\begin{aligned}
dU^h_{kl1b}/dt &= \lambda^h_{kl1}Z^{3-h}_{kl1b} + \tilde{\gamma}^{3-h}_{k1}\gamma^{12}_{k1}Y^{12}_{kl1b} \\
&\quad - \left(\phi_{kl1b} + \gamma^h_{k1} + \sum_s \theta^h_{ks} + \theta^h_{gk} + \Delta_{k1} + \mu_{k1} + d_{k1}\right)U^h_{kl1b}, \\
dU^h_{klib}/dt &= d_{ki-1}U^h_{kli-1b} + \lambda^h_{kli}Z^{3-h}_{klib} + \tilde{\gamma}^{3-h}_{ki}\gamma^{12}_{ki}Y^{12}_{klib} \\
&\quad - \left(\phi_{klib} + \gamma^h_{ki} + \sum_s \theta^h_{ks} + \theta^h_{gk} + \Delta_{ki} + \mu_{ki} + d_{ki}\right)U^h_{klib}.
\end{aligned} \tag{5}$$

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_{kli} and enter category V. The vaccine-induced immunity of those in the vaccinated class V wanes, so that people eventually move to the a 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 $\varphi^h_k\lambda^h_{kli}$. The ODEs for category V are

$$\begin{aligned}
dV_{kl1b}/dt &= B_{klb}\phi_{kl0b} + \phi_{kl1b}X_{kl1b} \\
&\quad - \left(\sum_h \varphi^h_k\lambda^h_{kl1} + \sigma_{k1} + \Delta_{k1} + \mu_{k1} + d_{k1}\right)V_{kl1b}, \\
dV_{klib}/dt &= d_{ki-1}V_{kli-1b} + \phi_{klib}X_{klib} \\
&\quad - \left(\sum_h \varphi^h_k\lambda^h_{kli} + \sigma_{ki} + \Delta_{ki} + \mu_{ki} + d_{ki}\right)V_{klib}.
\end{aligned} \tag{6}$$

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

$$
\begin{aligned}
dS_{kl1b}/dt &= \sigma_{k1} V_{kl1b} - \left(\sum_h \lambda_{kl1}^h + \Delta_{k1} + \mu_{k1} + d_{k1} \right) S_{kl1b}, \\
dS_{klib}/dt &= d_{ki-1} S_{kli-1b} + \sigma_{ki} V_{klib} - \left(\sum_h \lambda_{kli}^h + \Delta_{ki} + \mu_{ki} + d_{ki} \right) S_{klib}.
\end{aligned} \tag{7}
$$

3.1.7. Infectious vaccinated individuals W

If vaccinated, individuals infected with one type and susceptible to the other move to category W. 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

$$
\begin{aligned}
dW_{kl1b}^h/dt &= \varphi_k^h \lambda_{kl1}^h V_{kl1b} + \phi_{kl1b} Y_{kl1b}^h \\
&\quad - \left(\varphi_k^{3-h} \lambda_{kl1}^{3-h} + \alpha_{k1}^h \gamma_{k1}^h + \sum_s \theta_{wks}^h + \theta_{gkw}^h + \Delta_{k1} + \mu_{k1} + d_{k1} \right) W_{kl1b}^h, \\
dW_{klib}^h/dt &= d_{ki-1} W_{kli-1b}^h + \varphi_k^h \lambda_{kli}^h V_{klib} + \phi_{klib} Y_{klib}^h \\
&\quad - \left(\varphi_k^{3-h} \lambda_{kli}^{3-h} + \alpha_{ki}^h \gamma_{ki}^h + \sum_s \theta_{wks}^h + \theta_{gkw}^h + \Delta_{ki} + \mu_{ki} + d_{ki} \right) W_{klib}^h.
\end{aligned} \tag{8}
$$

The ODEs for coinfection category W^{12} are

$$
\begin{aligned}
dW_{kl1b}^{12}/dt &= \varphi_k^1 \varphi_k^2 \lambda_{kl1}^{12} V_{kl1b} + \sum_h \varphi_k^h \lambda_{kl1}^h W_{kl1b}^{3-h} + \phi_{kl1b} Y_{kl1b}^{12} \\
&\quad - \left(\alpha_{k1}^{12} \gamma_{k1}^{12} + \sum_s \theta_{wcks}^{12} + \theta_{kgw}^{12} + \Delta_{k1} + \mu_{k1} + d_{k1} \right) W_{kl1b}^{12}, \\
dW_{klib}^{12}/dt &= d_{ki-1} W_{kli-1b}^{12} + \varphi_k^1 \varphi_k^2 \lambda_{kli}^{12} V_{klib} + \sum_h \varphi_k^h \lambda_{kli}^h W_{klib}^{3-h} + \phi_{klib} Y_{klib}^{12} \\
&\quad - \left(\alpha_{ki}^{12} \gamma_{ki}^{12} + \sum_s \theta_{wcks}^{12} + \theta_{gwk}^{12} + \Delta_{ki} + \mu_{ki} + d_{ki} \right) W_{klib}^{12}.
\end{aligned}
$$

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

$$
\begin{aligned}
dQ_{kl1b}^h/dt &= \alpha_{k1}^h \gamma_{k1}^h W_{kl1b}^h + \phi_{kl1b} Z_{kl1b}^h \\
&\quad - \left(\varphi_k^{3-h} \lambda_{kl1}^{3-h} + \Delta_{k1} + \mu_{k1} + d_{k1} \right) Q_{kl1b}^h, \\
dQ_{klib}^h/dt &= d_{ki-1} Q_{kli-1b}^h + \alpha_{ki}^h \gamma_{ki}^h W_{klib}^h + \phi_{klib} Z_{klib}^h \\
&\quad - \left(\varphi_k^{3-h} \lambda_{kli}^{3-h} + \Delta_{ki} + \mu_{ki} + d_{ki} \right) Q_{klib}^h.
\end{aligned} \tag{9}
$$

The ODEs for Q^{12} are

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

3.1.9. Vaccinated, infected individuals with partial immunity P

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

$$\begin{aligned} dP^h_{kl1b}/dt &= \varphi^h_k\lambda^h_{kl1}Q^{3-h}_{kl1b} + \alpha^{3-h}_{k1}\tilde{\gamma}^{3-h}_{k1}\gamma^{12}_{k1}W^{12}_{kl1b} + \phi_{kl1b}U^h_{kl1b} \\ &\quad - \left(\alpha^h_{k1}\gamma^h_{k1} + \sum_s \theta^h_{wks} + \theta^h_{gwk} + \Delta_{k1} + \mu_{k1} + d_{k1}\right)P^h_{kl1b}, \\ dP^h_{klib}/dt &= d_{ki-1}P^h_{kli-1b} + \varphi^h_k\lambda^h_{kli}Q^{3-h}_{klib} + \alpha^{3-h}_{ki}\tilde{\gamma}^{3-h}_{ki}\gamma^{12}_{ki}W^{12}_{klib} + \phi_{klib}U^h_{klib} \\ &\quad - \left(\alpha^h_{ki}\gamma^h_{ki} + \sum_s \theta^h_{wks} + \theta^h_{gwk} + \Delta_{ki} + \mu_{ki} + d_{ki}\right)P^h_{klib}. \end{aligned} \tag{10}$$

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

3.2. Cervical intraepithelial neoplasia CIN

Infected females (whether vaccinated or not) can develop cervical intraepithelial neoplasia (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 (CIN1), CIN grade 2 (CIN2), and CIN grade 3 (CIN3). Females in the CIN and cancer stages are further classified into undetected, 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 $(1-\psi_s)\Gamma_s$. Women in these two states are considered to be at no risk of developing cervical cancer (Myers et al., 2000). However, females with hysterectomies for benign conditions can be infected and are at risk of developing genital warts (Castle et al., 2004). Further, to take into account the fact that treatment of CIN does not completely eliminate the virus, another category of treated CIN that 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 infection is cleared.

An infected woman 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 (Fig. 5). The respective progression rates given coinfection are θ^h_{cfs} and θ^h_{cwfs}. For the base case, it is assumed that coinfection cases progress to CIN according to the rate of HPV 16/18 types. That is, $\theta^1_{cfs} = \theta^1_{fs}$,

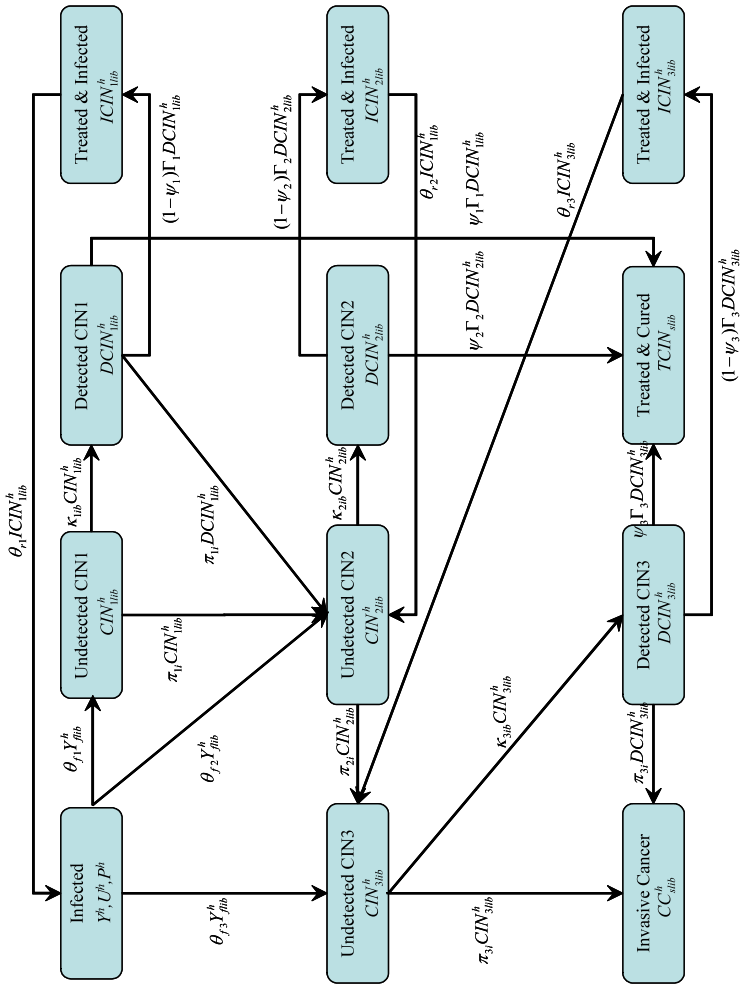

Fig. 5 A simplified schematic presentation of the cervical intraepithelial neoplasia (CIN) model. Females can develop CIN and progress though several histological states: infected with a normal cervix, CIN1, CIN2, CIN3, and early invasive local cervical cancer. Females with CIN can regress to normal with or without HPV infection.

$\theta^2_{cfs} = 0$, $\theta^1_{cwfs} = \theta^1_{wfs}$, and $\theta^2_{cwfs} = 0$. It is assumed that infected women classified as CIN can progress only to higher CIN states (CIN1 to CIN2, CIN2 to CIN3), or cancer state (CIN3 to early invasive localized cervical cancer, LCC) at rate π^h_s, regress to normal at rate τ^h_s or CIN stage 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 move 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. Detection through screening κ_{sib}, spontaneous regression τ^h_{fs}, and progression to higher disease grades π^h_{si} reduce the number of females in this category. ODEs for undetected CIN are

$$
\begin{aligned}
dCIN^h_{1l1b}/dt &= \theta^h_{f1}\big(Y^h_{fl1b} + U^h_{fl1b}\big) + \theta^h_{cf1}Y^{12}_{fl1b} + \theta^h_{wf1}\big(W^h_{fl1b} + P^h_{fl1b}\big) \\
&\quad + \theta^h_{wcf1}W^{12}_{fl1b} + \theta^h_{r1}ICIN^h_{1l1b} + \tau^h_{f21}CIN^h_{2l1b} + \tau^h_{f31}CIN^h_{3l1b} \\
&\quad - \big(\tau^h_{f1} + \pi^h_{11} + \Delta_{f1} + \kappa_{11b} + \mu_{f1} + d_{f1}\big)CIN^h_{1l1b}, \\
dCIN^h_{1lib}/dt &= d_{fi-1}CIN^h_{1li-1b} + \theta^h_{f1}\big(Y^h_{flib} + U^h_{flib}\big) + \theta^h_{cf1}Y^{12}_{flib} \\
&\quad + \theta^h_{wfi}\big(W^h_{flib} + P^h_{flib}\big) + \theta^h_{wcfi}W^{12}_{flib} + \theta_{rs}ICIN^h_{1lib} \\
&\quad + \tau^h_{f21}CIN^h_{2lib} + \tau^h_{f31}CIN^h_{3lib} \\
&\quad - \big(\tau^h_{f1} + \pi^h_{1i} + \Delta_{fi} + \kappa_{1ib} + \mu_{fi} + d_{fi}\big)CIN^h_{1lib}, \\
dCIN^h_{sl1b}/dt &= \theta^h_{fs}\big(Y^h_{fl1b} + U^h_{fl1b}\big) + \theta^h_{cfs}Y^{12}_{fl1} + \theta^h_{wfs}\big(W^h_{fl1b} + P^h_{fl1b}\big) \\
&\quad + \theta^h_{wcfs}W^{12}_{fl1b} + \theta^h_{rs}ICIN^h_{1l1b} + \pi^h_{s-11}\big(CIN^h_{s-1l1b} + DCIN^h_{s-1l1b}\big) \\
&\quad + \tau^h_{fs+1s}CIN^h_{s+1l1b} - \big(\tau^h_{fs} + \tau^h_{fss-1} + \tau^h_{fss-2} + \pi^h_{s1} + \Delta_{f1} \\
&\quad + \kappa_{s1b} + \mu_{f1} + d_{f1}\big)CIN^h_{sl1b}, \\
dCIN^h_{slib}/dt &= d_{fi-1}CIN^h_{sli-1b} + \theta^h_{fs}\big(Y^h_{flib} + U^h_{flib}\big) + \theta^h_{cfs}Y^{12}_{flib} \\
&\quad + \theta^h_{wfs}\big(W^h_{flib} + P^h_{flib}\big) + \theta^h_{wcfi}W^{12}_{flib} + \theta^h_{rs}ICIN^h_{1lib} \\
&\quad + \pi^h_{s-1i}\big(CIN^h_{s-1lib} + DCIN^h_{s-1lib}\big) + \tau^h_{fs+1s}CIN^h_{s+1lib} \\
&\quad - \big(\tau^h_{fs} + \tau^h_{fss-1} + \tau^h_{fss-2} + \pi^h_{si} + \Delta_{fi}\kappa_{sib} + \mu_{fi} + d_{fi}\big)CIN^h_{slib},
\end{aligned}
\tag{11}
$$

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 Γ_s, a CIN can progress to a higher grade π^h_{si}. Equations for detected CIN are

$$\begin{aligned} dDCIN^h_{sl1b}/dt &= \kappa_{s1b} CIN^h_{sl1b} - \left(\tau^h_{fs} + \pi^h_{s1} + \Delta_{f1} + \Gamma_s + \mu_{f1} + d_{f1}\right) DCIN^h_{sl1b}, \\ dDCIN^h_{slib}/dt &= d_{fi-1} DCIN^h_{sli-1b} + \kappa_{sib} CIN^h_{slib} \\ &\quad - \left(\tau^h_{fs} + \pi^h_{si} + \Delta_{fi} + \Gamma_s + \mu_{fi} + d_{fi}\right) DCIN^h_{slib}, \end{aligned} \tag{12}$$

where $s = 1, 2, 3$.

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

$$\begin{aligned} dTCIN_{sl1}/dt &= (1-\psi_s)\Gamma_s \sum_h \sum_b DCIN^h_{sl1b} - (\Delta_{f1} + \mu_{f1} + d_{f1}) TCIN_{sl1}, \\ dTCIN_{sli}/dt &= d_{fi-1} TCIN_{li-1} + (1-\psi_s)\Gamma_s \sum_h \sum_b DCIN^h_{slib} \\ &\quad - (\Delta_{fi} + \mu_{fi} + d_{fi}) TCIN_{sli}, \end{aligned} \tag{13}$$

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

$$\begin{aligned} dICIN^h_{sl1b}/dt &= \psi_s \Gamma_s DCIN^h_{sl1b} - \left(\gamma^h_{f1} + \theta^h_{rs} + \Delta_1 + \mu_{f1} + d_{f1}\right) ICIN^h_{sl1b}, \\ dICIN^h_{slib}/dt &= d_{fi-1} ICIN^h_{sli-1b} + \psi_s \Gamma_s DCIN^h_{slib} \\ &\quad - \left(\gamma^h_{fi} + \theta^h_{rs} + \Delta_i + \mu_{fi} + d_{fi}\right) ICIN^h_{slib}, \end{aligned} \tag{14}$$

where $s = 1, 2, 3$.

3.3. Cervical carcinoma in situ CIS

It is assumed that females classified as CIN can progress to carcinoma in situ (CIS). Because women spend, on average, a long time in CIS, two CIS states are modeled (CIS1 and CIS2). It is assumed that regression from CIS states is not possible. The 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 CIN3 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

$$\begin{aligned}
dCIS^h_{1l1b}/dt &= \theta^h_{r4} ICIS^h_{1l1b} + \pi^h_{31}\left(CIN^h_{3l1b} + DCIN^h_{3l1b}\right) \\
&\quad - \left(\pi^h_{41} + \Delta_{f1} + \kappa_{41b} + \mu_{f1} + d_{f1}\right) CIS^h_{1l1b}, \\
dCIS^h_{1lib}/dt &= d_{fi-1} CIS^h_{1li-1b} + \theta^h_{r4} ICIS^h_{1lib} + \pi^h_{3i}\left(CIN^h_{3lib} + DCIN^h_{3lib}\right) \\
&\quad - \left(\pi^h_{4i} + \Delta_{fi} + \kappa_{4ib} + \mu_{fi} + d_{fi}\right) CIN^h_{1lib}, \\
dCIS^h_{2l1b}/dt &= \theta^h_{r5} ICIS^h_{2l1b} + \pi^h_{41}\left(CIS^h_{1l1b} + DCIS^h_{1l1b}\right) \\
&\quad - \left(\pi^h_{51} + \Delta_{f1} + \kappa_{51b} + \mu_{f1} + d_{f1}\right) CIS^h_{2l1b}, \\
dCIS^h_{2lib}/dt &= d_{fi-1} CIS^h_{2li-1b} + \theta^h_{r5} ICIS^h_{2lib} + \pi^h_{4i}\left(CIS^h_{2lib} + DCIS^h_{2lib}\right) \\
&\quad - \left(\pi^h_{51} + \Delta_{f1} + \kappa_{51b} + \mu_{f1} + d_{f1}\right) CIS^h_{2l1b}.
\end{aligned} \tag{15}$$

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}, a CIS can progress to a higher grade π^h_{3+si} or cancer. ODEs for detected CIS are

$$\begin{aligned}
dDCIS^h_{sl1b}/dt &= \kappa_{3+s1b} CIS^h_{sl1b} - \left(\pi^h_{3+s1} + \Delta_{f1} + \Gamma_{3+s} + \mu_{f1} + d_{f1}\right) DCIS^h_{sl1b}, \\
dDCIS^h_{slib}/dt &= d_{fi-1} DCIS^h_{sli-1b} + \kappa_{3+sib} CIS^h_{slib} \\
&\quad - \left(\pi^h_{3+si} + \Delta_{fi} + \Gamma_{3+s} + \mu_{fi} + d_{fi}\right) DCIS^h_{slib},
\end{aligned} \tag{16}$$

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 $ICIS_s$. ODEs for treated CIN are

$$\begin{aligned}
dTCIS_{sl1}/dt &= (1 - \psi_{3+s})\Gamma_{3+s} \sum_h \sum_b DCIS^h_{sl1b} - (\Delta_{f1} + \mu_{f1} + d_{f1}) TCIS_{sl1}, \\
dTCIS_{sli}/dt &= d_{fi-1} TCIS_{li-1} + (1 - \psi_{3+s})\Gamma_{3+s} \sum_h \sum_b DCIS^h_{3+slib} \\
&\quad - (\Delta_{fi} + \mu_{fi} + d_{fi}) TCIS_{sli},
\end{aligned} \tag{17}$$

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 recurring CIS move to category CIS_s. Infection can also resolve and individuals enter category Z^h. ODEs for treated but infectious CIS are

$$\begin{aligned} dICIS^h_{sl1b}/dt &= \psi_{3+s}\Gamma_{3+s}DCIS^h_{sl1b} - \left(\gamma^h_{f1} + \theta^h_{r3+s} + \Delta_1 + \mu_{f1} + d_{f1}\right)ICIS^h_{sl1b}, \\ dICIS^h_{slib}/dt &= d_{fi-1}ICIS^h_{sli-1b} + \psi_{3+s}\Gamma_{3+s}DCIS^h_{slib} \\ &\quad - \left(\gamma^h_{fi} + \theta^h_{r3+s} + \Delta_i + \mu_{fi} + d_{fi}\right)ICIS^h_{slib}, \end{aligned} \tag{18}$$

where $s = 1, 2$.

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 (Fig. 6). Females in cancer stages are further classified into undetected, detected, or treated classes. A woman 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 women who were successfully treated for invasive cancer are no longer infectious.

3.4.1. Undetected cervical cancer CC_s

CIS2 cases that are not detected and treated can progress to localized cervical cancer at rate π^h_{3i}. Undetected cancer cases, if undetected at rate υ_{sib}, can progress to advanced stages at rate π_s, $s = L, R$. Cervical cancer has an additional mortality rate χ_{si}. Equations for undetected CC are

$$\begin{aligned} dCC^h_{Ll1b}/dt &= \pi^h_{51}\left(CIS^h_{2l1b} + DCIS^h_{2l1b}\right) - (\pi_L + \upsilon_{L1b} + \chi_{L1} + \mu_{f1} + d_{f1})CC^h_{Ll1b}, \\ dCC^h_{Llib}/dt &= d_{fi-1}CC^h_{Lli-1b} + \pi^h_{5i}\left(CIS^h_{5lib} + DCIS^h_{5lib}\right) \\ &\quad - (\pi_L + \upsilon_{Lib} + \chi_{Li} + \mu_{fi} + d_{fi})CC^h_{Llib}, \\ dCC^h_{Rl1b}/dt &= \pi_L CC^h_{Ll1b} - (\pi_R + \upsilon_{R1b} + \chi_{R1} + \mu_{f1} + d_{f1})CC^h_{Rl1b}, \\ dCC^h_{Rlib}/dt &= d_{fi-1}CC^h_{Rli-1b} + \pi_L CC^h_{Llib} \\ &\quad - (\pi_D + \upsilon_{Rib} + \chi_{Ri} + \mu_{fi} + d_{fi})CC^h_{Rlib}, \\ dCC^h_{Dl1b}/dt &= \pi_R CC^h_{Rl1b} - (\upsilon_{D1b} + \chi_{D1} + \mu_{f1} + d_{f1})CC^h_{Dl1b}, \\ dCC^h_{Dlib}/dt &= \pi_R CC^h_{Rlib} + d_{fi-1}CC^h_{Dli-1b} - (\upsilon_{Dib} + \chi_{Di} + \mu_{fi} + d_{fi})CC^h_{Dlib}, \end{aligned} \tag{19}$$

where $i \geq 2$.

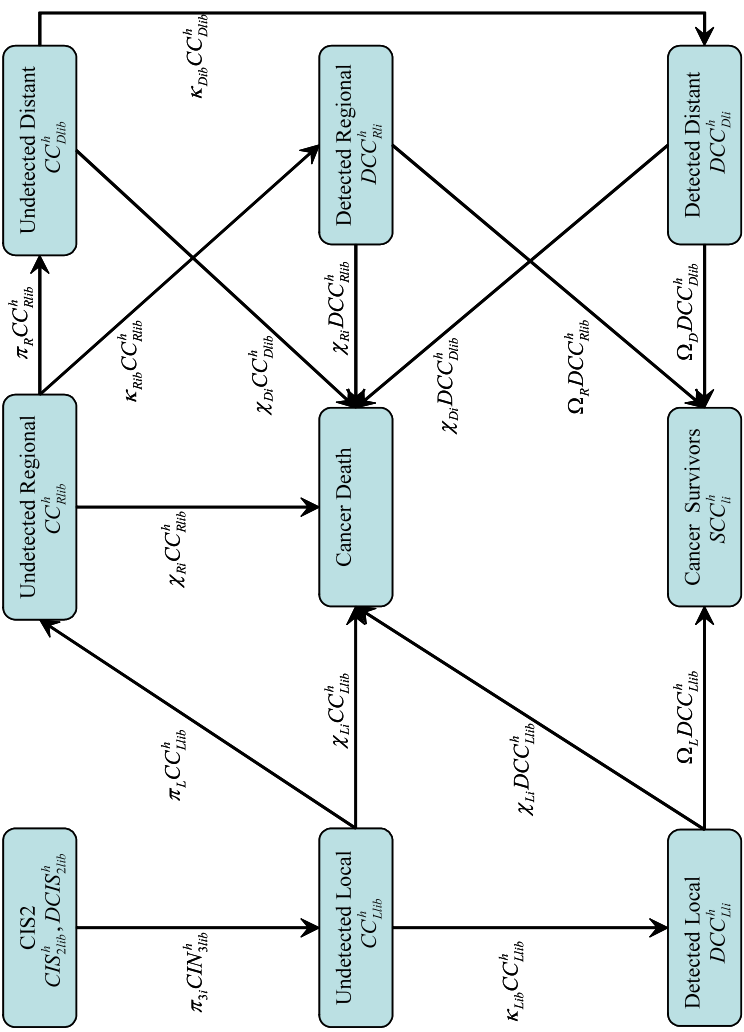

Fig. 6 Schematic presentation of the cervical cancer (CC) model. Females can develop cervical cancer from cervical intraepithelial neoplasia stage 3 (CIN3) and progress though several cancer stages: early invasive local cervical cancer, regional late invasive cervical cancer, and distant late invasive 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_{xi}.

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

$$\begin{aligned} dDCC_{sl1}/dt &= \sum_h \sum_b \upsilon_{s1b} CC^h_{sl1b} - (\Omega_s + \chi_{s1} + \mu_{f1} + d_{f1}) DCC_{sl1}, \\ dDCC_{sli}/dt &= d_{fi-1} DCC_{sli-1} + \sum_h \sum_b \upsilon_{sib} CC^h_{slib} \\ &\quad - (\Omega_s + \chi_{si} + \mu_{fi} + d_{fi}) DCC_{sli}, \end{aligned} \tag{20}$$

where $s = L, R, D$.

3.4.3. Cervical cancer survivors SCC

Equations for cancer survivors

$$\begin{aligned} dSCC_{l1}/dt &= \sum_s \Omega_s DCC_{sl1} - (\mu_{f1} + d_{f1}) SCC_{l1}, \\ dSCC_{li}/dt &= d_{fi-1} SCC_{li-1} + \sum_s \Omega_s DCC_{sli} - (\mu_{fi} + d_{fi}) SCC_{li}. \end{aligned} \tag{21}$$

3.5. Genital warts

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_{kg} move to class Z. It is assumed that only infection with HPV 6/11 types can cause genital warts whereas infection with HPV 16/18 types does not lead to genital warts (Winer et al., 2005). The asymptomatic genital warts class consists of following ODEs

$$\begin{aligned} dGW^2_{kl1b}/dt &= \theta_{gs}\big[\theta^2_{gk}\big(Y^2_{kl1b} + U^2_{kl1b}\big) + \theta^{12}_{gk} Y^{12}_{kl1b} + \theta^2_{gwk}\big(W^2_{kl1b} + P^2_{kl1b}\big) \\ [2mm] &\quad + \theta^{12}_{gwk} W^{12}_{kl1b}\big] - \big(\tau^2_{gk} + \Delta_{k1} + \mu_{k1} + d_{k1}\big) GW^2_{kl1b}, \\ dGW^2_{klib}/dt &= d_{ki-1} GW^2_{kli-1b} + \theta_{gs}\big[\theta^2_{gk}\big(Y^2_{klib} + U^2_{klib}\big) + \theta^{12}_{gk} Y^{12}_{klib} \\ &\quad + \theta^2_{gwk}\big(W^2_{klib} + P^2_{klib}\big) + \theta^{12}_{gwk} W^{12}_{klib}\big] \\ &\quad - \big(\tau^2_{gk} + \Delta_{ki} + \mu_{ki} + d_{ki}\big) GW^2_{kl1b}. \end{aligned} \tag{22}$$

The symptomatic genital warts class consists of the following ODEs

$$\begin{aligned} dDGW^2_{kl1b}/dt &= (1 - \theta_{gs})\big[\theta^2_{gk}\big(Y^2_{kl1b} + U^2_{kl1b}\big) + \theta^{12}_{gk} Y^{12}_{kl1b} \\ &\quad + \theta^2_{gwk}\big(W^2_{kl1b} + P^2_{kl1b}\big) + \theta^{12}_{gwk} W^{12}_{kl1b}\big] \\ &\quad - \big(\tau^2_{gk} + \Delta_{k1} + \mu_{k1} + d_{k1}\big) DGW^2_{kl1b}, \\ dDGW^2_{klib}/dt &= d_{ki-1} GW^2_{kli-1b} + (1 - \theta_{gs})\big[\theta^2_{gk}\big(Y^2_{klib} + U^2_{klib}\big) \\ &\quad + \theta^{12}_{gk} Y^{12}_{klib} + \theta^2_{gwk}\big(W^2_{klib} + P^2_{klib}\big) + \theta^{12}_{gwk} W^{12}_{klib}\big] \\ &\quad - \big(\tau^2_{gk} + \Delta_{ki} + \mu_{ki} + d_{ki}\big) DGW^2_{klib}. \end{aligned} \tag{23}$$

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

$$dHX_{fl1}/dt = \sum_b \left(\Delta_{f1} X_{fl1b} + \sum_h \sigma^h_{zf1} HZ^h_{fl1b} \right) - \left(\sum_h \lambda^h_{fl1} + \mu_{f1} + d_{f1} \right) HX_{fl1},$$

$$dHX_{fli}/dt = d_{fi-1} HX_{fli-1} + \sum_b \left(\Delta_{fi} X_{flib} + \sum_h \sigma^h_{zfi} HZ^h_{flib} \right) - \left(\sum_h \lambda^h_{fli} + \mu_{fi} + d_{fi} \right) HX_{fli},$$

3.6.2. Infected individuals HY

The ODEs for category HY are

$$dHY^h_{fl1}/dt = \lambda^h_{fl1}(HX_{fl1} + HS_{fl1}) - \left(\lambda^{3-h}_{fl1} + \gamma^h_{f1} + \theta^h_{gf} + \mu_{f1} + d_{f1}\right) HY^h_{fl1} + \sum_b \Delta_{f1} \left[Y^h_{fl1b} + \sum_s \left(CIN^h_{sl1b} + DCIN^h_{sl1b} + ICIN^h_{sl1b} \right) \right],$$

$$dHY^h_{fli}/dt = d_{fi-1} HY^h_{fli-1} + \lambda^h_{fli}(HX_{fli} + HS_{fli}) - \left(\lambda^{3-h}_{fli} + \gamma^h_{fi} + \theta^h_{gf} + \mu_{fi} + d_{fi}\right) HY^h_{fli} + \sum_b \Delta_{fi} \left[Y^h_{flib} + \sum_s \left(CIN^h_{slib} + DCIN^h_{slib} + ICIN^h_{slib} \right) \right].$$

The ODEs for HY^{12} are

$$dHY^{12}_{fl1}/dt = \lambda^{12}_{fl1}(HX_{fl1} + HS_{fl1}) + \sum_h \lambda^h_{fl1} HY^{3-h}_{fl1} + \Delta_{f1} \sum_b Y^{12}_{fl1b} - \left(\gamma^{12}_{f1} + \theta^{12}_{gf} + \mu_{f1} + d_{f1}\right) HY^{12}_{fl1},$$

$$dHY^{12}_{fli}/dt = d_{fi-1} HY^{12}_{fli-1} + \lambda^{12}_{fli}(HX_{fli} + HS_{fli}) + \sum_h \lambda^h_{fli} HY^{3-h}_{fli} + \Delta_{fi} \sum_b Y^{12}_{flib} - \left(\gamma^{12}_{fi} + \theta^{12}_{gf} + \mu_{fi} + d_{fi}\right) HY^{12}_{fli}.$$

3.6.3. Partially immune individuals HZ
The ODEs for category *HZ* are

$$\begin{aligned}
dHZ^h_{fl1}/dt &= \gamma^h_{f1} HY^h_{fl1} + \Delta_{f1} \sum_b Z^h_{fl1b} + \tau^h_{gf}\big(HGW^h_{fl1} + DHGW^h_{fl1}\big) \\
&\quad - \big(\lambda^{3-h}_{fl1} + \sigma^h_{zfl1} + \mu_{f1} + d_{f1}\big) HZ^h_{fl1}, \\
dHZ^h_{fli}/dt &= d_{fi-1} HZ^h_{fli-1} + \gamma^h_{fi} HY^h_{fli} + \Delta_{fi} \sum_b Z^h_{flib} \\
&\quad + \tau^h_{gf}\big(HGW^h_{fli} + DHGW^h_{fli}\big) - \big(\lambda^{3-h}_{fli} + \sigma^h_{zfli} + \mu_{fi} + d_{fi}\big) HZ^h_{fli}.
\end{aligned}$$

The ODEs for HZ^{12} are

$$\begin{aligned}
dHZ^{12}_{fl1}/dt &= \tilde{\gamma}^{12}_{f1} \gamma^2_{f1} HY^{12}_{fl1} + \sum_h \gamma^h_{f1} HU^h_{fl1} + \Delta_{f1}\left(\sum_b Z^{12}_{fl1b} + \sum_s TCIN_{sl1}\right) \\
&\quad - \big(\sigma^{12}_{zfl1} + \mu_{f1} + d_{f1}\big) HZ^{12}_{fl1}, \\
dHZ^{12}_{fli}/dt &= d_{fi-1} HZ^{12}_{fli-1} + \tilde{\gamma}^{12}_{fi} \gamma^2_{fi} HY^{12}_{fli} + \sum_h \gamma^h_{fi} U^h_{flib} \\
&\quad + \Delta_{fi}\left(\sum_b Z^{12}_{flib} + \sum_s TCIN_{sli}\right) - \big(\sigma^h_{zfli} + \mu_{fi} + d_{fi}\big) HZ^{12}_{fli}.
\end{aligned}$$

3.6.4. Infected individuals with partial immunity HU
The ODEs for category *HU* are

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

3.6.5. Vaccinated individuals HV
The ODEs for category *HV* are

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

3.6.6. Vaccinated individuals with waned immunity HS
The ODEs for classes *HS* are

$$dHS_{fl1}/dt = \sigma_{f1} HV_{fl1} + \Delta_{f1} \sum_b S_{fl1b} - \left(\sum_h \lambda^h_{fl1} + \Delta_{f1} + \mu_{f1} + d_{f1} \right) HS_{fl1},$$

$$dHS_{fli}/dt = d_{fi-1} HS_{fli-1} + \sigma_{fi} HV_{fli} + \Delta_{fi} \sum_b S_{flib} - \left(\sum_h \lambda^h_{fli} + \mu_{fi} + d_{fi} \right) HS_{fli}.$$

3.6.7. Infectious vaccinated individuals HW
The ODEs for category *HW* are

$$dHW^h_{fl1}/dt = \varphi^h_f \lambda^h_{fl1} HV_{fl1} + \Delta_{f1} \sum_b W^h_{fl1b} - \left(\varphi^{3-h}_f \lambda^{3-h}_{fl1} + \alpha^h_{f1} \gamma^h_{f1} + \theta^h_{gfw} + \mu_{f1} + d_{f1}\right) HW^h_{fl1},$$

$$dHW^h_{fli}/dt = d_{fi-1} HW^h_{fli-1} + \varphi^h_f \lambda^h_{fli} HV_{fli} + \Delta_{fi} \sum_b W^h_{flib} - \left(\varphi^{3-h}_f \lambda^{3-h}_{fli} + \alpha^h_{fi} \gamma^h_{fi} + \theta^h_{gfw} + \mu_{fi} + d_{fi}\right) HW^h_{fli}.$$

The ODEs for HW^{12} are

$$dHW^{12}_{fl1}/dt = \varphi^1_f \varphi^2_f \lambda^{12}_{fl1} HV_{fl1} + \sum_h \varphi^h_f \lambda^h_{fl1} HW^{3-h}_{fl1} + \Delta_{f1} \sum_b W^{12}_{fl1b} - \left(\alpha^{12}_{f1} \gamma^{12}_{f1} + \theta^{12}_{gwf} + \mu_{f1} + d_{f1}\right) HW^{12}_{fl1},$$

$$dHW^{12}_{fli}/dt = d_{fi-1} HW^{12}_{fli-1} + \varphi^1_f \varphi^2_f \lambda^{12}_{fli} HV_{fli} + \sum_h \varphi^h_f \lambda^h_{fli} HW^{3-h}_{fli} + \Delta_{fi} \sum_b W^{12}_{flib} - \left(\alpha^{12}_{fi} \gamma^{12}_{fi} + \theta^{12}_{gwf} + \mu_{fi} + d_{fi}\right) HW^{12}_{fli}.$$

3.6.8. Vaccinated, partially immune individuals HQ
The ODEs for category *HQ* are

$$dHQ^h_{fl1}/dt = \alpha^h_{f1} \gamma^h_{f1} HW^h_{fl1} + \Delta_{f1} \sum_b Q^h_{fl1b} - \left(\varphi^{3-h}_f \lambda^{3-h}_{fl1} + \mu_{f1} + d_{f1}\right) HQ^h_{fl1},$$

$$dHQ^h_{fli}/dt = d_{fi-1} HQ^h_{fli-1} + \alpha^h_{fi} \gamma^h_{fi} HW^h_{fli} + \Delta_{fi} \sum_b Q^h_{flib} - \left(\varphi^{3-h}_f \lambda^{3-h}_{fli} + \mu_{fi} + d_{fi}\right) HQ^h_{fli}.$$

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

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

3.6.10. Genital warts HGW
The genital warts class consists of following ODEs

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

The symptomatic genital warts class consists of the following ODEs

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

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 sexual partnerships and way they form partnerships with individuals of the opposite gender k', the fraction of infected sexual partners, and the transmission probability β^h_k per partnership. The force of HPV infection λ^h_{kli} is given by

$$\begin{aligned}
\lambda^h_{mli} = \beta^h_m \sum_{j=1}^{17}\sum_{a=1}^{3} c_{mlaij}\rho_{mlaij}\Bigg(\sum_{b=1}^{2}\Bigg[& r_f\big(W^h_{fajb} + P^h_{fajb} + W^{12}_{fajb}\big) + Y^h_{fajb} \\
& + Y^{12}_{fajb} + U^h_{fajb} + \sum_{s}^{3}\big(CIN^h_{sajb} + DCIN^h_{sajb} + ICIN^h_{sajb}\big) + GW^h_{fajb} \\
& + DGW^h_{fajb} + \sum_{g}^{L,R,D} CC^h_{gajb} + \sum_{s}^{2}\big(CIS^h_{sajb} + DCIS^h_{sajb} + ICIS^h_{sajb}\big)\Bigg] \\
& + r_f\big(HP^h_{faj} + HW^h_{faj} + HW^{12}_{faj}\big) + HU^h_{faj} + HY^{12}_{faj} \\
& + HGW^h_{faj} + DHGW^h_{faj}\Bigg)/N_{faj}, \\
\lambda^h_{fli} = \beta^h_f \sum_{j=1}^{17}\sum_{a=1}^{3} c_{flaij}\rho_{flaij}\big(Y^h_{maj} + U^h_{maj} + Y^{12}_{maj} + GW^h_{maj} + DGW^h_{maj} \\
& + r_m\big(W^h_{maj} + W^{12}_{maj} + P^h_{maj}\big)\big)/N_{maj},
\end{aligned} \tag{24}$$

$h = 1, 2$. Coinfection occurs at

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

3.8. Mixing preferences

3.8.1. Mixing matrix ρ

The way sexual 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 has a partner from the opposite gender from sexual activity group m, age class j.

This depends on the proportion of sexual 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 $\epsilon_1 = \epsilon_2 = 1$ (Garnett and Anderson, 1993a, 1993b, 1994; Garnett et al., 1996). The mixing matrix ρ_{klmij} is given by

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

The model should satisfy the constraints balancing the supply and demand of 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 sexual partner change as functions of the initial imbalance in the supply and demand of sexual partnerships. Thus,

$$c_{klmij} = c_{kli}B_{lmij}^{0.5},$$

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 sexual partnerships. There are few options for rectifying this. One option is to let the rates of sexual 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 sexual partner change vary over time so as to balance the supply of and demand for sexual partnerships (Garnett and Anderson, 1994). However, this latter option requires adding additional ODEs 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 (Garnett and Anderson, 1993a, 1993b, 1994; Garnett et al., 1996), 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

Table 3 Baseline behavioral parameter values for the sexually active population

Activity group	Proportion of population, %		Relative partner acquisition rate (RPAR), pc_l	Reference (Lauman et al., 1994)
	Males, ω_m	Females, ω_f		
1 (highest)	2.56	2.56	11.29	
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		(Abma and Sonenstein, 2001)
15–17	1.18	0.3		(Abma and Sonenstein, 2001)
18–19	2.42	1.3		(Lauman et al., 1994)
20–24	2.61	1.3		(Lauman et al., 1994)
25–29	2.55	1.3		(Lauman et al., 1994)
30–34	1.72	1.3		(Lauman et al., 1994)
35–39	1.65	1.3		(Lauman et al., 1994)
40–44	1.53	1.3		(Lauman et al., 1994)
45–49	1.38	1.3		(Lauman et al., 1994)
50–54	1.25	1.3		(Lauman et al., 1994)
55–59	1.00	1.3		(Lauman et al., 1994)
60–69	0.61	0.5		Assumed
≥70	0.44	0.5		Assumed
	Males, N_m	Females, N_f		
Population size	50,000	50,000		

the parameters ϵ_1 and ϵ_2 whose respective values are set to 0.6 and 0.7 in the baseline analysis and varied by ±20% in the sensitivity analysis. These estimates are obtained from the National Health and Social Life Survey (NHSLS) (Lauman et al., 1994; Michael et al., 1994, 1998). Higher values for ϵ_2 are reported for high-risk populations. For example, Garnett et al. (1996) 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 sexual 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 (1993a, 1994). 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 sexual partner change for individuals in age groups 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 sexual partner change rate for individuals in the age groups 18–59. 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 (Lauman et al., 1994). 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 (Abma and

Sonenstein, 2001). It is assumed 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 ($i = 1, 2, \ldots, 17$) 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,

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

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 ODEs in the entire model is 7,191.

3.10. Estimates of epidemiological parameters

A comprehensive search of the literature was conducted in order to obtain baseline values for the biological and other epidemiological parameters.

3.10.1. Estimates of natural history parameters

The values of biological parameters are reported in Tables 4 and 5. The way these estimates were derived is explained elsewhere (Insinga et al., 2006).

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

Parameter	Estimate	Reference
Probability of transmission per partnership		(Hughes et al., 2002)
From males to females	0.8	
From females to males	0.7	
Mean duration of HPV infection, years		(Insinga et al., 2007)
HPV 16/18, $1/(\gamma_{ki}^1 + \sum_s \theta_{ks}^1)$	1.2	
HPV 6/11, $1/(\gamma_{ki}^2 + \theta_{kg}^2 + \sum_s \theta_{ks}^2)$	0.7	
Rate of waning natural immunity, σ_{zki}^h, per year	0	
Progression in the presence of HPV 16/18 per year, %		
Normal to CIN1, θ_{k1}^1	9.4	(Hoyer et al., 2005)
Normal to CIN2, θ_{k2}^1	5.8	(Winer et al., 2005)
Normal to CIN3, θ_{k3}^1	5.3	(Winer et al., 2005)
CIN1 to CIN2, π_{1i}^1	13.6	(Insinga, 2007)
CIN2 to CIN3, π_{2i}^1	14	(De Aloysio et al., 1994; Kataja et al., 1989)
CIN3 to CIS1, π_{3i}^1	42	(Kataja et al., 1989; Westergaard and Norgaard, 1981)
CIS1 to CIS2, π_{4i}^1	5	
CIS to LCC, π_{5i}^1	18	
LCC to RCC, π_{Li}^1	10	(Goldie et al., 2004; Sanders and Taira, 2003; Myers et al., 2000)
RCC to DCC, π_{Ri}^1	30	(Myers et al., 2000)
Progression in the presence of HPV 6/11 per year, %		
Normal to CIN1, θ_{k1}^2	9.5	(Insinga, 2007)
Normal to CIN2, θ_{k2}^2	1.9	(Insinga, 2007; Aoyama et al., 1998; Evans et al., 2002; Isacson et al., 1996; Quade et al., 1998)
CIN1 to CIN2, π_{1i}^2	0	(Insinga, 2007; Aoyama et al., 1998; Evans et al., 2002; Isacson et al., 1996; Quade et al., 1998)
Normal to genital warts, θ_{kg}^2	57	(Winer et al., 2005)
Regression in the presence of HPV 16/18 per year, %		
CIN1 to normal/HPV, τ_{f1}^1	32.9	(Insinga, 2007; Sastre-Garau et al., 2004)
CIN2 to normal/HPV, τ_{f2}^1	31	(Kataja et al., 1989; De Aloysio et al., 1994; Matsumoto et al., 2006)
CIN2 to CIN1, τ_{f21}^1	13.3	(De Aloysio et al., 1994)
CIN3 to normal/HPV, τ_{f3}^1	11	(Kataja et al., 1989)
CIN3 to CIN1, τ_{f31}^1	3	(De Aloysio et al., 1994; Kataja et al., 1989)
CIN3 to CIN2, τ_{f32}^1	3	(De Aloysio et al., 1994; Kataja et al., 1989)

Table 4 (*Continued*)

Parameter	Estimate	Reference
Regression in the presence of HPV 6/11 per year, %		
CIN1 to normal/HPV, τ^2_{f1}	55.2	
CIN2 to CIN1, τ^2_{f21}	13.3	(De Aloysio et al., 1994)
Genital warts to normal/HPV, τ^2_{gk}	87.5	(Winer et al., 2005)
Hysterectomy rate, % per year, Δ_i		(Keshavarz et al., 2002)
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	
≥55 years	0.36	

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

Parameter	Estimate	Reference
Age-specific cervical cancer mortality rates, per year, %		(Surveillance, Epidemiology, and End Results (SEER) Program, 2004)
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	
≥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	
≥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	
≥70 years	70.3	

3.10.2. Estimates of other clinical parameters

The values of screening, diagnosis, and treatment parameters are reported in Table 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 (Koutsky et al., 2002; Villa et al., 2005). We assumed the vaccine does not affect the natural course of disease. The duration of immunity conferred by vaccination

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

Parameter	Estimate	Reference
Routine cervical screening, $cover_i$, % per year		(Insinga et al., 2004a)
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	(Bigras and de Marval, 2005)
for ≥CIN 2/3	59	(Bigras and de Marval, 2005)
Liquid-based cytology specificity, $papsp_s$, %	94	(Bigras and de Marval, 2005; Coste et al., 2003)
Colposcopy sensitivity, $colpsn$,%	96	(Mitchell et al., 1998)
Colposcopy specificity, $colpsp$,%	48	(Mitchell et al., 1998)
Genital wart patients seeking physician care, $1-\theta_{gs}$, %	75	
Symptoms recognition, %		(Chesson et al., 2004)
LCC, $recog_L$	3.8	
RCC, $recog_R$	18	
DCC, $recog_D$	90	
Cure rate with treatment per year, %		
for CIN1, $cure_1$	96	(Flannelly et al., 1997)
for CIN2, Γ_2	92	(Flannelly et al., 1997)
for CIN3, Γ_3	92	(Flannelly et al., 1997)
for LCC, Ω_L	92	(Ries et al., 2005)
for RCC, Ω_R	53	(Ries et al., 2005)
for DCC, Ω_D	17	(Ries et al., 2005)
Persistence of HPV after treatment for CIN, ψ_s, %	34	(Cruickshank et al., 2002)

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 (Goldie et al., 2003) 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 (Sanders and Taira, 2003; Goldie et al., 2003). Coverage was also assumed to increase linearly from 0% up to 70% during the first 5 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 Figs. 7–13 and discussed below.

4.1. Years of life

The first final outcome measure is the total number of life 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 adjusted health states over the planning horizon $(0, T)$. Let $qcin_s$, $qcis_s$, qcc_s, qgw_k, and q_{ki} denote the quality of life weights for an individual in the 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

$$\begin{aligned} QALY_a = \int_0^T e^{-\xi t} \Bigg\{ & \sum_{l=1}^{3} \sum_{i=1}^{17} q_{mi} \left(N_{mli} - (1 - qgw_m) DGW^2_{mli} \right) \\ & + q_{fi} \Bigg[N_{fli} - (1 - qgw_f) \left(DHGW^2_{fli} + \sum_{b=1}^{2} DGW^2_{flib} \right) \\ & - (1 - qcc_L) SCC_{li} \\ & - \sum_{h=1}^{2} \left(\sum_{s=1}^{3} (1 - qcin_s) \sum_{b=1}^{2} DCIN^h_{slib} + \sum_{s=1}^{2} (1 - qcis_s) \sum_{b=1}^{2} DCIS^h_{slib} \right) \\ & - \sum_{s=L,R,D} (1 - qcc_s) DCC_{sli} \Bigg] \Bigg\} dt. \end{aligned} \tag{25}$$

Note that the quality-adjusted years of life for females are reduced by time spent in diagnosed genital warts, CIN, and cancer states $DCIN_s$, CC_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 person's health condition is not detected, the quality of life of that person will

Table 7 Quality of life weights

Condition	Estimate		Reference
	Females	Males	
Genital warts, qgw_k	0.91	0.91	(Myers et al., 2004)
CIN1, $qcin_1$	0.91		(Myers et al., 2004)
CIN2, $qcin_2$	0.87		(Myers et al., 2004)
CIN3, $qcin_3$	0.87		(Myers et al., 2004)
LCC, qcc_L	0.76		(Myers et al., 2004)
RCC, qcc_R	0.67		(Myers et al., 2004)
DCC, qcc_D	0.48		(Gold et al., 1998)
Cancer survivors, $qccs$	0.76		(Wenzel et al., 2005)
No condition, q_{ki}			
12–17 years	0.93	0.93	(Gold et al., 1998)
18–34 years	0.91	0.92	(Gold et al., 1998)
35–44 years	0.89	0.90	(Gold et al., 1998)
45–54 years	0.86	0.87	(Gold et al., 1998)
55–64 years	0.80	0.81	(Gold et al., 1998)
65–74 years	0.78	0.76	(Gold et al., 1998)
≥75 years	0.70	0.69	(Gold et al., 1998)

be the same as that of a person without the condition. This assumption biases the results against the vaccine. The magnitude of the quality of life improvements for persons with undetected conditions prevented by the vaccine can be quantified in a sensitivity analysis.

4.3. Estimates of quality of life weights

Table 7 summarizes the quality of life weights used to estimate QALYs. Females diagnosed with CIN1 and CIN 2/3 were assumed to have quality weight of 0.91 and 0.87, respectively (Myers et al., 2004; Kulasingam et al., 2002). The quality weight for genital warts is assumed to be 0.91 (Myers et al., 2004). Females with local and regional cancer are assumed to have a quality of life weight of 0.76 and 0.67, respectively (Myers et al., 2004). A quality weight for invasive distant cancer of 0.48 was derived from Gold et al. (1998) 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 (Andersen, 1996; Wenzel et al., 2005). 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 et al. (1998). Similar values were reported from the Beaver Dam Health Outcomes study (Fryback et al., 1993). 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.

5. Economic consequences of screening and vaccination strategies

The total costs of each strategy include cost 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 women in the hysterectomy class are not screened. However, this may not be the case as suggested by recent studies (Saint et al., 2005). 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 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 women in categories $TCIN_s$, $ICIN_s$, $ICIS_s$, 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:

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

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 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 all diagnosed CIN and cancer cases are treated, the number of cases treated at time t is the total number of 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. Thus, total treatment costs at time t if strategy a is adopted is:

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

5.3. Vaccination costs

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

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

5.4. Total costs

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

$$Cost_a=\int_0^T\left[Screen_a(t)+Treat_a(t)+Vaccinate_a(t)\right]e^{-\xi t}\,dt. \tag{26}$$

Table 8 Cost of screening, diagnosis, and treatment

Condition	Estimate		Reference
	Females	Males	
Cytology test, *scn*	\$99		(Medstat, 2001)
Colposcopy, *colp*	\$165		(Medstat, 2001)
Colposcopy and biopsy, *biopsy*	\$318		(Medstat, 2001)
Genital warts, cgw_k	\$489	\$489	(Insinga et al., 2003)
CIN1, $ctcin_1$	\$1,554		(Kim et al., 2002)
CIN2, $ctcin_2$	\$3,483		(Kim et al., 2002)
CIN3/CIS, $ctcin_3$	\$3,483		(Kim et al., 2002)
LCC, $ctcc_L$	\$26,470		(Kim et al., 2002)
RCC, $ctcc_R$	\$28,330		(Kim et al., 2002)
DCC, $ctcc_D$	\$45,376		(Kim et al., 2002)

5.5. Estimates of costs

Table 8 summarizes the cost of screening, diagnosis, and treatment. Direct medical costs for screening and diagnosis were estimated from the 2001 Medstat Marketscan® commercial insurance database (Medstat, 2001) and updated to 2005 dollar values by using the medical care component of the US consumer price index (US Bureau of Labor Statistics, 2002). 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. (2002) and updated to 2005 dollar values (US Bureau of Labor Statistics, 2002). The costs of CIN 1 were \$1554, CIN 2/3 \$3,483, local invasive cervical cancer \$26,470, regional invasive cervical cancer \$28,330, and local invasive cervical cancer \$45,376. Treatment of genital warts is assumed to cost \$489 in 2005 (Insinga et al., 2003).

5.6. Cost-effectiveness ratio

To compare mutually exclusive vaccination strategies a and a', we calculate the incremental cost-effectiveness ratio (Weinstein, 1996)

$$\frac{Cost_a - Cost_{a'}}{QALY_a - QALY_{a'}}. \tag{27}$$

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 nonstiff ODEs, the Explicit Runge–Kutta methods, with adaptive embedded pairs of 2(1) through 9(8), provide accurate and less expensive solutions (Wolfram, 2005). 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 prevaccination steady-state values of the variables. Second, the prevaccination 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 vaccination programs, including routine vaccination of 12-year 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 Hammerschmidt et al. (2003), Weinstein et al. (2003). 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® (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 (Giuliano et al., 2002; Jacobs et al., 2000; Sellors et al., 2000, 2002; Surveillance, Epidemiology, and End Results (SEER) Program, 2004; Insinga et al., 2003, 2004b). 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 (Gustafsson et al., 1997; McCrory et al., 1999).

6.3. Epidemiologic impact of the HPV vaccination strategies

Figure 7 shows HPV-16/18 prevalence among sexually active females by age over time if the females-only vaccination strategy is followed. HPV-6/11 prevalence among sexually active females by age over time if the females-only vaccination strategy is followed is shown in Fig. 8. Vaccination steadily reduces prevalence among all age groups. The greatest reduction in prevalence occurs among 20–34 year olds. This group has the highest prevalence before introducing vaccination. The impact of vaccination on the incidence of CIN 2/3 by age and time since vaccination is shown in Fig. 9. CIN 2/3 incidence rates across all age groups fall following vaccination. After 20 years following the start of vaccination, CIN 2/3 incidence rates are substantially lower compared with prevaccination rates.

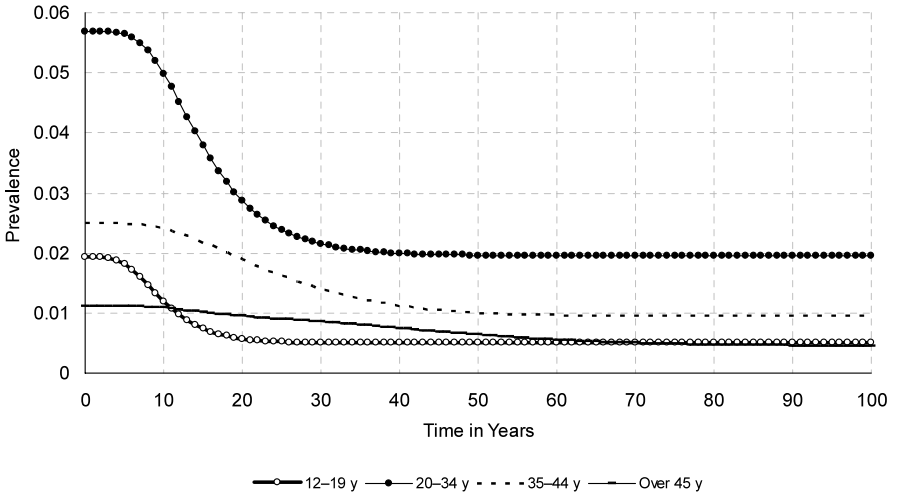

Fig. 7 Prevalence of HPV 16/18 infection among females by age, females-only vaccination, 70% vaccination coverage, lifelong duration of efficacy.

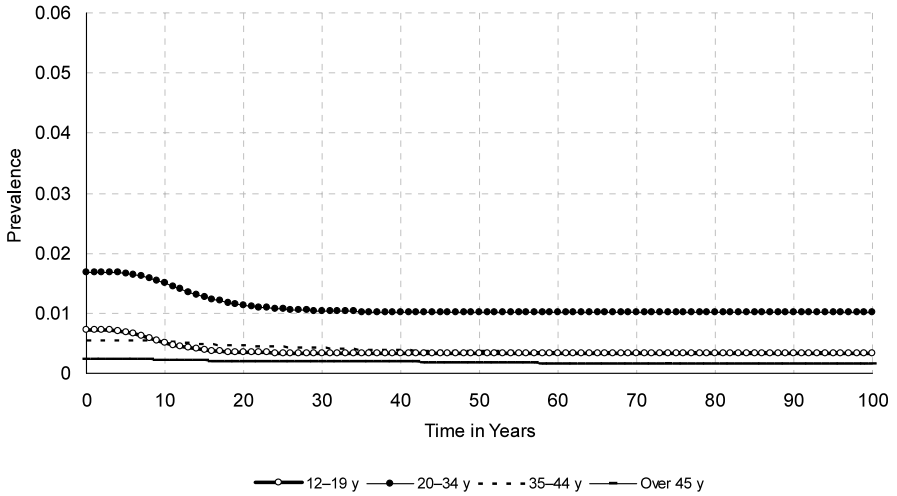

Fig. 8 Prevalence of HPV 6/11 infection among females by age, females-only vaccination, 70% vaccination coverage, lifelong duration of efficacy.

Vaccination programs disproportionately reduce infection and disease burden among younger as compared to older age groups. For example, the incidence of cervical cancer among old age groups becomes relatively larger compared to that among younger age groups after vaccination (Fig. 10). The upward shifting of the age of infection after initiation of vaccination is a common outcome of many vaccination programs (Hethcote, 1997).

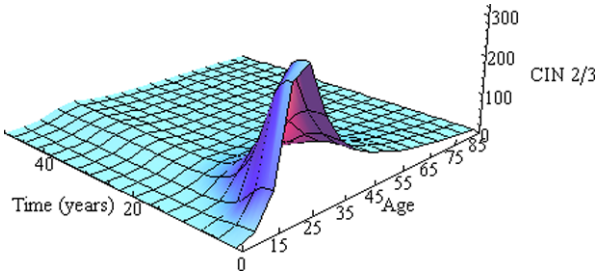

Fig. 9 Incidence of CIN 2/3 per 100,000 among females by age and time since vaccination, females and males (+ catch up) vaccination strategy.

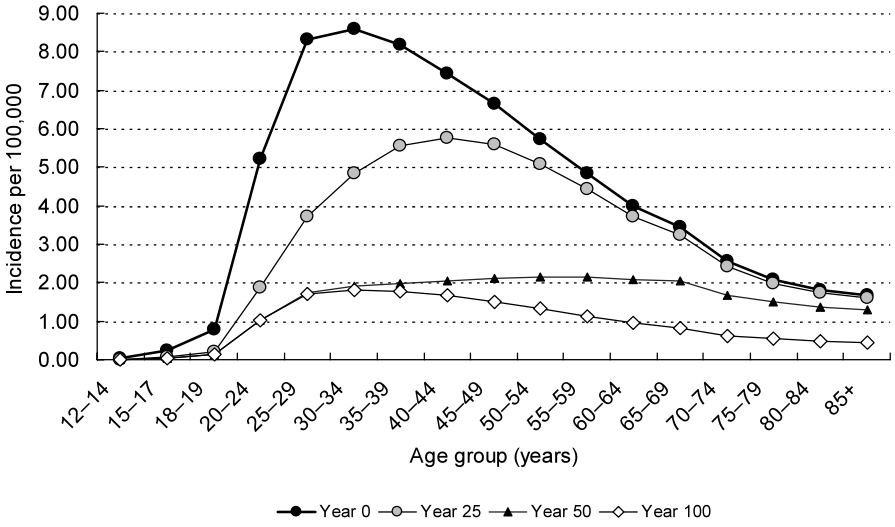

Fig. 10 Cervical cancer incidence by age group, years since vaccination, females-only vaccination strategy.

6.4. Economic impact of HPV vaccination strategies

The cost-effectiveness ratio for each of the vaccination strategies, assuming a lifelong duration of protection and vaccination cost of $360 per series, is shown in Table 9. We ordered the strategies in the table from least effective at the top (i.e., screening only, no vaccination) to most effective at the bottom (i.e., vaccination of females and males from 12 to 24). Overall, we found that routine females and males strategies that did not include a catch-up strategy were less effective and more costly than the other strategies (i.e., dominated). Table 9 includes only the incremental cost-effectiveness ratio (ICER) of nondominated strategies. Thus, the ICER for catch-up vaccination of females age 12–24 is $4,666, and the most effective strategy of vaccinating both genders had an ICER of $45,056. A commonly used bench mark ICER value below which interventions are considered cost-effective is $50,000 per QALYs (Weinstein, 1996). Therefore, vaccinating

Table 9 Cost-effectiveness analysis of alternative HPV vaccination strategies

Strategy	Discounted total		Incremental
	Costs	QALYs	$/QALY
No vaccination, screening only	72,659,302	2,698,711	–
Routine females	74,042,990	2,699,178	2,964
Routine females and males	78,707,825	2,699,327	Dominated
Routine + catch up females	74,815,667	2,699,343	4,666
Routine females and males + catch up females	79,746,357	2,699,461	41,803
Routine + catch up females and males	81,761,210	2,699,506	45,056

both genders and adding a catch up program can be considered potentially cost-effective according to this criterion.

6.5. Sensitivity analyses

The effect of varying duration of vaccine protection on disease outcomes and ICER is studied in Elbasha et al. (2007), and found to be an influential parameter. With 10 years duration of efficacy, vaccination reduced incidence rates steadily until about 10–15 years after vaccination when the loss of immunity among vaccinated individuals and accumulation of unvaccinated individuals reversed these trends and caused the incidence rates to rise. The rise in incidence continued until years 20–30, after which, incidence rates fell steadily until they approached their steady-state values. The timing and magnitude of the reduction and resurgence in incidence depended on the strategy. The largest reduction and rebound was accomplished by adding a catch up program to routine vaccination of both genders.

Another influential input was vaccine coverage. As female coverage rates decreased, male vaccination became more beneficial. The start age of vaccination also influences the results. Earlier vaccination resulted in greater benefits. In addition to these, other key inputs in the cost-effectiveness analysis are the quality of life weights used to estimate the QALYs and the cost of vaccination. The less HPV disease impacted quality of life or the higher the cost of vaccination, the more the ICERs increased.

We conducted various sensitivity analyses on assumptions regarding sexual behavior and mixing among age and sexual activity groups. We first considered the effects of changing the overall mean number of sex partner change in each of age groups 12–14, 15–17, 18–59, and over 60 years by ±20%. The results are shown in Fig. 11 by plotting the trajectory of the incidence of cervical cancer against time since start of vaccination. With higher (lower) sexual activity, the incidence of cervical cancer is higher (lower). For example, underestimating the overall number of sex partner change by 20%, results in an underestimation of the pre-vaccination and long-term postvaccination incidence by 17% and 27%, respectively. To assess the impact of heterogeneity in sex partners acquisition rates we ran three simulations, keeping all parameters constant, but setting: (1) the relative partner acquisition rates across sexual activity groups pc_l to 1 (heterogeneity with respect to age groups only); (2) the relative pa_i and mean $\bar{c}_j$ partner acquisition rates across age groups to 1 and to the overall mean of 0.97, respectively (heterogeneity with respect to sexual activity groups only); and (3) pc_l to 1, pa_i to 1, and $\bar{c}_j$ to 0.97 (no heterogeneity). The results are depicted in Fig. 12. The level of heterogeneity assumed has a significant

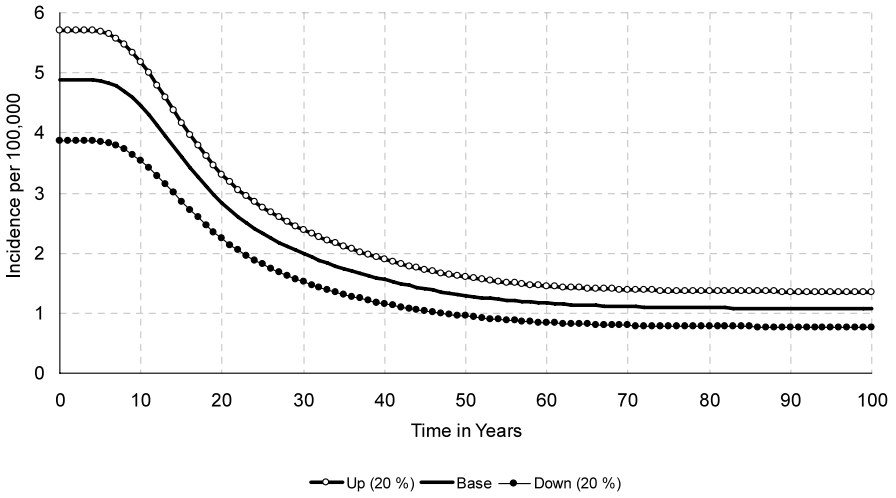

Fig. 11 Impact of number of partners on cervical cancer incidence per 100,000 among females (12–85y), females (+ catch up) vaccination strategy.

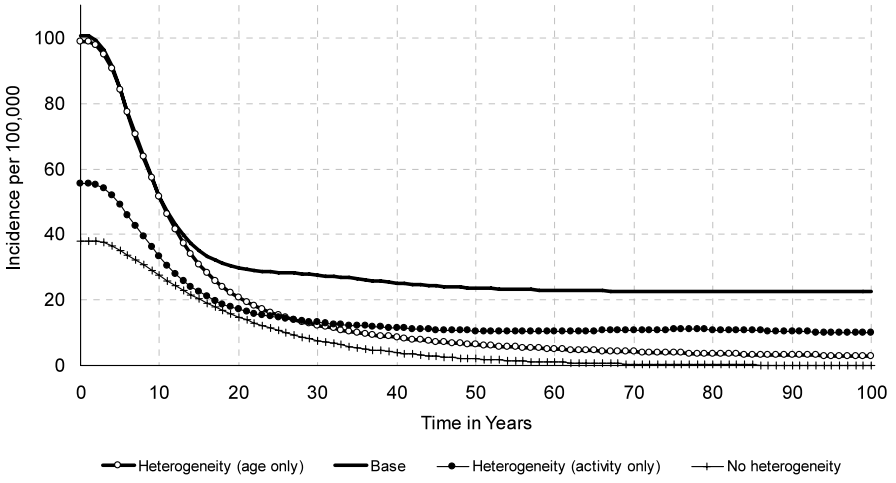

Fig. 12 The impact of heterogeneity in sex partners acquisition rates on incidence of CIN 2/3 per 100,000 among females (12–85y), females (+ catch up) vaccination strategy.

impact of the predicted incidence of CIN 2/3. By comparing the trajectories given no heterogeneity with that of the base case of heterogeneity across sexual activity and age groups, it is clear that more heterogeneity results in higher disease burden. Whereas our assumption of homogeneity with respect to sexual activity groups has little or no impact on predicted incidence of CIN 2/3 following vaccination initially, the impact in the long-term is significant. Furthermore, the shape of the postvaccination epidemic is impacted

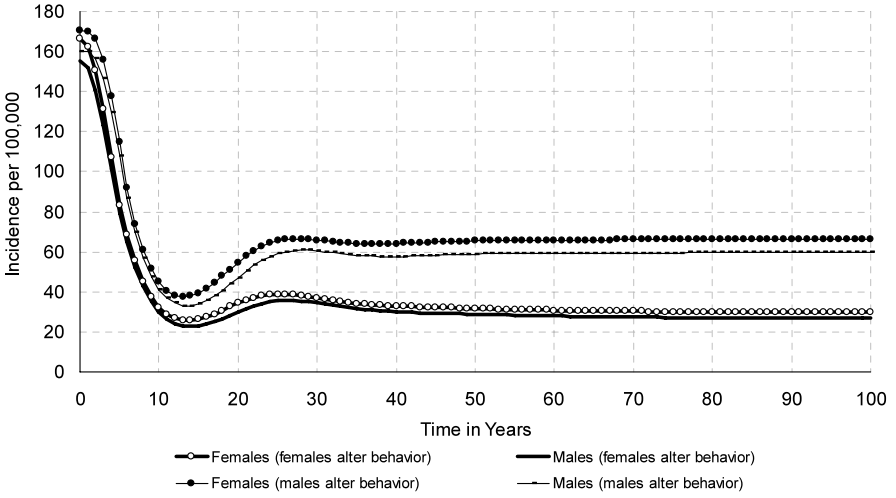

Fig. 13 The effects of the method of balancing the demand for and supply of sexual partnership on the incidence of genital warts per 100,000 among males and females (12–85y), females (+ catch up) vaccination strategy.

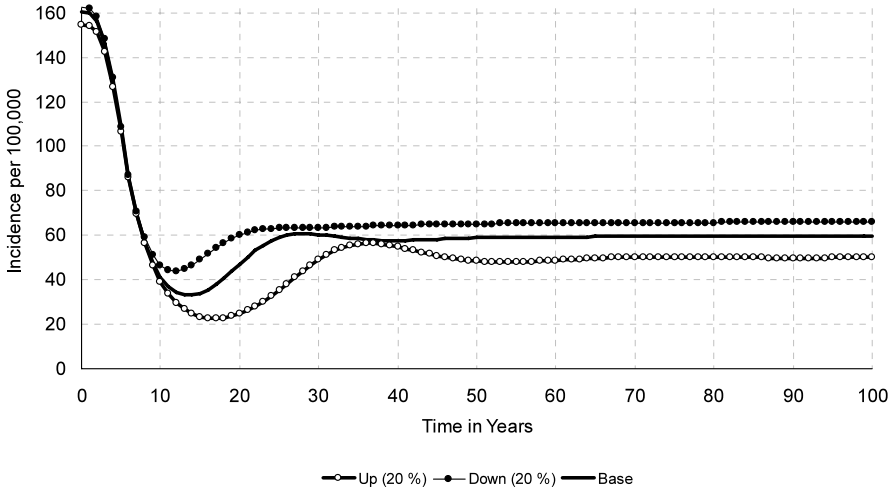

Fig. 14 Influence of mixing between sexual activity groups and age groups on the predicted incidence of genital warts per 100,000 among men (12–85y), females (+ catch up) vaccination strategy.

more by the level of heterogeneity among sexual activity groups than that among age groups.

The effects of which gender behavior is allowed to vary in order to balance the demand for and supply of sexual partnership on the incidence of genital warts is shown in Fig. 13. This figure illustrates that although the choice which gender sets the behavioral agenda

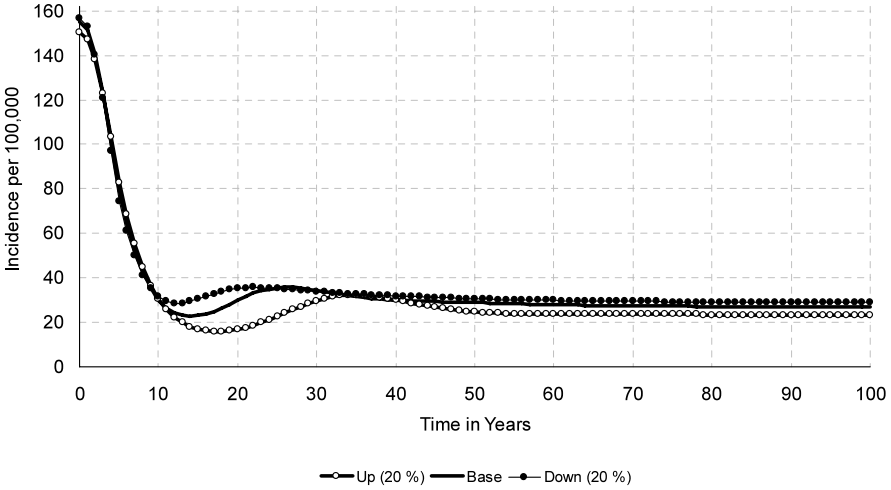

Fig. 15 Influence of mixing between sexual activity groups and age groups on the predicted incidence of genital warts per 100,000 among women (12–85y), females (+ catch up) vaccination strategy.

has some impact on the incidence of disease, the impact is rather limited. Note that this imbalance in the demand for and supply of sex partners is caused by the differential impact cervical cancer-induced mortality affecting only women. The initial imbalance is rectified by forcing each gender to compromise equally. We also assessed the influence of mixing patterns by varying values of ε_1 (sexual activity groups) and ε_2 (age groups) by $\pm 20\%$ on the incidence of genital warts (Figs. 14 and 15). These figures reveal that the influence of the degree of mixing on the predicted impact of a females-only vaccination program on disease among men is more than the impact on diseases among women. This is to be expected given that men are not vaccinated using this strategy. All the benefits to men were obtained indirectly from the protection of their contacts.

Finally, to estimate the additional value of preventing HPV 6/11 infection, we conducted a sensitivity analysis in which we assumed that all individuals had no protection against HPV 6/11 infection and related disease. The results of this analysis showed that the ICER of the female 12–24 vaccination strategy increased to $11,254/QALY, whereas the ICER of routinely vaccinating both genders and targeting 12–24 year olds with a catch up vaccination program increased to $74,151/QALY. These results suggest that the clinical and economic impact of protection against HPV 6/11 infection is relatively large due to occurrence of genital warts and low-grade lesions sooner after infection. Because these benefits are realized in the short-term, their contribution has more weight in the cost-effectiveness analysis due to discounting of future costs and effects. This is clearly illustrated in Fig. 16 where the annual discounted HPV-related disease treatment costs avoided by vaccinating females age 12–24 is shown over time for each HPV type. The results of the cost-effectiveness analysis suggest that protection against HPV 6/11 infection improves the efficiency of vaccination strategies that include males.

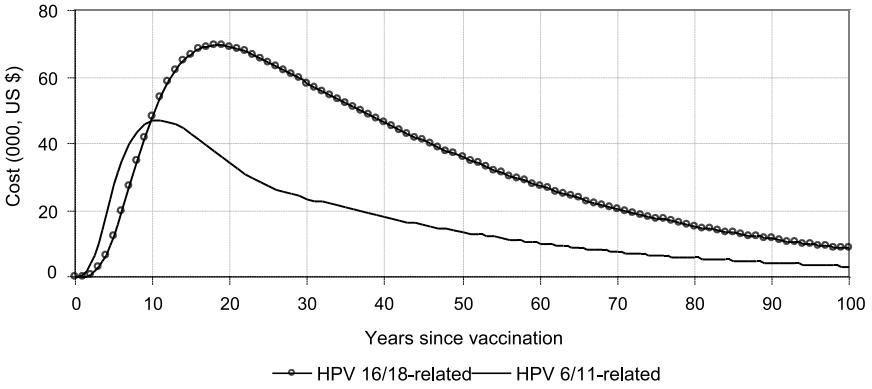

Fig. 16 Annual discounted HPV-related disease treatment costs (in thousands of US dollars) avoided by vaccinating females age 12–24 over time by HPV type.

7. Summary and conclusions

An efficacious prophylactic quadrivalent HPV (16/18/6/11) vaccine against infection and disease was approved by the US Food and Drug Administration (FDA) and other regulatory authorities in 2006. This paper presents an integrated economic evaluation and mathematical model of HPV transmission and HPV-related disease occurrences as a valuable tool for informing healthcare policy decisions. The paper addressed a number of key issues related to the epidemiologic and economic consequences of the quadrivalent vaccine. Valuable insights were obtained from comparing various vaccination strategies. Some of these include the substantial reduction in the health and economic burden of HPV-related disease following vaccination. We found that the reduction in incidence of HPV disease that takes less time to develop after infection (e.g., genital warts) occurs sooner compared to that of diseases that takes longer time to develop (e.g., cervical cancer). Another important finding is the crucial role of catch-up vaccination and targeting a broader age range in significantly reducing the burden of disease early on. From an efficiency perspective, this decrease in disease burden also reduced total costs relative to a vaccination program that did not include a catch-up program. As a result, strategies that did not include a catch-up program were generally less effective and less efficient. Vaccinating males can also play a significant role in reducing the burden of disease among both males and females. This, supplemented with catch-up vaccination, is the most effective strategy yielding the most QALYs for the entire population and can be potentially cost-effective when compared with accepted medical interventions (Center on the Evaluation of Value and Risk in Health, 2006). We also found that duration of protection and vaccination coverage are very influential inputs.

We found that higher level of sexual activity is associated with higher burden of disease and greater impact of vaccination strategies. The level of heterogeneity also has a significant impact of the predicted incidence of disease; more heterogeneity results in higher disease burden. We found that the shape of the postvaccination epidemic is impacted more by the level of heterogeneity among sexual activity groups than that among age groups. Also, the degree of mixing has more influence on the predicted vaccine impact on disease

among men than the impact on diseases among women when females-only vaccination strategies are adopted.

We found that when all individuals had no protection against HPV 6/11 infection and related disease the ICERs were higher, illustrating the additional value of a vaccine that prevents HPV 6/11 infection. The results also suggest that protection against HPV 6/11 infection improves the efficiency of vaccination strategies that include men.

As with any model there are limitations. As a result, a number of model enhancements and extensions are desired. First, more relevant data on the natural history of HPV infection and disease are needed. For example, epidemiologic studies of disease transmission are necessary to estimate the transmission probability per sexual contact (Barnabas et al., 2006; Burchell et al., 2006). Also, given the influence utility data have on the cost-effectiveness ratios, more studies are needed to collect health utility data for the HPV disease states considered in this model. Second, we modeled only two HPV types and their associated diseases and assumed that HPV types have independent natural histories with no interaction (whether synergistic or antagonistic) among them. If current or prior infection with one 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 benefits of reducing the prevalence of HPV infection with types not covered by the vaccine (Elbasha and Galvani, 2005). The evidence on interaction among HPV types to date is mixed (Elbasha and Galvani, 2005). Third, the model assumed that the sexually active population has equal access to health care, be it vaccination, screening, or treatment. However, this 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. Fourth, the current version of the model focuses on heterosexual transmission of HPV. It may be desirable to incorporate transmission between homosexuals and heterosexuals in a single model. Fifth, the scope of the model has been limited to cervical cancer, CIN, and genital warts. HPV infection has also been associated with cancers of the anus, penis, vagina, vulva, and head and neck, as well as recurrent respiratory papillomatosis. As evidence becomes available for modeling the potential effects of vaccination on these other HPV conditions, the scope of the model will be broaden to incorporate these conditions. Finally, it is possible that our model did not take into account the impact of "cohort effect" on HPV transmission and/or disease. For example, it is conceivable that the sexual revolution of 1960s induced a radical change in sexual behavior (individuals having more partners compared with individuals from older generations), and hence may have created cohort effects. In the absence of longitudinal data documenting changes in sexual behavior across generations, it is difficult to know whether the sexual revolution has generated cohort effects that significantly impacted the transmission of HPV. There is also uncertainty regarding sexual practices in the future and whether they will continue along past trajectories. In the face of this uncertainty, we have chosen inputs related to sexual behavior based on cross-sectional data, and decided not to include the impact of cohort effects in our model as was done in other simpler models (e.g., Rao et al., 2006). However, it should be noted that our approach is capable of modeling changing trends in sexual behavior over time in sensitivity analyses.

Despite these limitations, we believe our modeling approach has several strengths. First, we did extensive validation with existing epidemiologic data. The model is also flexible enough to incorporate better data as they become available. Second, this model stratifies the population based on whether or not women are screened during their lifetime

or not, and accounts for actual screening practices in the US. Third, output from this model is population-based and not cohort-based. Hence, the comparison of a dynamic models output with national registry data such as SEER is better aligned than comparison of cohort model output with population data. Finally, all equations and inputs for this model are available to replicate findings and facilitate independent review of the model.

In summary, the results from this model, in a setting of organized cervical cancer screening and for a plausible range of values of model inputs, suggest that widespread immunization with a prophylactic quadrivalent HPV (16/18/6/11) vaccine can: (1) substantially reduce genital warts, CIN, and cervical cancer, (2) increase survival rates among females, (3) improve quality of life among both males and females, and (4) be cost-effective when administered to females before age 12 and included in a temporary 12–24 years catch up program, (5) be cost-effective when implemented as a strategy that combines both females and males before age 12 vaccination with 12 to 24 years of age catch-up program compared with vaccinating females only before age 12 augmented by a female only 12–24 year olds catch-up program.

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