Modeling Human Papillomavirus transmission. Impact of a quadrivalent vaccine.

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Abstract

Human Papillomavirus is the most frequent sexually transmitted infection. Human Papillomavirus (HPV) is the primary cause of cervical cancer and its precursor lesions. Two prophylactic vaccines against HPV infections are available. Mathematical models can be used to compare several vaccine strategies. Consequently, most effective vaccine strategy can be enlightened and selected. Nevertheless, proposed HPV transmission models in the litterature have become very complex while some input values remain unknown or badly estimated. Our aim was to assess the variability in the outcome variable that is due to the uncertainty in estimating the input values. We carried out and calibrated a Susceptible-Infected-Susceptible model of heterosexual transmission of Human Papillomavirus infections for serotypes 6/11/16/18 which are covered by the quadrivalent vaccine. Immunity obtained from vaccination was considered. The basic and vaccinated basic reproduction numbers were expressed. Model prediction sensitivity to parameters uncertainty has been assessed using the Partial Rank Correlation Coefficients. Three scenarios of vaccination have been compared considering estimated HPV infection prevalences. Six posterior parameter sets among one million combination tested best fitted epidemiologic data. Sensitivity analysis showed that the significiance level of uncertainty was linked to the length of different serotype HPV infections in model predictions. Deterministic modeling of HPV infection transmission allowed us to compare potential efficiency of 3 vaccination scenarios. Additional vaccination of the half of men who enter annually in the sexually active population led to the same results when compared to an exclusive large vaccination rate of women (who enter annually in the sexually active population). Sensitivity analysis showed the importance of clearance rate in the precision of model predictions, therefore efforts have to been made to focus data collection concerning duration of HPV infections. Furthermore, usefulness of men's vaccination depends on women's vaccination rate.

Keywords: Human Papillomavirus, dynamic model, sensitivity analysis, vaccine.

Introduction

Human Papillomavirus (HPV) is the most frequent sexually transmitted infection. At least 70 per cent of sexually active men and women acquire HPV infection at some points in their lives [29]. Eighty per cent of HPV infection cases are cleared in a few months from the body by the immune system without treatment, the rest 20% infection become persistent. One hundred different HPV serotypes have been identified, there are low risk serotypes which are responsible for benign anogenital lesions, and high risk serotypes which can induce precancerous and cancerous lesions in the cervix. Serotype 16 is the most common in developed countries [4, 25]. Epidemiological studies on HPV infections establish the role of these viruses as the primary cause of cervical cancer [22]. These infections are also the cause of anogenital cancers, head and neck cancers, anogenital warts and recurrent respiratory papillomatosis among women and men. Invasive cervical cancer is the most common cancer among women worlwide [26]. It is estimated that HPV infections are responsible for approximately 500,000 cervical cancer cases worldwide each year [24]. Vaccination against HPV infections represents an effective way to decrease cervical cancer incidence,

particularly among young women. Two prophylactic vaccines against HPV infections have been found to be highly efficient in "naive" women [8].
HPV transmission models have become very complex. Several deterministic models have been developed to assess the potential impact of vaccination against HPV; Hughes et al [15] developped a SIR model of heterosexual transmission which included 3 sexual activity groups, their objective was to explore the effect of a mono-valent high-risk HPV vaccine on the steady-state endemic prevalence of HPV 16 in the population; Barnabas et al [2] explored the effect of a multivalent HPV vaccine using a SIR model which included sexual behaviour, smoking and age; Elbasha et al [11] simulated the progression of HPV disease in the population using 9 compartments, the used SIR model included 2 groups of serotype, sexual behaviour and 17 age-groups. Taira et al [30] assessed HPV vaccination programs using a SIS model regarding one serotype stratified by age and sexual activity.
Models cited above were based on numerical simulations with few analytical results. The variability of model predictions due to the uncertainty in estimating the input values was rarely explored. While some input parameters are usually unknown and are estimated in the calibration of the model, other parameters are assessed using epidemiological data. Uncertainty analysis may be used to investigate the prediction imprecision in the outcome variable that is due to the uncertainty in estimating the values of the input parameters [16].
In another paper, Elbasha computed the basic and vaccinated reproduction number of a simple SIR model regarding one HPV-serotype transmission [9]. The basic reproduction number $\mathcal{R}_0$ is a threshold quantity which determines if an epidemic can spread in a population or die out. It is defined by the expected number of secondary cases of HPV produced by an infected individual during its entire period of infectiousness, in a completely susceptible population [7].
SIR models are used assuming that individuals who clear HPV infections become immune to a new HPV infection. While efficient protective immunity against HPV following a first infection remains uncertain [17], SIS models may be employed. In this paper, we present a Susceptible-Infected-Susceptible (SIS) deterministic model of heterosexual transmission of HPV.
We developped and parametrized a two-sex model of HPV infection transmission in a sexually active population. We included the four serotypes of HPV which are covered by the quadrivalent vaccine. The basic and vaccinated reproduction numbers are given for the model considering the four HPV serotypes. We assessed the sensitivity of model predictions to parameter uncertainty. We estimated the potential impact of a quadrivalent HPV-vaccine on the occurrence of HPV infections comparing 3 vaccination scenarios.

Method

HPV model structure

The model with vaccination

The model describes HPV infection transmission in a heterosexually active population. We develop a deterministic model using a Susceptible-Infected-Susceptible (SIS) structure and considering vaccination. The model includes 2 classes of HPV genotypes: HPV-16/18 (high-oncogenic risk types) and HPV-6/11 (low-risk types). A possible co-infection 6/11/16/18 was also taken into account (figure 1).
Non-vaccinated (resp. vaccinated) women enter the sexually active population in the susceptible compartment X_{00} (resp. V_{00}) at a constant rate [(1- φ_f)Λ] (resp. [$\varphi_f\Lambda$]) and leave all compartments at rate μ. Non-vaccinated (resp. vaccinated) men enter the sexually active population in the susceptible compartment Y_{00} (resp. W_{00}) at a constant rate [(1- φ_m)Λ] (resp. [$\varphi_m\Lambda$]) and leave all compartments at rate μ. Then, women can move into infected compartments (if they have an infected contact with a man) in non-vaccinated population (resp. vaccinated): X_{01} for women infected with HPV 6/11(resp. V_{01}), X_{10} for women infected with HPV 16/18 (resp. V_{10}) and X_{11} for women infected with HPV 6/11/16/18

(resp. V_{11})(detail in Table 1). In the same way , non-vaccinated and vaccinated men can move to infected compartments. We assume that vaccinated people can be infected. The degree of vaccine protection is τ, the relative risk of a vaccinated individual experiencing a breakthrough infection is (1-τ). We assume that vaccinated and infected individuals can transmit HPV as much as non-vaccinated individuals. We assume that vaccine immunity does not decrease during their sexually active life. Women and men who clear HPV infection leave infected compartments and go back to the susceptible compartments or infected compartments with other serotype. Variables and parameters are described in Table 1.
Demographic and biological parameters are strictly positive.
The ordinary differential equations that represent this compartmental model are presented in Appendix.

Basic and Vaccinated Reproduction Number

In the abscence of vaccination, $\varphi_m = 0$ and $\varphi_f = 0$ as well as $V_{00} = V_{01} = V_{10} = V_{11} = W_{00} = W_{01} = W_{10} = W_{11} = 0$. The system of differential ordinary equations is as follows:

$$\begin{aligned}
\frac{dX_{00}}{dt} &= \Lambda - \frac{\sigma_f}{N_m}(Y_{01}+Y_{10}+Y_{11})X_{00} + \delta_{01}X_{01} + \delta_{10}X_{10} + \delta_{11}X_{11} - \mu X_{00} \\
\frac{dX_{01}}{dt} &= \frac{\sigma_f}{N_m}Y_{01}X_{00} - \frac{\sigma_f}{N_m}(Y_{11}+Y_{10})X_{01} - \delta_{01}X_{01} + \delta_{10}X_{11} - \mu X_{01} \\
\frac{dX_{10}}{dt} &= \frac{\sigma_f}{N_m}Y_{10}X_{00} - \frac{\sigma_f}{N_m}(Y_{11}+Y_{01})X_{10} - \delta_{10}X_{10} + \delta_{01}X_{11} - \mu X_{10} \\
\frac{dX_{11}}{dt} &= \frac{\sigma_f}{N_m}Y_{11}X_{00} + \frac{\sigma_f}{N_m}(Y_{11}+Y_{01})X_{10} + \frac{\sigma_f}{N_m}(Y_{11}+Y_{10})X_{01} - (\delta_{10}+\delta_{01}+\delta_{11}+\mu)X_{11} \quad (1) \\
\frac{dY_{00}}{dt} &= \Lambda - \frac{\sigma_m}{N_f}(X_{01}+X_{10}+X_{11})Y_{00} + \delta_{01}Y_{01} + \delta_{10}Y_{10} + \delta_{11}Y_{11} - \mu Y_{00} \\
\frac{dY_{01}}{dt} &= \frac{\sigma_m}{N_f}X_{01}Y_{00} - \frac{\sigma_m}{N_f}(X_{11}+X_{10})Y_{01} - \delta_{01}Y_{01} + \delta_{10}Y_{11} - \mu Y_{01} \\
\frac{dY_{10}}{dt} &= \frac{\sigma_m}{N_f}X_{10}Y_{00} - \frac{\sigma_m}{N_f}(X_{11}+X_{01})Y_{10} - \delta_{10}Y_{10} + \delta_{01}Y_{11} - \mu Y_{10} \\
\frac{dY_{11}}{dt} &= \frac{\sigma_m}{N_f}X_{11}Y_{00} + \frac{\sigma_m}{N_f}(X_{11}+X_{01})Y_{10} + \frac{\sigma_m}{N_f}(X_{11}+X_{10})Y_{01} - (\delta_{10}+\delta_{01}+\delta_{11}+\mu)Y_{11}
\end{aligned}$$

The disease free equilibrium (DFE) of this model is obtained by setting the right hand sides of the model equations to zero. P_0= (X^*_{00}, X^*_{01},X^*_{10},X^*_{11}, Y^*_{00}, Y^*_{01},Y^*_{10},Y^*_{11})= ($\frac{\Lambda}{\mu}$, 0,0,0 , $\frac{\Lambda}{\mu}$, 0,0,0) is the DFE.
The basic reproduction number $\mathcal{R}_0$ is a threshold quantity which determines if an epidemic can spread in a population or die out. It is defined by the expected number of secondary cases of HPV produced by an infected individual during its entire period of infectiousness, in a completely susceptible population [7]. We use the Next Generation Matrix (NGM) [32] to compute $\mathcal{R}_0$.

$\mathcal{R}_0$ is equal to the spectral radius of $F_1V_1^{-1}$ [6], thus: $\mathcal{R}_0 = \sqrt{\mathcal{R}_{0,f}\mathcal{R}_{0,m}}$

with: $\mathcal{R}_{0,f} = \dfrac{\sigma_f}{(\min(\delta_{01},\delta_{10})+\mu)}$ and $\mathcal{R}_{0,m} = \dfrac{\sigma_m}{(\min(\delta_{01},\delta_{10})+\mu)}$.

Note that $\mathcal{R}_0$ is the geometric mean of two values. In a one-sex model: $\mathcal{R}_{0,f} = \mathcal{R}_{0,m}$, we find

$$\mathcal{R}_0 = \frac{\sigma}{(\min(\delta_{01},\delta_{10})+\mu)}.$$

Then, considering the system including vaccination compartments (2) (see Appendix), we compute the

vaccinated reproduction number. The disease free equilibrium (DFE) of this model is:

$$\begin{aligned} Q_0 &= (X_{00}^{**}, X_{01}^{**}, X_{10}^{**}, X_{11}^{**}, Y_{00}^{**}, Y_{01}^{**}, Y_{10}^{**}, Y_{11}^{**}, V_{00}^{**}, V_{01}^{**}, V_{10}^{**}, V_{11}^{**}, W_{00}^{**}, W_{01}^{**}, W_{10}^{**}, W_{11}^{**}) \\ &= \left((1-\varphi_f)\frac{\Lambda}{\mu}, 0, 0, 0, (1-\varphi_m)\frac{\Lambda}{\mu}, 0, 0, 0, \varphi_f\frac{\Lambda}{\mu}, 0, 0, 0, \varphi_m\frac{\Lambda}{\mu}, 0, 0, 0\right) \end{aligned}$$

The vaccinated reproduction number takes into account vaccine protection. Following the same method used for the basic reproduction number computation (Next Generation Matrix),

$$\mathcal{R}_v = \frac{1}{(min(\delta_{01}, \delta_{10}) + \mu)}\sqrt{R_m R_f}$$

with $R_k = \sigma_k[(1-\varphi_k) + (1-\tau)\varphi_k]$, for k=f,m.

Also:

$$\mathcal{R}_v^2 = \mathcal{R}_0\sqrt{[(1-\varphi_m) + (1-\tau)\varphi_m][(1-\varphi_f) + (1-\tau)\varphi_f]}.$$

Note that terms inside brackets are less than one, $\mathcal{R}_v < \mathcal{R}_0$. The term under the square root shows how much vaccination reduces $\mathcal{R}_0$. This parameter is very important because it represents a threshold quantity and bringing it below one could allow the eradication of endemicity of HPV. The level of impact that is necessary to achieve epidemic elimination depends on the combined effects of male and female vaccination programs. Considering the basic reproduction number previously obtained, we plot the critical level of male vaccine coverage that is necessary to achieve epidemic elimination according to female vaccination rate (figure 2). The impact of female-only vaccination has to be more than 74% to achieve HPV elimination.

Model simulations

First, we program the system without vaccination in Scilab software. We solve it using a Runge-Kutta method. Input parameters were evaluated using published data. The rate of exit of the sexually active population can be estimated as the opposite of the duration of sexually active life [14]. Hughes et al [15] have estimated the average duration of sexually active life to 15 years. Assuming that the size of the population in the model is constant, the number of new recruits into the sexually active population (per year) was estimated to be 30,000. We performed a review of litterature to find published epidemiological data on HPV prevalences and average duration of HPV infections for the 4 serotypes 6/11/16/18 in each gender. We used available epidemiological data regarding general population. US data were used to estimate prevalences of HPV infection [23, 27]. The annual clearance rate is estimated as the opposite of the average duration of the infection (in years) [14]. We assumed that clearance rates were similar in male and female and according to vaccine status. However, clearance rates varied according to serotypes. Clearance rates in presence of multiple infections were defined as the clearance rate corresponding to the longest infections. The mean durations of HPV infection estimated in the litterature were different according to the explored population. Therefore, type-specific clearance rates were assigned using a prior uniform distribution between the minimum and maximum estimates found in the litterature review [11, 13, 15, 19, 20, 21, 28, 31].

Two annual infection rates were defined in male and female and were similar for all serotypes. The infection rate was the same for a susceptible individual or for someone already infected with other serotypes. Published estimations of infection rates could not be employed as they depended on the caracteristics of models used. Consequently, these parameters were generated from a uniform distribution on [0,5]. See Table 2.

A fitting procedure was performed to identify different sets of infection rate. Infection rates were judged to produce acceptable fit when the associated model prediction fell simultaneously within prespecified targets defined using the epidemiological data of prevalence. The outputs of the model reached the target if they were inside intervals of $\pm$ 10% of inputs. Inputs were the size of the 8 model compartments. Among the million randomly sampled combinations of parameters, 6 sets of natural history parameters met our predifined goodness-of-fit criteria. Model simulations were based on one posterior parameter set that was identified during model fitting.

Sensitivity analysis

An uncertainty analysis was performed. First, we studied the impact of a 20% parameter variation on model predictions. We considered variations of new recruit and retirment rate of the sexually active population together, then variations of clearance rates and infection rates together, finally variations of initial prevalences. Each time, the predictions of the model were compared to the pre-specified target. Then, in sensitivity analysis, we identified the most influential parameters on model predictions computing Partial Rank Correlation Coefficient (PRCC)[5]. Calculation of PRCC enables the determination of the statistical relationships between each input parameter and each outcome variable while keeping all of the other input parameters constant. The magnitude of the PRCC indicates the importance of the uncertainty in estimating the value of the outcome variable. However, in this analysis we only kept outcome variables which were monotonically related to the input parameters. In this analysis, we used R sofware (www.r-project.org).

Vaccine characteristics

Base-case vaccine characteristics were assumed to be as follows: reduction in susceptibility to HPV 6/11/16/18 (vaccine efficacy) was 90%, vaccine duration is lifelong, vaccinated people which are infected are as infectious as the non-vaccinated infected people. We compared 3 scenarios of vaccination (Table 2) considering a significant reduction of HPV-16/18 infected men and women. We calculated how many years were necessary after introduction of vaccination to have the size of HPV-16/18 infected compartments below 10,000.

Results

Model fit and validation

Of one million different combinations of parameters sampled from the uniform distributions, 6 parameter sets produced model results within the prespecified targets (Table 3).
These 6 combinations were different. In each of the 6 combinations, a 10% variation of one parameter while keeping the others constant did not produced output in the pre-defined target. The third combination was used in the analyses that follow. We could assess a $\mathcal{R}_0$ value at 1.73. As expected, this value was above 1 because HPV infections have reached an endemic state. This value did not give an estimation for the time which was necessary to eradicate HPV infections. In the section for vaccine scenario, we estimate how many years are needed in order to observe a significant diminution of HPV infected individuals.

Sensitivity analysis

In a first step, we assessed the effect of parameter variations in a scale of 20% (increase or decrease) on the predictions of the model. When considering prevalence parameters, predictions of the model achieved the pre-specified target. Nonetheless, modification regarding the rates of entrance and withdrawal from

sexually active population influenced in a moderate way model predictions. On the contrary, clearance and infection rate variations led to predictions outside the target.
In a second step, we conducted a sensitivity analysis using PRCC. Monotonicity between each input variables and output variables was assessed considering scatterplots. Only outcome variables which were monotically related to the input parameters were used to compare the PRCC. We computed PRCC between each 4 input parameters (female infection rate, men infection rate, HPV-6/11 clearance rate and HPV-16/18 infection rate) and the 8 output variables (size of the 8 non-vaccinated compartments). The relative importance of the input variables could be directly evaluated by comparing these PRCC (Table 4).
Considering significant results of PRCC, it can be found that the uncertainties in estimating the values of clearance rate for HPV 6/11 and HPV 16/18 are the most important in affecting the prediction precision of susceptible population. Female infection rate estimation uncertainties contribute to prediction precision of HPV-6/11 infected men and women. In this case, PRCC relating to men are smaller that PRCC relating to women but it can been explain by the non-monotonous relation for men infection rate with all output variables. In this case, it could implicate that the PRCC is low.

Vaccine scenarios

In the case of a low vaccine coverage for women (50% of women who enter annually the sexually active population) and without men's vaccination (scenario 1), 50 years were necessary, after vaccine introduction, to observe less than 10,000 HPV-16/18 infected women (figure 3). Introduction of men's vaccine in scenario 2 reduced by half this time. The third scenario was caracterised by a high vaccine coverage among women (90% of women who enter, annually, the sexually active population) and the absence of men's vaccination. In this case, we found the same time again that with the second scenario in which half of men and women, who enter annually the sexually active population, were vaccinated.

Discussion

Two prophylactic vaccines against HPV infections are proposed to young women in several countries. In the United States, the Centers for Disease Control and Prevention (CDC) recommend vaccination for girls and women 11 to 26 years old with quadrivalent vaccine, in order to prevent cervical cancer, pre-cancerous lesions and genital warts caused by serotypes 6, 11, 16 and 18. In Europe, several countries recommend vaccination against HPV infection, vaccination against HPV starts at different ages, between 9 and 14 years [1]. Actually, the question of vaccination for boys is being studied [3, 12, 18, 10]. Mathematical models are useful to appreciate the impact of prophylactic vaccination against HPV and the effectiveness of vaccination strategies, for instance introduction of boy's vaccination. Previously, no SIS model including the four HPV serotypes covered by the quadrivalent vaccine have been developped. Only Taira et al [30] have published a SIS model including only one serotype of HPV. In this paper, we developped a deterministic SIS model of heterosexually HPV transmission including the four serotypes covered by the quadrivalent vaccine. We derived explicit formula for the basic and vaccinated reproduction numbers that characterizes whether the epidemic will be contained following vaccination or not. We found that the basic reproduction number is

$$\mathcal{R}_0 = \sqrt{\frac{\sigma_f}{(\min(\delta_{01}, \delta_{10}) + \mu)} \frac{\sigma_m}{(\min(\delta_{01}, \delta_{10}) + \mu)}}$$

and the vaccinated reproduction number was assessed:

$$\mathcal{R}_v = \mathcal{R}_0 \sqrt{[(1 - \varphi_m) + (1 - \tau)\varphi_m][(1 - \varphi_f) + (1 - \tau)\varphi_f]}$$

Then we have estimated the infection and clearance rates in calibration step. As expected, female infection rates were above male infection rates because the transmission risk from an infected man to a susceptible woman is higher than from an infected woman to a susceptible man [2, 11, 15]. The estimated infection rates were hardly comparable with those found in the litterature because most of the published models are stratified on sexual behavior and age [2, 11, 15]. Parameters assessed in these models are the probability of transmission. Sexual behavior is introduced using average rate of sexual partner change and a mixing matrice which describes how partnerships between men and women are formed. The clearance rates (Table 2) were near to the lower values found in the litterature. They corresponded to longer durations of infection. Furthermore, sensitivity analysis showed that clearance rates have an important impact on model predictions. In published studies, infected women are seen every 6 months to assess the average duration of HPV infection, this period implicates an uncertainty with respect to the exact time of HPV clearance [28, 31, 33]. Thus, more accurate epidemiological data on the duration of HPV infections could improve the precision of model predictions.
Introduction of vaccination in the model allowed us to compare 3 scenarios for vaccination. In the first scenario, we considered that 50% of women who enter annually in the sexually active population were vaccinated. Since vaccine recommandations in US are vaccination at 12 years old (and a catch-up programm for 13-26 years old girls) this scenario corresponded to half of the 14 years old girls, who enter annually in the model protected by the vaccine. Introduction of men's vaccination besides women's vaccination (scenario 2 vs scenario 1) allows to obtain a twice as fast diminution of HPV-16/18 infected individual number. Nevertheless, we found the same fastness with an exclusive high female vaccine coverage (90%) (scenario 3). Therefore, men's vaccination effectiveness has to be discussed according to vaccine coverage acquired for women. These results come from a simplified model and have to be confirmed by developing a model including age and sexual behaviour.

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Appendix

The ordinary differential equations that represent the compartmental model including vaccination are :

$$
\begin{aligned}
\frac{dX_{00}}{dt} &= (1-\varphi_f)\Lambda - \frac{\sigma_f}{N_m}(Y_{01}+Y_{10}+Y_{11}+W_{01}+W_{10}+W_{11})X_{00} + \delta_{01}X_{01} + \delta_{10}X_{10} + \delta_{11}X_{11} - \mu X_{00} \\
\frac{dX_{01}}{dt} &= \frac{\sigma_f}{N_m}(Y_{01}+W_{01})X_{00} - \frac{\sigma_f}{N_m}(Y_{11}+W_{11}+Y_{10}+W_{10})X_{01} - \delta_{01}X_{01} + \delta_{10}X_{11} - \mu X_{01} \\
\frac{dX_{10}}{dt} &= \frac{\sigma_f}{N_m}(Y_{10}+W_{10})X_{00} - \frac{\sigma_f}{N_m}(Y_{11}+W_{11}+Y_{01}+W_{01})X_{10} - \delta_{10}X_{10} + \delta_{01}X_{11} - \mu X_{10} \\
\frac{dX_{11}}{dt} &= \frac{\sigma_f}{N_m}(Y_{11}+W_{11})X_{00} + \frac{\sigma_f}{N_m}(Y_{11}+W_{11}+Y_{01}+W_{01})X_{10} \\
&\quad + \frac{\sigma_f}{N_m}(Y_{11}+W_{11}+Y_{10}+W_{10})X_{01} - (\delta_{10}+\delta_{01}+\delta_{11}+\mu)X_{11} \\
\frac{dY_{00}}{dt} &= (1-\varphi_m)\Lambda - \frac{\sigma_m}{N_f}(X_{01}+X_{10}+X_{11}+V_{01}+V_{10}+V_{11})Y_{00} + \delta_{01}Y_{01} + \delta_{10}Y_{10} + \delta_{11}Y_{11} - \mu Y_{00} \\
\frac{dY_{01}}{dt} &= \frac{\sigma_m}{N_f}(X_{01}+V_{01})Y_{00} - \frac{\sigma_m}{N_f}(X_{11}+V_{11}+X_{10}+V_{10})Y_{01} - \delta_{01}Y_{01} + \delta_{10}Y_{11} - \mu Y_{01} \\
\frac{dY_{10}}{dt} &= \frac{\sigma_m}{N_f}(X_{10}+V_{10})Y_{00} - \frac{\sigma_m}{N_f}(X_{11}+V_{11}+X_{01}+V_{01})Y_{10} - \delta_{10}Y_{10} + \delta_{01}Y_{11} - \mu Y_{10} \\
\frac{dY_{11}}{dt} &= \frac{\sigma_m}{N_f}(X_{11}+V_{11})Y_{00} + \frac{\sigma_m}{N_f}(X_{11}+V_{11}+X_{01}+V_{01})Y_{10} \\
&\quad + \frac{\sigma_m}{N_f}(X_{11}+V_{11}+X_{10}+V_{10})Y_{01} - (\delta_{10}+\delta_{01}+\delta_{11}+\mu)Y_{11} \\
\frac{dV_{00}}{dt} &= \varphi_f\Lambda - (1-\tau)\frac{\sigma_f}{N_m}(Y_{01}+Y_{10}+Y_{11}+W_{01}+W_{10}+W_{11})V_{00} + \delta_{01}V_{01} + \delta_{10}V_{10} + \delta_{11}V_{11} - \mu V_{00} \quad (2) \\
\frac{dV_{01}}{dt} &= (1-\tau)\frac{\sigma_f}{N_m}(Y_{01}+W_{01})V_{00} - (1-\tau)\frac{\sigma_f}{N_m}(Y_{11}+W_{11}+Y_{10}+W_{10})V_{01} - \delta_{01}V_{01} + \delta_{10}V_{11} - \mu V_{01} \\
\frac{dV_{10}}{dt} &= (1-\tau)\frac{\sigma_f}{N_m}(Y_{10}+W_{10})V_{00} - (1-\tau)\frac{\sigma_f}{N_m}(Y_{11}+W_{11}+Y_{01}+W_{01})V_{10} - \delta_{10}V_{10} + \delta_{01}V_{11} - \mu V_{10} \\
\frac{dV_{11}}{dt} &= (1-\tau)\frac{\sigma_f}{N_m}(Y_{11}+W_{11})V_{00} + (1-\tau)\frac{\sigma_f}{N_m}(Y_{11}+W_{11}+Y_{01}+W_{01})V_{10} \\
&\quad + (1-\tau)\frac{\sigma_f}{N_m}(Y_{11}+W_{11}+Y_{10}+W_{10})V_{01} - (\delta_{10}+\delta_{01}+\delta_{11}+\mu)V_{11} \\
\frac{dW_{00}}{dt} &= \varphi_m\Lambda - (1-\tau)\frac{\sigma_m}{N_f}(X_{01}+X_{10}+X_{11}+V_{01}+V_{10}+V_{11})W_{00} + \delta_{01}W_{01} + \delta_{10}W_{10} + \delta_{11}W_{11} - \mu W_{00} \\
\frac{dW_{01}}{dt} &= (1-\tau)\frac{\sigma_m}{N_f}(X_{01}+V_{01})W_{00} - (1-\tau)\frac{\sigma_m}{N_f}(X_{11}+V_{11}+X_{10}+V_{10})W_{01} - \delta_{01}W_{01} + \delta_{10}W_{11} - \mu W_{01} \\
\frac{dW_{10}}{dt} &= (1-\tau)\frac{\sigma_m}{N_f}(X_{10}+V_{10})W_{00} - (1-\tau)\frac{\sigma_m}{N_f}(X_{11}+V_{11}+X_{01}+V_{01})W_{10} - \delta_{10}W_{10} + \delta_{01}W_{11} - \mu W_{10} \\
\frac{dW_{11}}{dt} &= (1-\tau)\frac{\sigma_m}{N_f}(X_{11}+V_{11})W_{00} + (1-\tau)\frac{\sigma_m}{N_f}(X_{11}+V_{11}+X_{01}+V_{01})W_{10} \\
&\quad + (1-\tau)\frac{\sigma_m}{N_f}(X_{11}+V_{11}+X_{10}+V_{10})W_{01} - (\delta_{10}+\delta_{01}+\delta_{11}+\mu)W_{11}
\end{aligned}
$$

with

$$\begin{aligned} N_f &= X_{00} + X_{01} + X_{10} + X_{11} + +V_{00} + V_{01} + V_{10} + V_{11} \\ N_m &= Y_{00} + Y_{01} + Y_{10} + Y_{11} + +W_{00} + W_{01} + W_{10} + W_{11} \\ N &= N_f + N_m. \end{aligned}$$

N is the size of the sexually active population. We have

$$N' = 2\Lambda - \mu N.$$

Since at equilibrium $N^* = 2\frac{\Lambda}{\mu}$.

Figures

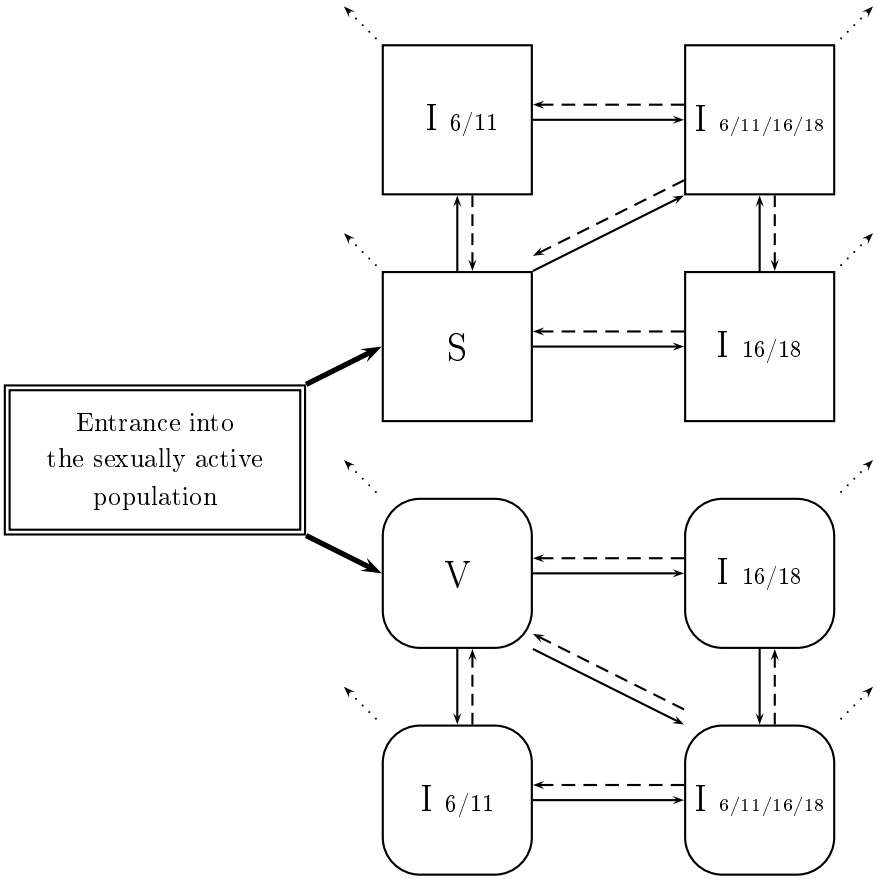

Figure 1. Transfer diagram of the HPV model. The different compartments represent individuals in each state of HPV infection (rounded up corner for vaccinated population, S: non- vaccinated and susceptible, V: vaccinated and susceptible, I 6/11: infected with HPV-6 or/and HPV-11, I 16/18: infected with HPV-16 or/and HPV-18, I $_{6/11/16/18}$: infected with HPV-6 or/and HPV-11 and HPV-16 or/and HPV-18). The arrows represent the flow between these states (bold lines represent entrance into the sexually-active population, solid lines represent infection, dashed lines represent clearance and regression, dotted lines represent the exit of the model).

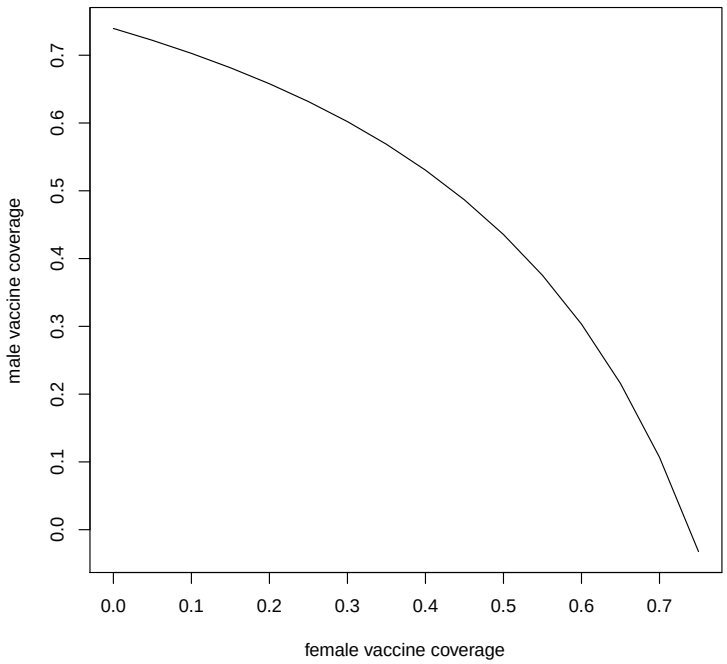

Figure 2. Gender-specific vaccine impact necessary to achieve epidemic elimination when $R_0^2 = 2.99$.

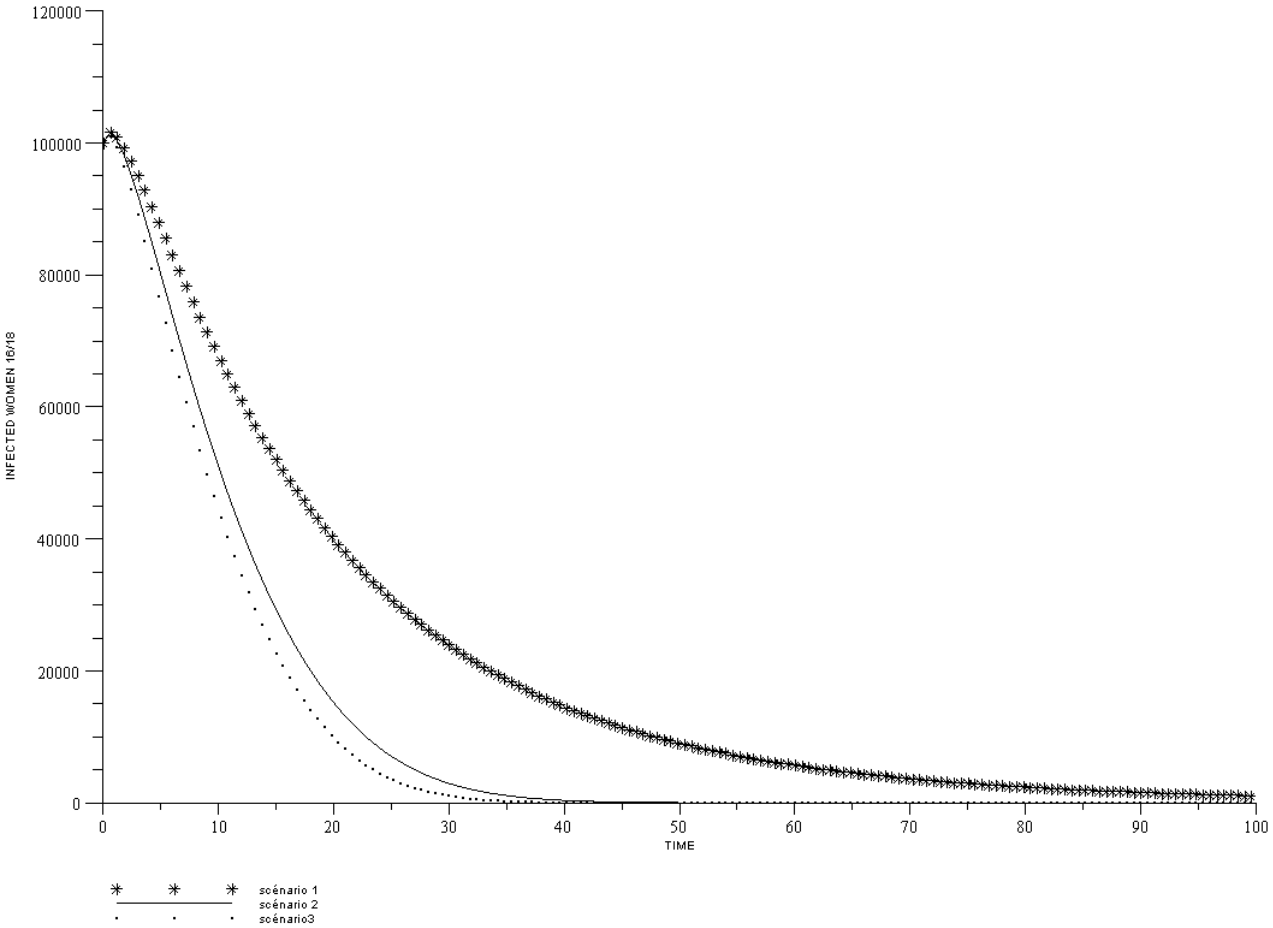

Figure 3. Prevalences of HPV-16/18 infected women considering 3 scenarios of vaccination. At t=0 introduction of vaccine, stars represent the scenario 1, solid line represents the scenario 2, dashed line represents the scenario 3.

Tables

Table 1. Description of variables and parameters

Symbol	Description
Variables	
Non-vaccinated (Vaccinated population)	
$X_{00}(t)$ $(V_{00}(t))$	Susceptible women
$X_{01}(t)$ $(V_{01}(t))$	Infected women with HPV 6/11
$X_{10}(t)$ $(V_{10}(t))$	Infected women with HPV 16/18
$X_{11}(t)$ $(V_{11}(t))$	Infected women with HPV 6/11/16/18
$Y_{00}(t)$ $(W_{00}(t))$	Susceptible men
$Y_{01}(t)$ $(W_{01}(t))$	Infected men with HPV 6/11
$Y_{10}(t)$ $(W_{10}(t))$	Infected men with HPV 16/18
$Y_{11}(t)$ $(W_{11}(t))$	Infected men with HPV 6/11/16/18
Demographic parameters	
Λ	New recruits into the sexually active population
μ	Death or remove rate from the sexually active population
Biological parameters	
σ_f	Infection rate for women
σ_m	Infection rate for men
δ_{01}	Clearance rate for HPV 6/11
δ_{10}	Clearance rate for HPV 16/18
δ_{11}	Clearance rate for HPV 6/11/16/18
Vaccines Parameters	
φ_f	female vaccination rate
φ_m	male vaccination rate
τ	degree of vaccine protection

Table 2. Model's parameters

Parameters	Values	Reference number(s)
Demographic		
Size of women population N_f	500,000	*
Size of men population N_m	500,000	*
New recruits into the sexually active population (per year) Λ	30,000	$\frac{1}{2}\mu N$ †
Death or remove rate from the sexually active population (per year) μ	6%	[15]
Natural history ‡	Parameter range	
Infection rate for women σ_f	0-5	Assumption
Infection rate for men σ_m	0-5	Assumption
Clearance rate for HPV 6/11 (δ_{01}), 16/18 (δ_{10})	0.6-2	[11, 13, 15, 20, 21, 28, 31]
Clearance rate for HPV 6/11/16/18 (δ_{11})	$= \delta_{10}$	longest duration
Vaccines		
Degree of vaccine protection τ	90%	[8]
Vaccination rate	Female	Male
Scenario 1	50%	0%
Scenario 2	50%	50%
Scenario 3	90%	0%

* compartment size large enough to apply a deterministic model
† assumption to have a constant population size in the model
‡ The natural history parameters are annual transition rates

Table 3. Combinations of parameters which product results within the prespecified target

	1	2	3†	4	5	6
Infection rate for women*	1.02	1.14	1.49	1.57	2.36	2.37
Infection rate for men*	0.75	0.68	0.90	0.95	1.75	1.52
Clearance rate HPV-6/11*	0.64 (18.8)	0.65 (18.5)	0.87 (13.8)	0.91 (13.2)	1.55 (7.7)	1.46 (8.2)
Clearance rate HPV-16/18*	0.62 (19.4)	0.63 (19.0)	0.84 (14.3)	0.88 (13.6)	1.5 (8.0)	1.42 (8.4)

*Annual rates
Duration of infection are in parentheses (in months)
† combination used in the sensitivity analyses and the comparison of vaccination scenarios.

Table 4. Partial rank correlation coefficients

	Female inf. rate	Male inf. rate	HPV-6/11 clear. rate	HPV-16/18 clear. rate
Size of compartment:				
Susceptible women	-0.77	-0.44 †	0.66*	0.67*
HPV-6/11 inf. women	0.64*	0.39*†	-0.86	0.41*†
HPV-16/18 inf. women	0.57*†	0.36*†	0.47*†	-0.85
HPV-6/11/16/18 inf. women	0.4*	0.26*†	-0.36†	-0.45 †
Susceptible men	-0.7	-0.62†	0.66*	0.67*
HPV-6/11 inf. men	0.61*	0.46*†	-0.86	0.41*†
HPV-16/18 inf. men	0.53*†	0.44*†	0.46*†	-0.85
HPV-6/11/16/18 inf. men	0.4*	0.27*†	-0.36†	-0.44†

* the results are significant at the 0.001 level

† non monotonous link between input and output