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► **To cite this version:**

Laureen Ribassin-Majed, Rachid Lounes. A SIS model for Human Papillomavirus transmission. 2010.
hal-00555733v2

HAL Id: hal-00555733

<https://hal.science/hal-00555733v2>

Preprint submitted on 11 Feb 2011 (v2), last revised 10 Aug 2012 (v3)

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A SIS model for Human Papillomavirus transmission

L.Ribassin-Majed¹, R. Lounes¹

29/11/2010

Abstract

Human Papillomavirus (HPV) infections are 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. A Susceptible-Infected-Susceptible model of heterosexual transmission of Human Papillomavirus infections is developed. Immunity obtained from vaccination is taken into account. The basic and vaccinated reproduction number are derived using the Next Generation Matrice. We find that if the vaccinated reproduction number is greater than unity, the disease free equilibrium (DFE) is unstable and we prove the existence and uniqueness of endemic equilibrium. If the vaccinated reproduction number is less than unity, there is a locally stable DFE and HPV genotypes covered by the vaccine will be eliminated.

Keywords: HPV; SIS model; equilibrium; stability; reproduction number.

(1) Mathématiques Appliquées Paris 5 (MAP5) CNRS UMR 8145, Paris Descartes University, France.

1 Introduction

Human Papillomavirus is the most common sexually transmitted infection. At least 70 per cent of sexually active people acquire HPV infection at some point in their lives [26]. Eighty per cent of HPV infection cases are cleared in a few months from the body by the immune system without treatment, the remaining 20% infections 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 [3, 24]. Epidemiological studies on HPV infections establish the role of these viruses as the primary cause of cervical cancer [21]. 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 worldwide [25]. It is estimated that HPV infections are responsible for approximately 500,000 cervical cancer cases worldwide each year [23]. Vaccination against HPV infections represents an effective way to decrease cervical cancer incidence, particularly among young women. Actually, 2 prophylactic vaccines against HPV infections have been found to be highly efficient in "naive" women [14]. Several deterministic models have been developed to assess the potential impact of vaccination against HPV; Hughes et al [17] developed 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 [1] explored the effect of a multivalent HPV vaccine using a SIR model which included sexual behaviour, smoking and age; Elbasha et al [10] simulated the progression of HPV disease in the population using 9 compartments, they developed a SIR model included 2 groups of serotype, sexual behaviour and 17 age-group. Taira et al [27] evaluated HPV vaccination programs using a SIS model regarding one serotype stratified by age and sexual activity.

These models were based on numerical simulations with few analytical results. Complexity of those models doesn't allow studying local and global stability of equilibrium. Only Elbasha in other papers studied local and global stability of equilibrium using a SIR model [8, 9, 11]. Models which assume that people who clear infections have immunity against a new HPV infection use SIR model. But actually, this

hypothesis isn't biologically proved in oncogenic serotypes, and the duration of a hypothetical immunity is unknown [18]. Furthermore, there is no immunity against a new HPV infection in low-risk types, and reinfections are frequent. In this paper, we present a Susceptible-Infected-Susceptible (SIS) deterministic model of heterosexual transmission of HPV.

Mathematical models have been developed to study communicable disease such as measles, influenza, rubeola, and chicken pox in some of them equilibria were not globally asymptotically stable and multiple coexistence equilibrium existed [12, 22]. In a non-linear model applied to HIV/AIDS epidemic, de Arozoza et al [4] have found that an equilibrium was not globally asymptotically stable in the feasible region. In model with vaccination, bringing the vaccinated reproduction number below one may not be sufficient to eradicate endemicity of disease if multiple locally stable equilibrium coexist [20, 29]. In the present paper, our aim is to develop a two-sex model of HPV infection transmission in the sexually active population and to analyze the stability of its equilibrium. In section 2, a global model of HPV infection transmission in the sexually active population is presented with vaccination. Then we consider the model without vaccination in section 3.1. The basic reproduction number \mathcal{R}_0 is computed and we prove existence and local stability of disease free (DFE) and endemic equilibria under assumptions of \mathcal{R}_0 values. Using a suitable Lyapunov function, we prove that the DFE is globally asymptotically stable if $\mathcal{R}_0 < 1$. Furthermore numerical calculations are conducted to assess the hypothesis of global stability of endemic equilibrium. In a second step, we consider the model with vaccination. The vaccinated reproduction number is expressed. Existence and local stability of disease free equilibrium are studied. Existence and uniqueness of endemic equilibrium are demonstrated. Numerical simulations suggest global stability of DFE and endemic equilibria.

2 HPV model

The model describe HPV infection transmission in a heterosexually active population. We developed a deterministic model using a Susceptible-Infected-Susceptible (SIS) structure and vaccination is taken into account. Table 1 describes variables and parameters.

Non-vaccinated (resp. vaccinated) women enter the sexually active population in the susceptible compartment X_S (resp. V_S) at constant rate $[(1-\varphi_f)\Lambda]$ (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_S (resp. W_S) at constant rate $[(1-\varphi_m)\Lambda]$ (resp. $[\varphi_m\Lambda]$) and leave all compartments at rate μ . Susceptible individuals are infected with HPV at a per capita rate λ_m and λ_f , this the force of infection. It depends on : the infection rate (σ_m for men and σ_f for women) and the HPV infection prevalence in the opposite sex, then, they move into infected compartments: X_I for women, Y_I for men in non-vaccinated population. We assume that vaccinated persons can be infected. The degree of protection due to the vaccine is τ , the relative risk of a vaccinated person experiencing a breakthrough infection is $(1-\tau)$. We assume that vaccinated infected persons are as infectious as non-vaccinated persons. We assume that vaccine immunity doesn't wane during all of the sexually active life. Women and men who clear HPV infection at rate δ leave infected compartments and go back to susceptible compartments. Demographic and biological parameters are strictly positive.

The non-linear system that represent this compartmental model is:

$$\begin{aligned}
\frac{dX_S}{dt} &= (1 - \varphi_f)\Lambda - \lambda_f X_S + \delta X_I - \mu X_S \\
\frac{dX_I}{dt} &= \lambda_f X_S - (\delta + \mu)X_I \\
\frac{dY_S}{dt} &= (1 - \varphi_m)\Lambda - \lambda_m Y_S + \delta Y_I - \mu Y_S \\
\frac{dY_I}{dt} &= \lambda_m Y_S - (\delta + \mu)Y_I \\
\frac{dV_S}{dt} &= \varphi_f \Lambda - (1 - \tau)\lambda_f V_S + \delta V_I - \mu V_S \\
\frac{dV_I}{dt} &= (1 - \tau)\lambda_f V_S - (\delta + \mu)V_I \\
\frac{dW_S}{dt} &= \varphi_m \Lambda - (1 - \tau)\lambda_m W_S + \delta W_I - \mu W_S \\
\frac{dW_I}{dt} &= (1 - \tau)\lambda_m W_S - (\delta + \mu)W_I
\end{aligned} \tag{1}$$

It is a non linear system because the forces of infection depend on infection rates and the prevalences of HPV infection in the opposite gender

$$\begin{aligned}
\lambda_f &= \sigma_f \frac{(Y_I + W_I)}{N_m} \\
\lambda_m &= \sigma_m \frac{(X_I + V_I)}{N_f}
\end{aligned}$$

To have a constant size of population in the model, we have

$$\begin{aligned}
N_f &= X_S + X_I + V_S + V_I \\
N_m &= Y_S + Y_I + W_S + W_I \\
N &= N_f + N_m.
\end{aligned}$$

Thus

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

Since at equilibrium $N^* = \frac{2\Lambda}{\mu}$, we only need to analyze the asymptotically autonomous limiting system where N is replaced by its equilibrium value. We consider the system only in the region

$$D = \left\{ (X_S, X_I, Y_S, Y_I, V_S, V_I, W_S, W_I) \in \mathbb{R}_+^8, X_S + X_I + Y_S + Y_I + V_S + V_I + W_S + W_I \leq \frac{2\Lambda}{\mu} \right\}.$$

It can be verified that D is positively invariant for this system and unique solutions exist in D for all positive time. The model is epidemiologically and mathematically well posed.

3 Analysis of equilibria and reproduction numbers

3.1 The model without vaccination

Here we consider the model without vaccination to explore the existence and the stability of equilibria.

3.1.1 Existence of DFE

In the absence of vaccination, $\varphi_m = 0$ and $\varphi_f = 0$ as well as $V_S = V_I = W_S = W_I = 0$. The system of differential ordinary equations is as follows:

$$\begin{aligned}\frac{dX_S}{dt} &= \Lambda - \lambda_f X_S + \delta X_I - \mu X_S \\ \frac{dX_I}{dt} &= \lambda_f X_S - (\delta + \mu) X_I \\ \frac{dY_S}{dt} &= \Lambda - \lambda_m Y_S + \delta Y_I - \mu Y_S \\ \frac{dY_I}{dt} &= \lambda_m Y_S - (\delta + \mu) Y_I\end{aligned}\tag{2}$$

with $\lambda_f = \frac{\sigma_f Y_I}{N_m}$ and $\lambda_m = \frac{\sigma_m X_I}{N_f}$.

The equilibria of this model are obtained by setting the right hand sides of the model equations to zero. The system (2) has two equilibria, one at $P_0 = (X_S^*, X_I^*, Y_S^*, Y_I^*) = (\frac{\Lambda}{\mu}, 0, \frac{\Lambda}{\mu}, 0)$ which is the DFE, and $P_1 = (X_S^{**}, X_I^{**}, Y_S^{**}, Y_I^{**})$ the endemic equilibrium, where

$$\begin{aligned}X_S^{**} &= \frac{dN(\delta + \mu)}{\sigma_f}, \\ X_I^{**} &= \frac{\Lambda}{\mu} - \frac{dN(\delta + \mu)}{\sigma_f}, \\ Y_S^{**} &= \frac{\Lambda}{\mu}(1 - 1/d) + \frac{N(\delta + \mu)}{\sigma_f}, \\ Y_I^{**} &= \frac{\Lambda}{d\mu} - \frac{N(\delta + \mu)}{\sigma_f}.\end{aligned}$$

with

$$d = \frac{\sigma_m \sigma_f + \sigma_f(\delta + \mu)}{\sigma_m \sigma_f + \sigma_m(\delta + \mu)}.$$

We established the existence of DFE, we need to compute the basic reproduction number \mathcal{R}_0 to analyze local and global stability of the DFE depending on \mathcal{R}_0 values.

3.1.2 Basic reproduction number

The basic reproduction number \mathcal{R}_0 is a threshold quantity which determine 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 [6]. We use the Next Generation Matrice (NGM) [28] to compute \mathcal{R}_0 . We define the system (3) with the first two components corresponding to infected compartments and the last two components corresponding to susceptible compartments:

$$\dot{x} = (\dot{X}_I, \dot{Y}_I, \dot{X}_S, \dot{Y}_S)^T = (0, 0, 0, 0)^T.\tag{3}$$

Following the Next Generation Matrice method [28], we break up \dot{x} into $\mathcal{F} - \mathcal{V}$, it gives:

$$\mathcal{F} = \begin{pmatrix} \sigma_f \frac{Y_I}{N_m} X_S \\ \sigma_m \frac{X_I}{N_f} Y_S \\ 0 \\ 0 \end{pmatrix} \text{ and } \mathcal{V} = \begin{pmatrix} (\delta + \mu) X_I \\ (\delta + \mu) Y_I \\ -\Lambda + \lambda_f X_S - \delta X_I + \mu X_S \\ -\Lambda + \lambda_m Y_S - \delta Y_I + \mu Y_S \end{pmatrix}$$

Then, the Jacobian matrices of \mathcal{F} and \mathcal{V} are evaluated at the disease-free equilibrium (DFE). Using the relation: $N = 2 \frac{\Lambda}{\mu}$

$$d\mathcal{F}(P_0) = \left(\begin{array}{c|c} F & 0 \\ \hline 0 & 0 \end{array} \right) \text{ and } d\mathcal{V}(P_0) = \left(\begin{array}{c|c} V & 0 \\ \hline W & \mu I_2 \end{array} \right)$$

with

$$F = \left(\begin{array}{cc} 0 & \sigma_f \\ \sigma_m & 0 \end{array} \right) \text{ and } V = \left(\begin{array}{cc} \delta + \mu & 0 \\ 0 & \delta + \mu \end{array} \right)$$

So,

$$(FV)^{-1} = \frac{1}{(\delta + \mu)} \left(\begin{array}{cc} 0 & \sigma_f \\ \sigma_m & 0 \end{array} \right)$$

\mathcal{R}_0 is equal to the spectral radius of $(FV)^{-1}$ [5], thus:

$$\mathcal{R}_0 = \sqrt{\mathcal{R}_{0,f} \mathcal{R}_{0,m}}$$

with: $\mathcal{R}_{0,f} = \frac{\sigma_f}{(\delta + \mu)}$ and $\mathcal{R}_{0,m} = \frac{\sigma_m}{(\delta + \mu)}$.

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 $\mathcal{R}_0 = \frac{\sigma}{(\delta + \mu)}$ which is a classic expression of \mathcal{R}_0 in simple SIS model.

$\mathcal{R}_{0,f}$ is the number of secondary infections generated by one infected woman in a population of susceptible men during her infectious period. Then, each infected men can infect in mean $\mathcal{R}_{0,m}$ susceptible women during his infectious period.

3.1.3 Local and global stability of DFE

In this section, we focus on the stability of the DFE.

Theorem 1 *if $\mathcal{R}_0 < 1$ then the DFE is locally asymptotically stable.*

Proof The Jacobian matrix of the system without vaccination ($\dot{x} = (0, 0, 0, 0)^T$ (3)) is evaluated at the DFE P_0 :

$$\mathcal{J}(P_0) = \left(\begin{array}{cccc} -(\delta + \mu) & \sigma_f & 0 & 0 \\ \sigma_m & -(\delta + \mu) & 0 & 0 \\ \delta & -\sigma_f & -\mu & 0 \\ -\sigma_m & -\delta & 0 & -\mu \end{array} \right)$$

We define:

$$A_1 = \left(\begin{array}{cc} -(\delta + \mu) & \sigma_f \\ \sigma_m & -(\delta + \mu) \end{array} \right)$$

$\text{Tr}(A_1) < 0$ and $\det(A_1) > 0$ if $\mathcal{R}_0 < 1$. Thus, if $\mathcal{R}_0 < 1$, all eigenvalues of the jacobian matrix linearized system around the DFE have strictly negative real parts, therefore the DFE, P_0 , is locally asymptotically stable if $\mathcal{R}_0 < 1$.

If $\mathcal{R}_0 > 1$, one eigenvalue has positive real part and the DFE is locally unstable.

Theorem 2 *The DFE is globally asymptotically stable if and only if $\mathcal{R}_0 \leq 1$.*

Proof: Consider the Lyapunov function in D

$$V = X_I + \mathcal{R}_{0,f} Y_I$$

The derivative of V along the solution of (3) is given by

$$\begin{aligned} V' &= X_I' + \mathcal{R}_{0,f} Y_I' \\ &= \left(\mathcal{R}_{0,f} \sigma_m \frac{Y_S}{N_f} - (\delta + \mu) \right) X_I + \left(\sigma_f \frac{X_S}{N_m} - \mathcal{R}_{0,f} (\delta + \mu) \right) Y_I \end{aligned}$$

Using $Y_S \leq Y_S^*$ (because $Y_S \leq Y_S + Y_I \leq Y_S^* + Y_I^*$); $X_S \leq X_S^*$ and $N_f = N_m = \frac{\Lambda}{\mu}$

$$\begin{aligned} V' &\leq (\mathcal{R}_{0,f} \sigma_m - (\delta + \mu)) X_I + (\sigma_f - \mathcal{R}_{0,f} (\delta + \mu)) Y_I \\ V' &\leq (\delta + \mu) (\mathcal{R}_0^2 - 1) X_I \end{aligned}$$

If $\mathcal{R}_0 \leq 1$ then $V' \leq 0$ and $V' = 0$ only in P_0 .

lemma 1 $V' = 0$ only in P_0

Proof The equality $V'=0$ holds only at the DFE or when $\mathcal{R}_0 = 1$ and $(X_S, Y_S) = (X_S^*, Y_S^*)$.

But $X_S + X_I + Y_S + Y_I \leq \frac{2\Lambda}{\mu}$.

Therefore $X_S^* + X_I + Y_S^* + Y_I \leq \frac{2\Lambda}{\mu}$ and $X_S^* + Y_S^* = \frac{2\Lambda}{\mu}$. It implies that $X_I = Y_I = 0$ and $V'=0$ only in P_0 .

The Lasalle-Liapunov theory [15] implies that all paths in D approach the largest positively invariant subset of the set E where $V'=0$. Here, we have proved in lemma 1 that the only positively invariant subset is P_0 so P_0 is globally asymptotically stable for $\mathcal{R}_0 \leq 1$.

3.1.4 Local stability of Endemic equilibrium

We can rewrite P_1 as:

$$\begin{aligned} X_S^{**} &= \frac{\Lambda}{\mu} \left(\frac{\mathcal{R}_0^2 + \mathcal{R}_{0,f}}{\mathcal{R}_0^2 + \mathcal{R}_{0,m}} \right) \frac{1}{\mathcal{R}_{0,f}} \\ X_I^{**} &= \frac{\Lambda}{\mu} \frac{\mathcal{R}_0^2 - 1}{\mathcal{R}_0^2 + \mathcal{R}_{0,m}} \\ Y_S^{**} &= \frac{\Lambda}{\mu} \frac{1 + \mathcal{R}_{0,f}}{\mathcal{R}_0^2 + \mathcal{R}_{0,f}} \\ Y_I^{**} &= \frac{\Lambda}{\mu} \frac{\mathcal{R}_0^2 - 1}{\mathcal{R}_0^2 + \mathcal{R}_{0,f}}. \end{aligned}$$

The endemic equilibrium is feasible (i.e. $P_1 \in \mathcal{D}$) if and only if $\mathcal{R}_0 \geq 1$ (with $P_1 = P_0$ where $\mathcal{R}_0 = 1$).

Theorem 3 *The endemic equilibrium is locally asymptotically stable if and only if $\mathcal{R}_0 > 1$.*

Proof The Jacobian matrix of the system (3) is evaluated at the endemic equilibrium P_1 :

$$\mathcal{J}(P_1) = \begin{pmatrix} -(\delta + \mu) & \frac{\sigma_f}{N_m} X_S^{**} & \frac{\sigma_f}{N_m} Y_I^{**} & 0 \\ \frac{\sigma_m}{N_f} Y_S^{**} & -(\delta + \mu) & 0 & \frac{\sigma_m}{N_f} X_I^{**} \\ \delta & -\frac{\sigma_f}{N_m} X_S^{**} & -\frac{\sigma_f}{N_m} Y_I^{**} - \mu & 0 \\ -\frac{\sigma_m}{N_f} Y_S^{**} & \delta & 0 & -\frac{\sigma_m}{N_f} X_I^{**} - \mu \end{pmatrix}$$

The characteristic polynomial is:

$$p(x) = (\mu + x)^2 \left[(\delta + \mu + x)^2 + \frac{\sigma_m X_I^{**}}{N_f} (\delta + \mu + x) - \frac{\sigma_m \sigma_f}{N_f N_m} X_S^{**} Y_S^{**} + \frac{\sigma_f Y_I^{**}}{N_m} \left(\delta + \mu + x + \frac{\sigma_m X_I^{**}}{N_f} \right) \right].$$

Thus $-\mu$ is a double eigenvalue of this matrix. The two other eigenvalues are the roots of the following polynomial:

$$q(x) = x^2 + [2(\delta + \mu) + \frac{\sigma_m}{N_f} X_I^{**} + \frac{\sigma_f}{N_m} Y_I^{**}]x + [(\delta + \mu)^2 + (\delta + \mu) \frac{\sigma_m}{N_f} X_I^{**} + \frac{\sigma_f}{N_m} Y_I^{**} + \frac{\sigma_f \sigma_m}{N_f N_m} (X_I^{**} Y_I^{**} - X_S^{**} Y_S^{**})]$$

$$\Delta = \left[2(\delta + \mu) + \frac{\sigma_m}{N_f} X_I^{**} + \frac{\sigma_f}{N_m} Y_I^{**} \right]^2 - 4 \left[(\delta + \mu)^2 + (\delta + \mu) \frac{\sigma_m}{N_f} X_I^{**} + \frac{\sigma_f}{N_m} Y_I^{**} + \frac{\sigma_f \sigma_m}{N_f N_m} (X_I^{**} Y_I^{**} - X_S^{**} Y_S^{**}) \right].$$

The discriminant is positive: $\Delta = \underbrace{\left(\frac{\sigma_m}{N_f} X_I^{**} - \frac{\sigma_f}{N_m} Y_I^{**} \right)^2}_{>0} + 4 \underbrace{\frac{\sigma_m \sigma_f}{N_f N_m} X_S^{**} Y_S^{**}}_{>0}$.

Therefore the 2 solutions of q, x_1 and x_2 are eigenvalues of $\mathcal{J}(P_1)$.

$$x_1 = \frac{-[2(\delta + \mu) + \frac{\sigma_m}{N_f} X_I^{**} + \frac{\sigma_f}{N_m} Y_I^{**}] - \sqrt{\Delta}}{2},$$

$$x_2 = \frac{-[2(\delta + \mu) + \frac{\sigma_m}{N_f} X_I^{**} + \frac{\sigma_f}{N_m} Y_I^{**}] + \sqrt{\Delta}}{2}.$$

x_1 is negative, we have to study the sign of x_2 . We prove that x_2 is negative if and only if $\mathcal{R}_0 > 1$.

lemma 2 $x_2 < 0$ if and only if $\mathcal{R}_0 > 1$.

Proof: We denote the characteristic polynomial $p(x) = x^2 + bx + c$ with

$$b = 2(\delta + \mu) + \frac{\sigma_m}{N_f} X_I^{**} + \frac{\sigma_f}{N_m} Y_I^{**} \text{ and } c = (\delta + \mu)^2 + (\delta + \mu) \frac{\sigma_m}{N_f} X_I^{**} + \frac{\sigma_f}{N_m} Y_I^{**} + \frac{\sigma_f \sigma_m}{N_f N_m} (X_I^{**} Y_I^{**} - X_S^{**} Y_S^{**})$$

So,

$$x_2 = \frac{-b + \sqrt{b^2 - 4c}}{2} = \frac{b}{2} \left(-1 + \sqrt{1 - \frac{4c}{b^2}} \right)$$

$$x_2 < 0 \Leftrightarrow \sqrt{1 - \frac{4c}{b^2}} < 1$$

Let us prove that $c > 0 \Leftrightarrow \mathcal{R}_0 > 1$.

Using values of $X_S^{**}, Y_S^{**}, X_I^{**}, Y_I^{**}$ and $N_f = N_m = \frac{\Lambda}{\mu}$, we have:

$$c = (\delta + \mu)^2 + (\delta + \mu)^2 \left(\mathcal{R}_{0,m} - \frac{\mathcal{R}_{0,m}}{\mathcal{R}_{0,f}} \frac{\mathcal{R}_0^2 + \mathcal{R}_{0,f}}{\mathcal{R}_0^2 + \mathcal{R}_{0,m}} + \mathcal{R}_{0,f} \frac{\mathcal{R}_0^2 + \mathcal{R}_{0,m}}{\mathcal{R}_0^2 + \mathcal{R}_{0,f}} - 1 \right)$$

$$+ (\delta + \mu)^2 \mathcal{R}_0^2 \left(\left(1 - \frac{1}{\mathcal{R}_{0,f}} \frac{\mathcal{R}_0^2 + \mathcal{R}_{0,f}}{\mathcal{R}_0^2 + \mathcal{R}_{0,m}} \right) \left(\frac{\mathcal{R}_0^2 + \mathcal{R}_{0,m}}{\mathcal{R}_0^2 + \mathcal{R}_{0,f}} - \frac{1}{\mathcal{R}_{0,f}} \right) - \left(\frac{1}{\mathcal{R}_{0,f}} \frac{\mathcal{R}_0^2 + \mathcal{R}_{0,f}}{\mathcal{R}_0^2 + \mathcal{R}_{0,m}} \right) \left(1 + \frac{1}{\mathcal{R}_{0,f}} - \frac{\mathcal{R}_0^2 + \mathcal{R}_{0,m}}{\mathcal{R}_0^2 + \mathcal{R}_{0,f}} \right) \right)$$

Rearranging and after simplifying

$$c = \underbrace{(\delta + \mu)^2 \mathcal{R}_0^2 (\mathcal{R}_{0,m} + \mathcal{R}_{0,f} + \mathcal{R}_0^2 + 1) \mathcal{R}_{0,f}}_{>0} (\mathcal{R}_0^2 - 1)$$

c is the product of a strictly positive number and $(\mathcal{R}_0^2 - 1)$.

We conclude that: $c > 0$ iff $\mathcal{R}_0 > 1$.

Therefore, the endemic equilibrium is locally asymptotically stable if and only if $\mathcal{R}_0 > 1$. The endemic equilibrium is probably also globally asymptotically stable for $\mathcal{R}_0 > 1$ but the Lyapunov function used in Theorem 2 does not work. Numerical calculations suggest asymptotic stability.

Now, let us consider the model including vaccination compartments.

3.2 The model with vaccination

Here we focus on the model including vaccination. As we did in the previous sections, we want to study stability of DFE and endemic equilibrium. In a first step, we compute the Vaccinated reproduction number.

3.2.1 The Vaccinated reproduction number

We can find the DFE of (1) given by

$$Q_0 = \left((1 - \varphi_f) \frac{\Lambda}{\mu}, 0, (1 - \varphi_m) \frac{\Lambda}{\mu}, 0, \varphi_f \frac{\Lambda}{\mu}, 0, \varphi_m \frac{\Lambda}{\mu}, 0 \right).$$

The Next Generation approach uses only equations of infected persons. We define

$$\dot{x} = (\dot{X}_1, \dot{V}_1, \dot{Y}_1, \dot{W}_1)^T \quad (4)$$

We break up \dot{y} into $\mathcal{F}_1 - \mathcal{V}_1$, we compute the Jacobian matrices of \mathcal{F}_1 and \mathcal{V}_1 linearized around the DFE Q_0 . Thus:

$$F_1 = d\mathcal{F}_1(Q_0) = \begin{pmatrix} 0 & 0 & \sigma_f(1 - \varphi_f) & \sigma_f(1 - \varphi_f) \\ 0 & 0 & (1 - \tau)\sigma_f\varphi_f & (1 - \tau)\sigma_f\varphi_f \\ \sigma_m(1 - \varphi_m) & \sigma_m(1 - \varphi_m) & 0 & 0 \\ (1 - \tau)\sigma_m\varphi_m & (1 - \tau)\sigma_m\varphi_m & 0 & 0 \end{pmatrix}$$

$$V_1 = d\mathcal{V}_1(Q_0) = \begin{pmatrix} (\delta + \mu) & 0 & 0 & 0 \\ 0 & (\delta + \mu) & 0 & 0 \\ 0 & 0 & (\delta + \mu) & 0 \\ 0 & 0 & 0 & (\delta + \mu) \end{pmatrix}$$

We compute $(F_1 V_1)^{-1}$

$$(F_1 V_1)^{-1} = \begin{pmatrix} 0 & 0 & \frac{\sigma_f}{(\delta + \mu)}(1 - \varphi_f) & \frac{\sigma_f}{(\delta + \mu)}(1 - \varphi_f) \\ 0 & 0 & (1 - \tau) \frac{\sigma_f}{(\delta + \mu)} \varphi_f & (1 - \tau) \frac{\sigma_f}{(\delta + \mu)} \varphi_f \\ \frac{\sigma_m}{(\delta + \mu)}(1 - \varphi_m) & \frac{\sigma_m}{(\delta + \mu)}(1 - \varphi_m) & 0 & 0 \\ (1 - \tau) \frac{\sigma_m}{(\delta + \mu)} \varphi_m & (1 - \tau) \frac{\sigma_m}{(\delta + \mu)} \varphi_m & 0 & 0 \end{pmatrix}$$

We find an estimate of the vaccinated reproduction number \mathcal{R}_v which is the spectral radius of $(F_1 V_1)^{-1}$:

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

with $\mathcal{R}_f(\varphi_f) = \mathcal{R}_{0,f}[(1 - \varphi_f) + (1 - \tau)\varphi_f]$ and $\mathcal{R}_m(\varphi_m) = \mathcal{R}_{0,m}[(1 - \varphi_m) + (1 - \tau)\varphi_m]$.

Note that the terms inside brackets are less than one, so $\mathcal{R}_v < \mathcal{R}_0$. The term under square root shows how much the vaccination reduces \mathcal{R}_0 .

3.2.2 Local stability of DFE

We prove the local stability of the DFE considering \mathcal{R}_v values.

Theorem 4 *The DFE is locally asymptotically stable if and only if $\mathcal{R}_v < 1$.*

Proof We define the system

$$(\dot{X}_1, \dot{V}_1, \dot{Y}_1, \dot{W}_1, \dot{X}_0, \dot{V}_0, \dot{Y}_0, \dot{W}_0)^T = (0, 0, 0, 0, 0, 0, 0, 0)^T \quad (5)$$

We compute the Jacobian matrix of the system (5) at its DFE Q_0 .

$$J_1 = \begin{pmatrix} A_1 & 0 \\ A_2 & D_1 \end{pmatrix}$$

with $A_1 = F_1 - V_1$ and $D_1 = -\mu I_4$, I_4 being identity matrix of size 4;

Therefore, $(-\mu)$ is an eigenvalue of J_1 of order four. We consider the matrix $-A_1$:

$$-A_1 = \begin{pmatrix} (\delta + \mu) & 0 & -\sigma_f(1 - \varphi_f) & -\sigma_f(1 - \varphi_f) \\ 0 & (\delta + \mu) & -(1 - \tau)\sigma_f\varphi_f & -(1 - \tau)\sigma_f\varphi_f \\ -\sigma_m(1 - \varphi_m) & -\sigma_m(1 - \varphi_m) & (\delta + \mu) & 0 \\ -(1 - \tau)\sigma_m\varphi_m & -(1 - \tau)\sigma_m\varphi_m & 0 & (\delta + \mu) \end{pmatrix}$$

All diagonal elements of $-A_1$ are non-negative and all off-diagonal entries are non-positive. Therefore, $-A_1$ is a Z-matrice. Principal minors of $-A_1$ are:

$$C_1 = \delta + \mu$$

$$C_2 = (\delta + \mu)^2$$

$$C_3 = \begin{vmatrix} (\delta + \mu) & 0 & -\sigma_f(1 - \varphi_f) \\ 0 & (\delta + \mu) & -(1 - \tau)\sigma_f\varphi_f \\ -\sigma_m(1 - \varphi_m) & -\sigma_m(1 - \varphi_m) & (\delta + \mu) \end{vmatrix}$$

$$C_4 = \det(-A_1).$$

After some calculations, we express more simply C_3 and C_4 to determine their signs, therefore:

$$C_3 = C_1 C_2 \left[1 - \mathcal{R}_v^2 + \mathcal{R}_f(\varphi_f) \frac{\sigma_m}{(\delta + \mu)} (1 - \tau)\varphi_m \right]$$

$$C_4 = (\delta + \mu)^4 (1 - \mathcal{R}_v^2)$$

C_3 and C_4 are positive iff $\mathcal{R}_v < 1$. If $\mathcal{R}_v < 1$, all principal minors of the Z-matrice $-A_1$ are positive, so $-A_1$ is a M-matrice [16]. The real parts of each eigenvalues of $(-A_1)$ are strictly positive, thus real parts of each eigenvalues of (A_1) are strictly negative. Then, the DFE Q_0 is locally asymptotically stable if $\mathcal{R}_v < 1$. Otherwise, if $\mathcal{R}_v > 1$: $C_4 < 0$, at least one of principal minors of $-A_1$ is negative, so, at least one of its eigenvalues is negative. At least one of the eigenvalue of A_1 has a positive real part which induces that Q_0 is locally asymptotically unstable. We proved that the DFE of the model with vaccination is locally asymptotically stable if and only if $\mathcal{R}_v < 1$.

When $\mathcal{R}_v < 1$ the DFE is probably also globally asymptotically stable. Numerical calculations suggest asymptotic stability.

3.2.3 Existence and Uniqueness of Endemic Equilibrium

Theorem 5 *If $\mathcal{R}_v > 1$ the endemic equilibrium exists and it's unique.*

If $\mathcal{R}_v < 1$ there isn't any endemic equilibrium.

Proof We solve the system (4) in term of λ_f and λ_m .

We obtain:

$$\begin{aligned}\lambda_f &= \sigma_f \left[(1 - \varphi_m) \frac{\lambda_m}{\lambda_m + \delta + \mu} + \varphi_m \frac{(1 - \tau)\lambda_m}{(1 - \tau)\lambda_m + \delta + \mu} \right] \\ \lambda_m &= \sigma_m \left[(1 - \varphi_m) \frac{\lambda_f}{\lambda_f + \delta + \mu} + \varphi_f \frac{(1 - \tau)\lambda_f}{(1 - \tau)\lambda_f + \delta + \mu} \right].\end{aligned}$$

We define 2 level curves:

$$\begin{aligned}G_f(\lambda_f, \lambda_m) &= -\lambda_f + \sigma_f \left[(1 - \varphi_m) \frac{\lambda_m}{\lambda_m + \delta + \mu} + \varphi_m \frac{(1 - \tau)\lambda_m}{(1 - \tau)\lambda_m + \delta + \mu} \right] \\ G_m(\lambda_f, \lambda_m) &= -\lambda_m + \sigma_m \left[(1 - \varphi_m) \frac{\lambda_f}{\lambda_f + \delta + \mu} + \varphi_f \frac{(1 - \tau)\lambda_f}{(1 - \tau)\lambda_f + \delta + \mu} \right]\end{aligned}$$

The 2 levels curves go through the origin and $\lim_{\lambda_k \rightarrow \infty} \lambda_k > 0$. To prove the existence and uniqueness of endemic equilibrium, we have to prove that these 2 level curves intersect only once in the first positive quadrant ($\lambda_f > 0, \lambda_m > 0$). Following the method describe by Elbasha [8], we prove that : if $\mathcal{R}_v > 1$ the level curve G_m is above G_f around the origin, and the slopes of level curves are positives. Furthermore, each level curve intersect only once a ray from the origin. So, if $\mathcal{R}_v > 1$, the endemic equilibrium exists. To show the uniqueness of the endemic equilibrium, we have to show uniqueness of level curves' intersect in the first positive quadrant. We use, Poincare-Hopf theorem which implies that if the continuously differentiable function $G : K \rightarrow \mathcal{R}^2$, where K is a compact cube in \mathcal{R}^2 , satisfies a boundary condition and the Jacobian matrix $-DG(\Gamma)$ has positive determinant at all equilibria, then there is an unique equilibrium. The boundary condition choosen is: $G_k(\lambda_f, \lambda_m) = 0$ with $\lambda_k = 0, k = f, m$. The Jacobian matrix is:

$$-DG(\Gamma) = \begin{pmatrix} 1 & -\frac{\partial \lambda_f}{\partial \lambda_m} \Big|_{G_f(\lambda_f, \lambda_m)=0} \\ -\frac{\partial \lambda_m}{\partial \lambda_f} \Big|_{G_m(\lambda_f, \lambda_m)=0} & 1 \end{pmatrix}$$

We prove that $\det(-DG(\Gamma)) > 0$, i.e. $\frac{\partial \lambda_f}{\partial \lambda_m} \Big|_{G_f(\lambda_f, \lambda_m)=0} \times \frac{\partial \lambda_m}{\partial \lambda_f} \Big|_{G_m(\lambda_f, \lambda_m)=0} < 1$

lemma 3 $\det(-DG(\Gamma)) > 0$.

Proof:

$$\det(-DG(\Gamma)) > 0 \Leftrightarrow \frac{\partial \lambda_f}{\partial \lambda_m} \Big|_{G_f(\lambda_f, \lambda_m)=0} \times \frac{\partial \lambda_m}{\partial \lambda_f} \Big|_{G_m(\lambda_f, \lambda_m)=0} < 1$$

$$\lambda_f = \sigma_f \left(\frac{(1 - \varphi_m)}{1 + \frac{\delta + \mu}{\lambda_m}} + \frac{\varphi_m(1 - \tau)}{(1 - \tau) + \frac{\delta + \mu}{\lambda_m}} \right)$$

$$\frac{\partial \lambda_f}{\partial \lambda_m} \Big|_{G_f(\lambda_f, \lambda_m)=0} = \sigma_f \frac{\delta + \mu}{\lambda_m^2} \left(\frac{1 - \varphi_m}{(1 + \frac{\delta + \mu}{\lambda_m})^2} + \frac{\varphi_m(1 - \tau)}{((1 - \tau) + \frac{\delta + \mu}{\lambda_m})^2} \right)$$

Multiplying by λ_f the numerator and the denominator, we obtain:

$$\frac{\partial \lambda_f}{\partial \lambda_m} \Big|_{G_f(\lambda_f, \lambda_m)=0} = \frac{\lambda_f}{\lambda_m} \frac{\left(\frac{\delta + \mu}{\lambda_m} \right) \left(\frac{1 - \varphi_m}{(1 + \frac{\delta + \mu}{\lambda_m})^2} + \frac{\varphi_m(1 - \tau)}{((1 - \tau) + \frac{\delta + \mu}{\lambda_m})^2} \right)}{\left(\frac{1 - \varphi_m}{(1 + \frac{\delta + \mu}{\lambda_m})} + \frac{\varphi_m(1 - \tau)}{(1 - \tau) + \frac{\delta + \mu}{\lambda_m}} \right)}$$

Therefore,

$$\begin{aligned} \frac{\partial \lambda_f}{\partial \lambda_m} \Big|_{G_f(\lambda_f, \lambda_m)=0} \times \frac{\partial \lambda_m}{\partial \lambda_f} \Big|_{G_m(\lambda_f, \lambda_m)=0} &= \prod_{k=f,m} \frac{\left(\frac{\delta + \mu}{\lambda_k} \right) \left(\frac{1 - \varphi_k}{(1 + \frac{\delta + \mu}{\lambda_k})^2} + \frac{\varphi_k(1 - \tau)}{((1 - \tau) + \frac{\delta + \mu}{\lambda_k})^2} \right)}{\left(\frac{1 - \varphi_k}{1 + \frac{\delta + \mu}{\lambda_k}} + \frac{\varphi_k(1 - \tau)}{(1 - \tau) + \frac{\delta + \mu}{\lambda_k}} \right)} \\ &= \frac{\left(\frac{\delta + \mu}{\lambda_k} \right) \left(\frac{1 - \varphi_k}{(1 + \frac{\delta + \mu}{\lambda_k})^2} + \frac{\varphi_k(1 - \tau)}{((1 - \tau) + \frac{\delta + \mu}{\lambda_k})^2} \right)}{\left(\frac{1 - \varphi_k}{1 + \frac{\delta + \mu}{\lambda_k}} + \frac{\varphi_k(1 - \tau)}{(1 - \tau) + \frac{\delta + \mu}{\lambda_k}} \right)} < 1 \\ &\Leftrightarrow \left(\frac{\delta + \mu}{\lambda_k} \right) \left(\frac{1 - \varphi_k}{(1 + \frac{\delta + \mu}{\lambda_k})^2} + \frac{\varphi_k(1 - \tau)}{((1 - \tau) + \frac{\delta + \mu}{\lambda_k})^2} \right) < \left(\frac{1 - \varphi_k}{1 + \frac{\delta + \mu}{\lambda_k}} + \frac{\varphi_k(1 - \tau)}{(1 - \tau) + \frac{\delta + \mu}{\lambda_k}} \right) \\ &\Leftrightarrow \frac{\delta + \mu}{\lambda_k} (1 - \varphi_k) \left((1 - \tau) + \frac{\delta + \mu}{\lambda_k} \right)^2 + \frac{\delta + \mu}{\lambda_k} \varphi_k (1 - \tau) \left(1 + \frac{\delta + \mu}{\lambda_k} \right)^2 \\ &< (1 - \varphi_k) \left(1 + \frac{\delta + \mu}{\lambda_k} \right) \left((1 - \tau) + \frac{\delta + \mu}{\lambda_k} \right)^2 + \varphi_k (1 - \tau) \left(1 + \frac{\delta + \mu}{\lambda_k} \right)^2 \left((1 - \tau) + \frac{\delta + \mu}{\lambda_k} \right) \\ &\Leftrightarrow - \left((1 - \varphi_k) \left(1 - \tau + \frac{\delta + \mu}{\lambda_k} \right)^2 \right) - \left((1 - \tau)^2 \varphi_k^2 \left(1 + \frac{\delta + \mu}{\lambda_k} \right)^2 \right) < 0 \end{aligned}$$

So, we proved that each term of the product is less than one, therefore

$$\det(-DG(\Gamma)) > 0$$

Finally, we have proved that if the endemic equilibrium exists, it must be unique.

Furthermore, if $\mathcal{R}_v > 1$ the endemic equilibrium is probably globally asymptotically stable. Numerical calculations suggest this asymptotic behaviour.

4 Summary and Discussion

Actually, two prophylactic vaccines against HPV 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 [7]. The question of vaccination for boys is being studied [2, 13, 19]. 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.

The vaccinated reproduction number is a threshold which determines if an epidemic can spread or die out. Its expression depends on parameters as vaccine coverage for each sex. Thus, it gives tools for Public Health deciders to determine on which parameters they can act to eradicate the epidemic of HPV. But sometimes, driving out the basic reproduction number below one is not enough to eradicate the disease [29]. It is necessary to study asymptotic behavior of the model.

In this paper, we developed a deterministic SIS model of heterosexually HPV transmission. First, we considered the model without vaccination, we found that the basic reproduction number is

$$\mathcal{R}_0 = \sqrt{\frac{\sigma_f}{(\delta + \mu)} \frac{\sigma_m}{(\delta + \mu)}}$$

Using a suitable Lyapunov function, we proved that the disease free equilibrium P_0 is globally asymptotically stable if and only if $\mathcal{R}_0 \leq 1$ and the endemic equilibrium is globally asymptotically stable if and only if $\mathcal{R}_0 \geq 1$. Then we derived the vaccinated reproduction number \mathcal{R}_v in the model with vaccination:

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

We proved that if $\mathcal{R}_v > 1$, the endemic equilibrium exists and it's unique, if $\mathcal{R}_v < 1$, there isn't any endemic equilibrium. We proved that if the vaccinated reproduction number is less than 1, the DFE is locally asymptotically stable and HPV genotypes covered by the vaccine will be eliminated.

In future research, we'll have to prove global stability of equilibria in the model with vaccination.

Acknowledgments

The authors would like to thank Stephan Clemençon, Hector de Arazoza and Bilal Majed for their invaluable help.

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Symbol	Description
Variables	
Non-vaccinated population	
$X_S(t)$	Susceptible women
$Y_S(t)$	Susceptible men
$X_I(t)$	Infected women
$Y_I(t)$	Infected men
Vaccinated population	
$V_S(t)$	Susceptible women
$W_S(t)$	Susceptible men
$V_I(t)$	Infected women
$W_I(t)$	Infected men
λ_f	Force of infection for women
λ_m	Force of infection for men
Demographic parameters	
Λ	New recruits into the sexually active population
μ	Death rate or rate of exit from the sexually active population
Biological parameters	
σ_f	Infection rate for women
σ_m	Infection rate for men
δ	Clearance rate
Vaccines Parameters	
φ_k	Vaccination rate
τ	Degree of vaccine protection

Table 1: Description of variables and parameters