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Abstract

This paper is devoted to assess the impact of quadrivalent Human Papillomavirus (HPV) vaccine on prevalence of non-oncogenic HPV 6/11 types in French males and females. For this purpose, a non-linear dynamic model of heterosexual transmission for HPV 6/11 types infection is developed, which accounts for immunity due to vaccination in particular. The vaccinated reproduction number R_v is derived using the approach described by Diekmann (2010) called the Next Generation Operator approach. The model proposed is analyzed, with regard to existence and uniqueness of the solution, steady-state stability. Precisely, the stability of the model is investigated depending on the sign of $R_v - 1$. Prevalence data are used to fit a numerical HPV model, so as to assess infection rates. Our approach suggests that 10 years after introducting vaccination, the prevalence of HPV 6/11 types in females will be halved and that in males will be reduced by one quarter, assuming a sustained vaccine coverage of 30% among females. Using the formula we derived for the vaccinated reproduction number, we show that the non-oncogenic HPV 6/11 types would be eradicated if vaccine coverage in females is kept above 12%. Human Papillomavirus, deterministic epidemic model, equilibrium, stability, reproduction number, vaccination.

1 Introduction

Human Papillomavirus (HPV) 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 (Syrjänen *et al.*, 1990). Nearly one hundred HPV genotypes have been identified, among which there are low risk genotypes, causing benign anogenital lesions, and high risk genotypes, which induce pre-cancerous lesions in the cervix. Epidemiological studies on HPV infections establish the role of these viruses as the primary cause of cervical cancer (Muñoz, 2000). These infections are also the cause of anogenital cancers, head and neck cancers, anogenital warts and recurrent respiratory papillomatosis among women and men. While HPV 16/18 are incriminated in 70% of cervical cancer, HPV 6/11 are the primary cause of almost (90%) all genital warts and of most respiratory recurrent papillomatosis cases (Gissman *et al.*, 1983). While available epidemiological data in France indicate a prevalence of 1% in the general population for genital warts, a prevalence of 10% has been observed in young individuals aged 15 to 25 (Monsonego, 2008). Efficacy of curative treatment is limited in presence of a high recurrence rate for genital warts. Two prophylactic vaccines against HPV infections are available. The bivalent vaccine protects individuals from oncogenic HPV 16/18 types. The quadrivalent vaccine protects individuals from oncogenic HPV types 16/18 and non-oncogenic HPV types 6/11. The purpose of this paper is to assess the impact of the quadrivalent HPV vaccine on the prevalence of non-oncogenic HPV 6/11 types in French individuals.

Mathematical epidemic modeling provides useful tools for analyzing the spread and control of infectious diseases (Hethcote, 2000; Brauer *et al.*, 1945). In particular, it can be used in order to assess the impact of vaccination. Numerous mathematical models have been introduced in the literature to study epidemics of communicable diseases such as measles, influenza, rubeola, and chickenpox. References are much too numerous to be listed exhaustively, see Nuno *et al.*(2005) or Feng *et al.*(2000) for instance for recent accounts of (deterministic) epidemic models.

Since anti-HPV vaccines have been developed, several deterministic or hybrid models have been developed to assess the potential impact of vaccination on HPV prevalence and linked diseases (see e.g. Hughes *et al.* (2002); Barnabas *et al.* (2006); Elbasha *et al.* (2007); Taira *et al.* (2004); Ribassin-Majed *et al.* (2012a,b). However, the models documented in the literature are based on numerical simulations and offer very limited analytical results. It should be noticed in addition that the complexity of these models does not allow to study local and global stability for the equilibrium points. To the best of our knowledge, only Elbasha et al. studied local and global stability for equilibrium solutions in a simple Susceptible-Infected-Retired (SIR) model (Elbasha, 2006 and Elbasha, 2008).

In certain models developed for communicable diseases, the system of differential equations that describes the evolution of the epidemics is not globally asymptotically stable, multiple equilibrium points coexisting (Feng *et al.*, 2000; Nuño *et al.*, 2005). When considering vaccination, the vaccinated reproduction number R_v, in addition to the basic reproduction number R_0, is estimated to assess the spread of the disease of interest. The basic reproduction number R_0 is a threshold quantity establishing whether an epidemic is likely to spread out or not. It is defined as the expected number of secondary cases of HPV caused by an infected individual during the entire period of infectiousness, in a completely susceptible population (Dietz, 1975; Diekmann *et al.*, 1990). The vaccinated reproduction number represents the threshold in presence of vaccination. These values may determine the likeliest scenario for the evolution of the epidemic disease under study, depending on whether they are below or above the critical value 1. However, bringing the vaccinated reproduction number below 1 may not be sufficient to eradicate endemicity of the disease when multiple locally stable equilibrium solutions coexist (Kribs-Zaleta *et al.*, 2000). Hence, in dynamic models, investigating the asymptotic behavior is an important issue.

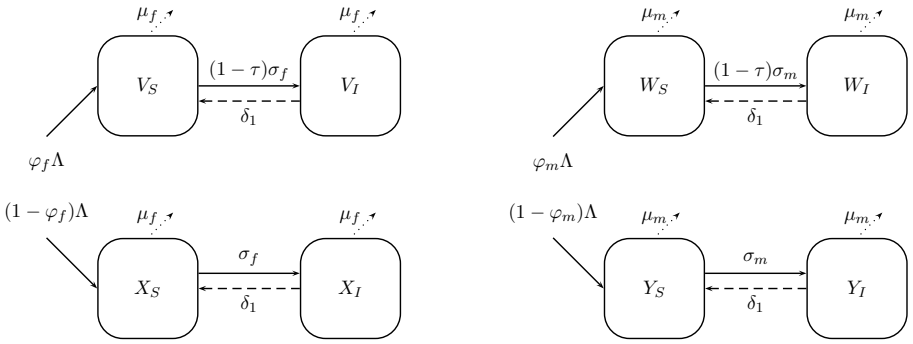
The main objective of this paper is to assess the impact of quadrivalent HPV vaccine on HPV 6/11 prevalences in French females and males. A deterministic model is presented using a system of ordinary differential equations to describe the heterosexual transmission of the virus in the French population, considering the real vaccine coverage observed in France. In addition, a mathematical analysis of the model is provided. Deterministic epidemic modeling for sexually transmitted infections, taking into account sex and vaccination both at the same time, are not well documented in the literature. Human Papillomavirus is the only sexually transmitted infection which can be avoided through vaccination. To the best of our knowledge, only Elbasha (2006, 2008) proposed a Susceptible-Infected-Retired (SIR) deterministic model for HPV transmission. This paper is thus the first to investigate specifically the impact of HPV vaccination on non-oncogenic HPV types, through a mathematical/numerical analysis of the dynamic model proposed.

The paper is structured as follows. In section 2, a two-sex model of HPV infection transmission in the sexually active population is introduced. We developed a deterministic model based on a system of ordinary differential equations for HPV 6/11 transmission considering vaccination, to evaluate the effects of vaccination campaigns in France. The basic reproduction number R_0 and vaccinated reproduction number R_v are derived from an analytic formula in section 3. The asymptotic behavior of the HPV models (with and without vaccination) is studied in section 3 and the stability of equilibrium solutions of the developed models is illustrated through simulations in section 4. Subsequently, numerical values for the infection rates are assessed by means of a fitting procedure based on prevalence data, and the impact of quadrivalent vaccine on HPV 6/11 prevalence in France for both sexes is quantified in section 5, considering the current vaccine coverage in France. The experimental results are finally discussed in section 6. Technical details are deferred to the Appendix section.

2 Human Papillomavirus model

In this paper we develop a deterministic model that describes the transmission mechanism of HPV 6/11 infection in a heterosexually active population. Classically, the sexually active population is divided into compartments. Non-oncogenic HPV types do not induce specific natural immunity (Monsonego, 2008), therefore we use a Susceptible-Infected-Susceptible (SIS) structure. In addition, vaccination is taken into account, see Figure 1.

Figure 1: Flow diagram.



Deterministic models are widely used to simulate the spread of sexually transmitted infectious diseases. Such models can be described using a system of ordinary differential equations, with females and males in different compartments. The transmission term is non-linear as it reflects the interaction between infectious and susceptible individuals. The use of a deterministic model allows us here to take into account herd immunity (indirect benefits of vaccination, see Garnett (2005)) in a simple manner, which corresponds to a decrease of HPV infections in non-vaccinated subpopulations due to vaccination coverage of other individuals. When non-vaccinated (respectively vaccinated) women enter in the female sexually active population (of size N_f), they move into the susceptible compartment X_S (respectively V_S) at the constant rate [(1- φ_f)Λ] (respectively [$\varphi_f\Lambda$]) and they leave all compartments at rate μ_f. We assume that the exit of the sexually active population balances the entrance in the sexually active population so that the population size N in the model remains constant. In a similar fashion, non-vaccinated (resp. vaccinated) men enter into the male sexually active population (of size N_m) into the susceptible compartment Y_S (resp. W_S) at constant rate [(1- φ_m)Λ] (respectively [$\varphi_m\Lambda$]) and leave all compartments at rate μ. Susceptible individuals are infected with HPV at a per capita rate λ_m or λ_f (annual rates), depending on their sex. The force of infection depends on infection rates (σ_m for men and σ_f for women) and on HPV infection prevalence in the opposite sex as well. Then, they move into infected compartments: X_I (resp. V_I) for women, Y_I (resp. W_I) for men in non-vaccinated population (resp. in vaccinated population), see the description of parameters on Table 1.

Table 1: Description of variables and parameters.

Symbol	Description	Estimates	References
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		
N_f	Number of females	500,000	
N_m	Number of males	500,000	
Biological parameters			
σ_f	Infection rate for women		calibration
σ_m	Infection rate for men		calibration
δ	Clearance rate	1.25	Trottier et al, 2008
Vaccines Parameters			
φ_f	Female vaccination rate	scenario 1: 30% scenario 2: 10%	Fagot et al, 2011
τ	Vaccine degree of protection	90%	Future, 2010
Demographic parameters			
Λ	Number of individuals in each sex who enter annually in the model	30,000	$\Lambda = \mu * N/2$
μ	retirement rate	6%	

The following assumptions shall also be required:

- Vaccinated people can be infected. The degree of protection of vaccine is τ, the relative risk of a vaccinated person experiencing a breakthrough infection is $1 - \tau$.
- Vaccinated infected individuals are as much infectious as non-vaccinated persons.
- Vaccine immunity does not wane during all 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 notation $\frac{d}{dt}(\cdot)$ is used for derivative.

The non-linear system of ordinary differential equations that represents this compartmental model is:

$$\begin{aligned}
\frac{dX_S}{dt} &= (1-\varphi_f)\Lambda - \lambda_f X_S + \delta X_I - \mu X_S \\
\frac{dX_I}{dt} &= \lambda_f X_S - (\delta+\mu) X_I \\
\frac{dY_S}{dt} &= (1-\varphi_m)\Lambda - \lambda_m Y_S + \delta Y_I - \mu Y_S \\
\frac{dY_I}{dt} &= \lambda_m Y_S - (\delta+\mu) Y_I \\
\frac{dV_S}{dt} &= \varphi_f \Lambda - (1-\tau)\lambda_f V_S + \delta V_I - \mu V_S \\
\frac{dV_I}{dt} &= (1-\tau)\lambda_f V_S - (\delta+\mu) V_I \\
\frac{dW_S}{dt} &= \varphi_m \Lambda - (1-\tau)\lambda_m W_S + \delta W_I - \mu W_S \\
\frac{dW_I}{dt} &= (1-\tau)\lambda_m W_S - (\delta+\mu) W_I
\end{aligned} \tag{2.1}$$

We highlight the fact that the system above is nonlinear, the forces of infection depend on infection rates and the prevalences of HPV infection in the opposite sex:

$$\lambda_f = \sigma_f \frac{(Y_I + W_I)}{N_m},$$
$$\lambda_m = \sigma_m \frac{(X_I + V_I)}{N_f}.$$

The population in the model is assumed to remain constant, that is:

$$N_f = X_S + X_I + V_S + V_I,$$
$$N_m = Y_S + Y_I + W_S + W_I,$$
$$N = N_f + N_m.$$

And we assume: $N_f = N_m$.
Thus

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

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

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

It can be verified that D is positively invariant for this system, which has a unique solution in D. The model is epidemiogically and mathematically well posed. In section 3, the equilibria of the model without vaccination are analyzed and a closed analytical form for the basic reproduction number is given.

3 Analysis of equilibria and reproduction numbers

In this section, we consider the model without vaccination as a first go. There are two possible equilibria: the Disease Free Equilibrium (DFE in abbreviated form) and the Endemic Equilibrium. In order to analyze the stability of these equilibria, the basic reproduction number R_0 is computed.

3.1 The model without vaccination

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

$$\begin{aligned}
\frac{dX_S}{dt} &= \Lambda - \frac{\sigma_f Y_I}{N_m} X_S + \delta X_I - \mu X_S \\
\frac{dX_I}{dt} &= \frac{\sigma_f Y_I}{N_m} X_S - (\delta + \mu) X_I \\
\frac{dY_S}{dt} &= \Lambda - \frac{\sigma_m X_I}{N_f} Y_S + \delta Y_I - \mu Y_S \\
\frac{dY_I}{dt} &= \frac{\sigma_m X_I}{N_f} Y_S - (\delta + \mu) Y_I
\end{aligned} \tag{3.1}$$

The equilibria of this model are obtained by setting the right hand sides of the model equations to zero. The system (3.1) 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:

$$\begin{aligned}
X_S^{**} &= \frac{dN(\delta + \mu)}{2\sigma_f}, \\
X_I^{**} &= \frac{\Lambda}{\mu} - \frac{dN(\delta + \mu)}{2\sigma_f} \\
Y_S^{**} &= \frac{\Lambda}{\mu}(1 - 1/d) + \frac{N(\delta + \mu)}{2\sigma_f} \\
Y_I^{**} &= \frac{\Lambda}{d\mu} - \frac{N(\delta + \mu)}{2\sigma_f}
\end{aligned}$$

with

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

The existence of the DFE is established. Following the Next Generation Matrix approach (NGM) (see Diekmann *et al.* (2010); van den Driessche & Watmough (2002)), the basic reproduction number R_0 is computed in order to analyze local and global stability of the DFE depending on R_0 values. Here we use the additional notations: $\dot{x}$ for the temporal derivative of the vector x and ^{T} for the transpose. The system (3.2) is defined with the first two components corresponding to compartments of infected individuals and the last two components corresponding to susceptible compartments:

$$\dot{x} = (\dot{X_I}, \dot{Y_I}, \dot{X_S}, \dot{Y_S})^T = (0, 0, 0, 0)^T. \tag{3.2}$$

Following the Next Generation Matrix Method (see e.g. van den Driessche & Watmough (2002)) we break up $\dot{x}$ into $\mathcal{F} - \mathcal{V}$ differentiating new infections from all other changes in population, 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

$$F = \begin{pmatrix} 0 & \sigma_f \\ \sigma_m & 0 \end{pmatrix} \text{ and } V = \begin{pmatrix} \delta+\mu & 0 \\ 0 & \delta+\mu \end{pmatrix}.$$

Here, W is a square matrix and I_2 is the unit matrix of size 2×2. So, the next generation matrix for the model (Diekmann *et al.*, 1990; van den Driessche & Watmough, 2002) is given by:

$$FV^{-1} = \frac{1}{(\delta+\mu)} \begin{pmatrix} 0 & \sigma_f \\ \sigma_m & 0 \end{pmatrix}.$$

The quantity R_0 is equal to the spectral radius of FV^{-1}, thus:

$$R_0 = \sqrt{R_{0,f} R_{0,m}},$$

where

$$R_{0,f} = \frac{\sigma_f}{(\delta+\mu)} \text{ and } R_{0,m} = \frac{\sigma_m}{(\delta+\mu)}.$$

The basic reproduction number depends on parameters which describe the dynamic of infection (clearance rate, male and female infection rates) and on the retirement rate. The basic reproduction number can be less than unity if the infection rate is lower than the sum of the clearance rate and of the rate of exit of the sexually active population for each sex. This corresponds to diseases which clear quickly with low infection rates. Please note that R_0 is the geometric mean of two values. In a one-sex model: $R_{0,f} = R_{0,m}$, we find $R_0 = \sigma/(\delta+\mu)$ which is a classic expression of R_0 in simple Susceptible-Infected-Susceptible model (Hethcote, 2000). The quantity $R_{0,f}$ is the number of secondary infections generated by one infected woman in a population of susceptible men during her infectious period. Then, each infected man can infect a mean number of $R_{0,m}$ susceptible women during his infectious period. We do not know how many secondary infections are generated by one infected individual in a population of susceptibles. Theoretical computation based on the HPV model may thus provide the means of estimating the basic reproduction number. In section 5, the value of the reproduction number for HPV epidemic is estimated using estimates of parameters involved in the expression of R_0. In addition, the basic reproduction number is a threshold value for the global dynamics of the model. We obtain the global stability of either disease-free or endemic steady state in terms of the basic reproduction number.
Now, the following Theorems focus on the stability of the Disease Free Equilibrium. Detailed proofs can be found in the Appendix.

THEOREM 3.1 if $R_0 < 1$ then the DFE is locally asymptotically stable.

To prove this result, we prove that all eigenvalues of the jacobian matrix evaluated at the DFE have strictly negative real parts.

THEOREM 3.2 The DFE is globally asymptotically stable if and only if $R_0 \leq 1$.

This Theorem is proved using a suitable Lyapunov function.
We proved the local and global stability of the DFE when $R_0 \leq 1$ in the model without vaccination. Now, the endemic equilibrium of the model without vaccination is considered. Using the expression of R_0, we

can rewrite P_1 as:

$$X_S^{**} = \frac{\Lambda}{\mu}\left(\frac{R_0^2 + R_{0,f}}{R_0^2 + R_{0,m}}\right)\frac{1}{R_{0,f}}$$

$$X_I^{**} = \frac{\Lambda}{\mu}\frac{R_0^2 - 1}{R_0^2 + R_{0,m}}$$

$$Y_S^{**} = \frac{\Lambda}{\mu}\frac{1 + R_{0,f}}{R_0^2 + R_{0,f}}$$

$$Y_I^{**} = \frac{\Lambda}{\mu}\frac{R_0^2 - 1}{R_0^2 + R_{0,f}}.$$

$X_I^{**} > 0$ and $Y_I^{**} > 0$, and then P_1 is feasible in $\mathcal{D}$, if and only if $R_0 > 1$ ($P_1 = P_0$ when $R_0 = 1$). Previously, we proved that the model without vaccination reaches a steady-state which is a Disease Free Equilibrium when $R_0 \leq 1$. The asymptotic behavior of the model has to be studied when $R_0 > 1$. The following theorem provides the condition for local stability of the endemic equilibrium:

THEOREM 3.3 The endemic equilibrium is locally asymptotically stable if and only if $R_0 > 1$.

To prove this result, we use the same method that for the DFE. We prove that eigenvalues of the jacobian matrix of the linearized system have strictly negative real parts when $R_0 > 1$. Also the endemic equilibrium is probably globally asymptotically stable for $R_0 > 1$, but the Lyapunov function used in Theorem 3.2 does not work. Numerical calculations suggest asymptotic stability (see numerical simulations in section 4). 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. The DFE of (2.1) is 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 $\dot{x} = (\dot{X_I}, \dot{V_I}, \dot{Y_I}, \dot{W_I})^T$. We break up $\dot{y}$ into $\mathcal{F}_1 - \mathcal{V}_1$ and compute the Jacobian matrices of $\mathcal{F}_1$ and $\mathcal{V}_1$, linearized around the DFE Q_0. The matrices F_1 and V_1 are defined by:

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

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

The next generation matrix is defined as $F_1V_1^{-1}$ with

$$F_1V_1^{-1} = \begin{pmatrix} 0 & 0 & \frac{\sigma_f}{(\delta+\mu)}(1-\varphi_f) & \frac{\sigma_f}{(\delta+\mu)}(1-\varphi_f) \\ 0 & 0 & (1-\tau)\frac{\sigma_f}{(\delta+\mu)}\varphi_f & (1-\tau)\frac{\sigma_f}{(\delta+\mu)}\varphi_f \\ \frac{\sigma_m}{(\delta+\mu)}(1-\varphi_m) & \frac{\sigma_m}{(\delta+\mu)}(1-\varphi_m) & 0 & 0 \\ (1-\tau)\frac{\sigma_m}{(\delta+\mu)}\varphi_m & (1-\tau)\frac{\sigma_m}{(\delta+\mu)}\varphi_m & 0 & 0 \end{pmatrix}.$$

An estimate of the vaccinated reproduction number R_v which is the spectral radius of $F_1V_1^{-1}$ is:

$$R_v = \sqrt{R_f(\varphi_f)R_m(\varphi_m)} = R_0\sqrt{[(1-\varphi_m)+(1-\tau)\varphi_m][(1-\varphi_f)+(1-\tau)\varphi_f]},$$

with $R_f(\varphi_f) = R_{0,f}[(1-\varphi_f)+(1-\tau)\varphi_f]$ and $R_m(\varphi_m) = R_{0,m}[(1-\varphi_m)+(1-\tau)\varphi_m]$.

This result is close to the expression for the vaccinated reproduction number using a S-I-R model for HPV found in Elbasha (2006, 2008). The vaccinated reproduction number depends on:

- The basic reproduction number R_0,
- Male and female vaccine coverage (φ_m and φ_f),
- Efficacy of vaccine τ.

Please note that the terms inside brackets are less than one, so $R_v < R_0$. The term under the square root shows how much the vaccination reduces R_0. The vaccinated reproduction number is a threshold quantity taking into account vaccination, its expression may assist in the identification of important parameters on which we can act. Bringing the vaccinated reproduction number under unity will lead to the eradication of the virus if the DFE is globally asymptotically stable.
The following theorems provide properties of the system 2.1.

THEOREM 3.4 The DFE is locally asymptotically stable if and only if $R_v < 1$.

When $R_v < 1$ the DFE is probably also globally asympotically stable. Numerical calculations suggest global asymptotic stability (see simulations in section 4). When $R_v > 1$, we prove the existence and uniqueness of endemic equilibrium of the vaccination model:

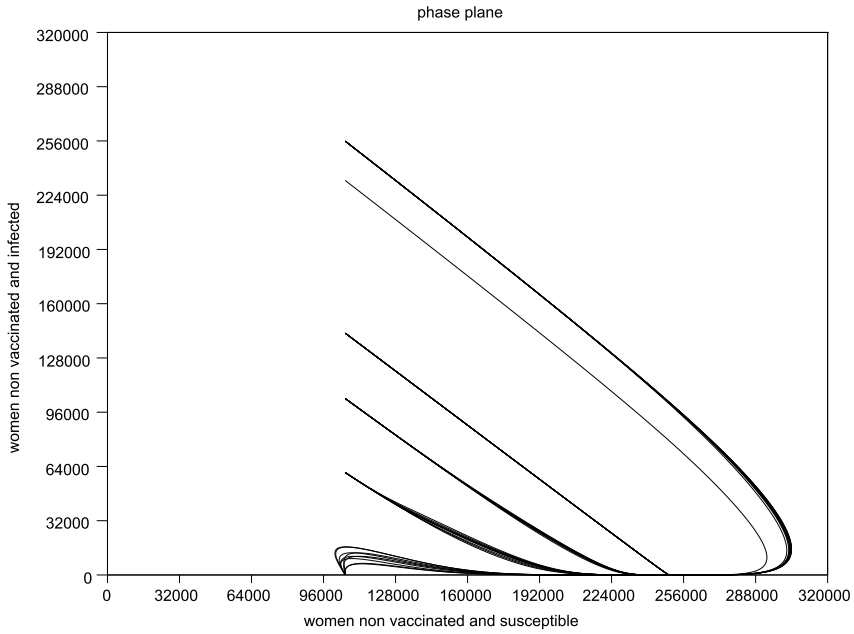
THEOREM 3.5 If $R_v > 1$ the endemic equilibrium exists and is unique.
If $R_v < 1$ there isn't any endemic equilibrium.

To prove these results (Theorem 3.4 and Theorem 3.5), we use the same method as Elbasha (2006), the HPV model developed therein is quite similar to our model, the difference is the use of a SIR structure which is more convenient for oncogenic HPV types. In our model, a SIS structure is developed corresponding to non-oncogenic HPV types. Proofs are provided in the Appendix.
Finally, we have proved that if the endemic equilibrium exists, it must be unique. Furthermore, if $R_v > 1$ the endemic equilibrium is probably globally asymptotically stable. Numerical calculations suggest this asymptotic behaviour (see simulations in section 4).
We proved that if $R_v < 1$, the vaccination model has a disease free equilibrium which is locally asymptotically stable and the endemic equilibrium does not exist; whereas if $R_v > 1$ the endemic equilibrium exists and is unique.

4 Simulations

In this section, we studied the global stability of the DFE in the model with vaccination (Q_0) and of endemic equilibrium in both models (2.1) and (3.1) (with and without vaccination) Q_1 and P_1 using numerical simulations.

Figure 2: Some trajectories in the phase plane portrait for the model with vaccination and considering several sets of initial male and female prevalences when $R_v < 1$

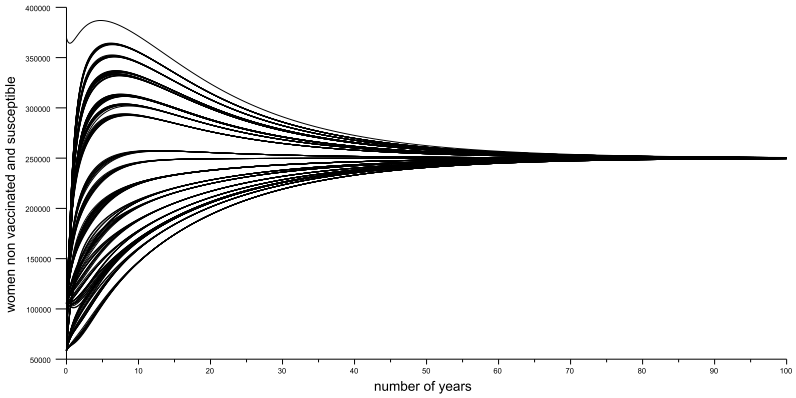


4.1 Stability of DFE and of the endemic equilibrium in the model with vaccination

In the model with vaccination, we did not find any Lyapunov function to show that the DFE Q_0 is globally asymptotically stable, thus we conducted analyses using simulations in order to study the asymptotic behavior of the model (2.1) (with vaccination) when the vaccinated reproduction number is less than one ($R_v < 1$). We used Scilab-5.1.1 software.

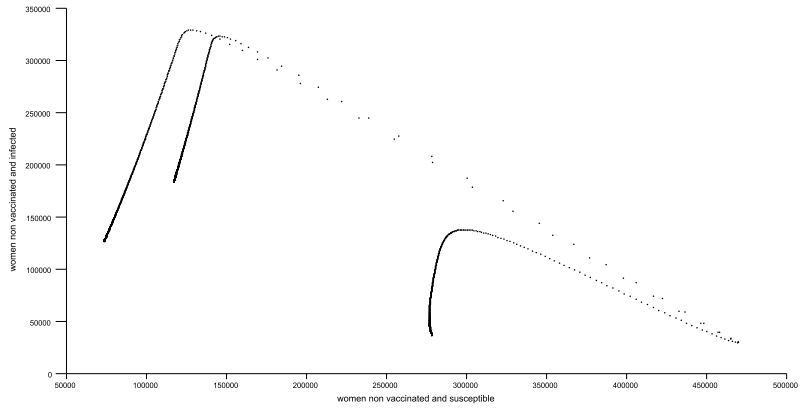
In section 3.2, we found an expression for Q_0, considering several initial conditions (according to parameters which satisfied $R_v < 1$). We simulated a set of 10,000 combinations for initial prevalences with the conditions $N_f = 500,000$ and $N_m = 500,000$. We considered several combinations of parameters such as the female and male infection rates, the clearance rate and the vaccination rate that satisfied the condition: $R_v < 1$. Thereafter, we compared the size of compartments at t=100 years to the expression of Q_0. Results suggest the stability of the DFE Q_0 when $R_v < 1$ (Figures 2 and 3).

Figure 3: Some trajectories for the model with vaccination and considering several sets of initial male and female prevalences when $R_v < 1$ (to test that Q_0 is globally asymptotically stable).



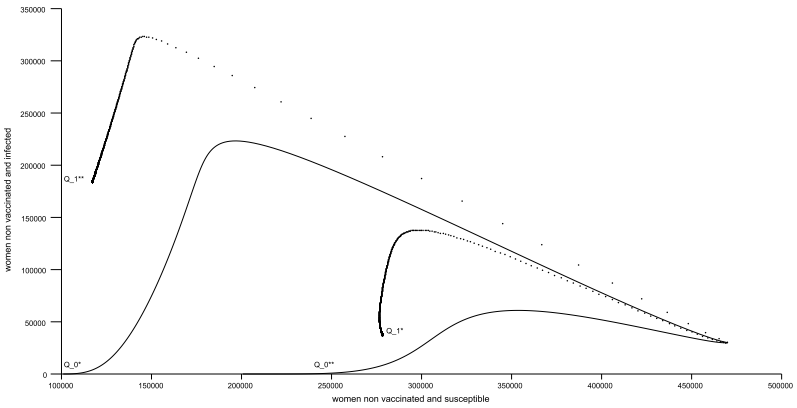
We used the same method to study the asymptotic behavior of the model with vaccination when $R_v > 1$ to study the hypothesis that Q_1 is globally asymptotically stable. The same set of 10,000 combinations for initial prevalences was used. Several sets of parameters (infection rates, clearance rates, vaccine coverage, efficacy of vaccine, retirement rate) were chosen to verify the condition: $R_v > 1$. Results suggest that the endemic equilibrium is globally asymptotically stable when $R_v > 1$ (Figure 4).

Figure 4: Some trajectories in the phase plane portrait for the model with vaccination and considering several sets of parameters values when $R_v > 1$. The system reaches a steady-state which is an endemic equilibrium



Based on this simulations, we expect the vaccination model to reach a steady-state depending on R_v values : Q_0 when $R_v < 1$ and Q_1 when $R_v > 1$ (Figure 5).

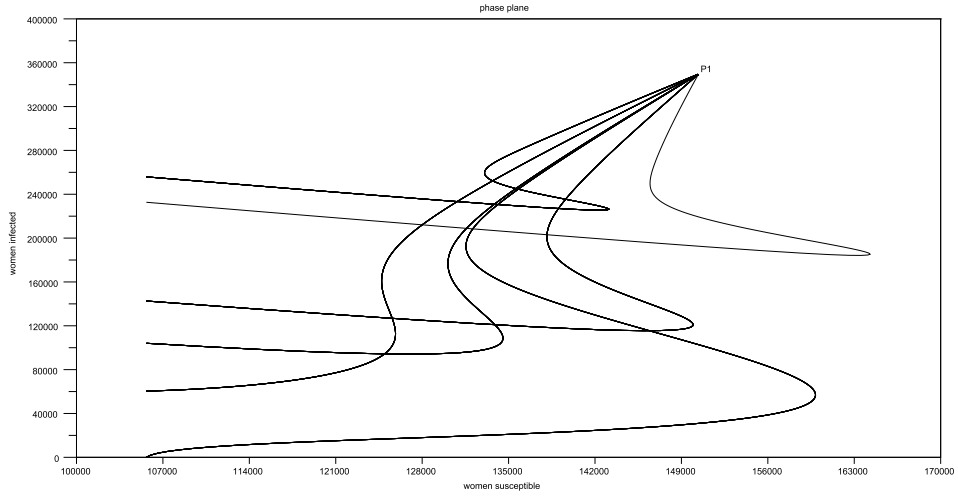
Figure 5: Some trajectories in the phase plane portrait for the model with vaccination considering the same initial female and male prevalences and several initial values for parameters (female and male infection rates, female and male vaccine coverage). The model with vaccination reaches a steady-state equilibrium which is: the DFE Q_0^* when $R_v = 0.71$, the DFE Q_0^{**} when $R_v = 0.44$, the endemic equilibrium Q_1^* when $R_v = 1.21$, the endemic equilibrium Q_1^{**} when $R_v = 4.58$



4.2 Global stability of the endemic equilibria P_1

We considered the model without vaccination. As described in the previous section, we simulated several set of initial conditions according to initial prevalences and parameters which verified the condition: $R_0 > 1$. Results are shown on Figure 6 and suggest that P_1 is probably also globally asymptotically stable when $R_0 > 1$.

Figure 6: Some trajectories in the phase plane portrait for the model without vaccination considering several sets of initial male and female prevalences when $R_0 > 1$



5 Application to Human Papillomavirus types 6/11

The model without vaccination (3.1) is used to fit the data of HPV 6/11 prevalences in male and female in order to assess the impact of HPV vaccination on HPV 6/11 prevalence.

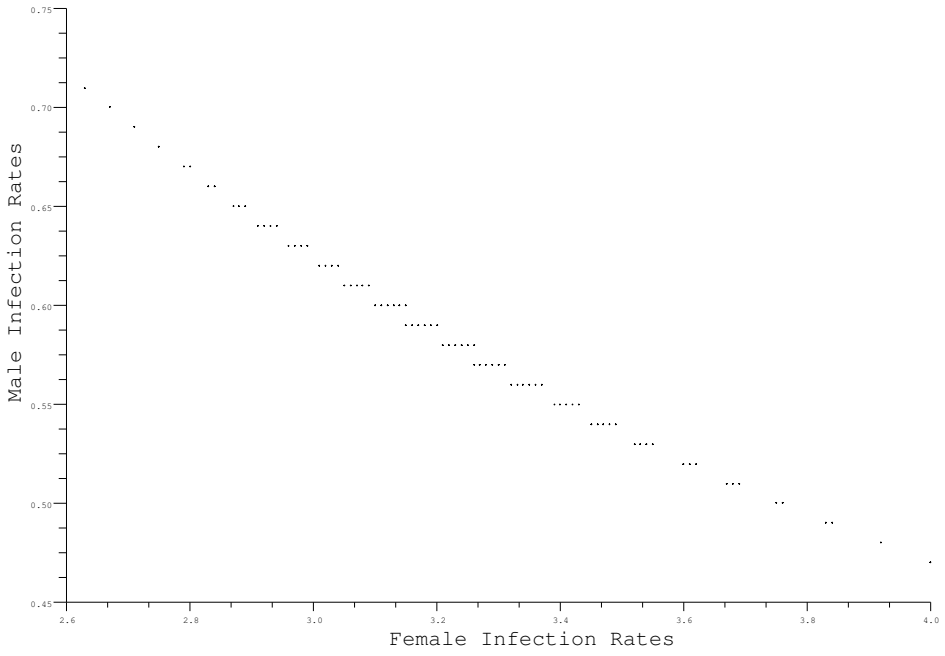
5.1 Calibration

Table 1 describes the values used for the parameters and inputs of the model. We set the population size in the model to N=1,000,000 individuals, equally divided into females ($N_f = 500,000$) and males ($N_m = 500,000$). We used the following values for the size of the 4 compartments at t=0 year (initial values):

- $X_S(0) = 470,000$
- $X_I(0) = 30,000$ corresponding to a female HPV 6/11 prevalence of 6% (Ralston, 2009)
- $Y_S(0) = 487,000$
- $Y_I(0) = 13,000$ corresponding to a male HPV 6/11 prevalence of 2.6% (Nielson, 2009)

Male and female infection rates are unknown and have to be assessed in the calibration step. Parameters which have to be assessed are not stochastic variables, thus they do not have a probability distribution describing the probabilities of different values occurring. The method which is used is as follows: a set of 250,000 pairs of infection rates were tested, per capita annual infection rates were selected in the interval [0,5]. Each value for the per capita annual male infection rate in the interval [0,5] was tested with 500 values of per capita annual female infection rates in the interval [0,5]. This procedure enables us to test all combinations of infection rates in the space $[0,5]^2$. The combinations of male and female infection rates which reproduced endemic prevalence of HPV 6/11 (before introduction of vaccination) in males and females within a precision of 10% are shown on Figure 7. On this figure, we can see that it is not possible to give a confidence interval for the estimation of the infection rates. Nonetheless, for some combinations of male and female infection rates which reach the target defined in calibration, several female infection rates could be linked with one male infection rate.

Figure 7: Combinations of annual infection rates for males and females estimated in calibration step.



Remark 5.1 (on the calibration results): Male infection rates which match with HPV 6/11 prevalences were lower than female infection rates; the explanation is that male HPV 6/11 prevalences used in the fitting procedure are lower than female HPV 6/11 prevalences. In order to fit HPV prevalence, we observed that the product of male and female infection rates was stable; its range was 1.86 to 1.89. This product appears in the expression of the basic reproduction number in section 3. Female and male infection rates which were used in the analysis above are respectively 2.63 and 0.71.

Using estimates for infections rates and expression of R_0, we found an estimation for the basic reproduction number: $R_0 = 1.04$. This value is close to unity corresponding to low prevalences used in the fitting procedure. In the analytical formula for the basic reproduction number, there are two kinds of parameters: the clearance rate δ and the retirement rate μ are estimated using data from the litterature, whereas female and male infection rates are assessed in the fitting procedure, these estimates depend on epidemiological data which are used to fit the model. This shows the importance in choosing data, they should be as representative as possible of the epidemiological reality of the infection or disease. HPV is a sexually transmitted infection, thus we need to consider male and female prevalences corresponding to the same sexually active population or the same country in order to model heterosexual transmission for HPV. There is very few published data on male HPV 6/11 prevalences, this is why we used data from the USA (Ralston *et al.*, 2009; Nielson *et al.*, 2009).

5.2 Impact of vaccination

Table 2 describes the expected reduction in HPV 6/11 prevalence in each scenario of vaccination in an horizon of 10, 20, 30 and 50 years after introduction of vaccination.

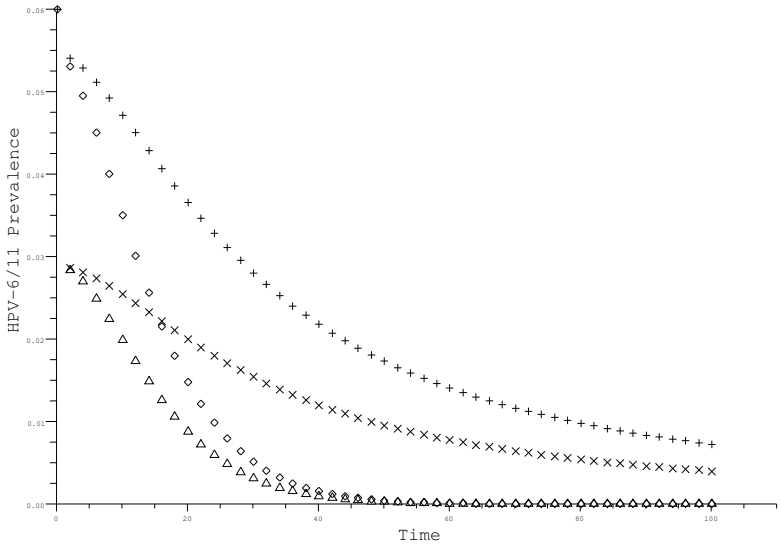
Table 2. Impact of vaccination on HPV 6/11 prevalence

Number of years after initiation of vaccination	Female prevalence	Male prevalence
Scenario 1		
10	3.55%	1.98%
20	1.52%	0.88%
30	0.005%	0.31%
50	4.10^{-3}%	2.10^{-4}%
Scenario 2		
10	4.74%	2.54%
20	3.68%	2.00%
30	2.83%	1.53%
50	1.75%	0.95%

Initial prevalences are 6% (Ralston *et al.*, 2009) in females and 2.6% in males (Nielson *et al.*, 2009). Vaccine coverage is assumed to be constant in time in each scenario. Efficacy of vaccine is assumed to be of 90% (Future I/II study group, 2010). We considered 2 scenarios of vaccination: in scenario 1, we assume that 30% of women (who enter annually in the sexually active population) received the 3 doses of vaccine and are protected, this scenario corresponds to the vaccine coverage observed in France at the launch of the vaccination campaign in 2007 (Fagot *et al.*, 2011). In scenario 2, we considered that 10% of women received 3 doses of vaccine, corresponding to the decrease in vaccine coverage observed in France a few years after HPV vaccine introduction (Fagot *et al.*, 2011). Considering the first scenario (30% of women who enter annually in the model are protected by the vaccine), a 50% reduction of female HPV 6/11 prevalence is expected 10 years after vaccine introduction, and the male HPV 6/11 prevalence is

reduced by one quarter. Thirty years after vaccine introduction, HPV 6/11 prevalences in males and females are expected to be very low (respectively 0.005% and 0.31%). Considering scenario 2, a lower vaccine coverage leads to a slower decrease in HPV prevalence (Table 2 and Figure 8).
According to R_0 estimates and expression of R_v, the minimum female vaccine coverage which is necessary to eradicate HPV 6/11 (i.e. to have $R_v < 1$) varies between 8.2% and 11%. Thus, if current vaccine coverage in France is maintained, HPV 6/11 will be eradicated.

Figure 8: HPV 6/11 Prevalence in males and females. At t=0 (year), introduction of vaccination considering scenario 1 (30% of women who enter annually in the model are vaccinated) and scenario 2 (10% of women who enter annually in the model are vaccinated). Diamond and triangle represent respectively female and male prevalences in scenario 1, + and X represent respectively female and male prevalences in scenario 2



6 Summary and Discussion

The developed model in our paper may help to appreciate impact of prophylactic vaccination against HPV on HPV 6/11 prevalence. In this paper, we developed a deterministic model of heterosexually HPV 6/11 transmission. A mathematical analysis of the model was carried out. We identify the vaccinated reproduction number R_v as a threshold quantity for the stability of equilibria: if $R_v > 1$, the endemic equilibrium exists and is globally asymptotically stable whereas if $R_v < 1$, the infection-free equilibrium exists and is globally asymptotically stable and HPV will be eliminated. The yielded vaccinated reproduction number from our model represents a reliable parameter establishing whether an epidemic can spread or die out. Its expression depends on other parameters such as vaccine coverage for each sex. Thus, such parameters represent consistent tools which can be used by Public Health policy-makers to improve policies that aim to control HPV epidemic. As an example, level of vaccine coverage can be targeted in order to yield a vaccinated reproduction number that precludes the spread of epidemic. However, driving out the basic reproduction number below one is not always sufficient to eradicate the disease (Zhang & Liu, 2009). It is necessary to study the asymptotic behavior of the model. Our analyses found that our model was asymptotically stable and supported the consistency of the derived parameters.
In a second part, we fitted the model on HPV 6/11 prevalences in order to estimate male and female infection rates. We studied the impact of French vaccine strategies on the prevalence of HPV 6/11. The basic reproduction number for these non-oncogenic HPV types was estimated at 1.04. As this value is

close to unity, a low proportion of individuals have to be vaccinated in order to eradicate HPV 6/11 in the population. We estimated that if more than 12% of women were vaccinated against HPV using quadrivalent vaccine, the non-oncogenic HPV 6/11 types would be eradicated. Non-oncogenic HPV types are responsible for 90% of genital warts, and the lesions caused by non-oncogenic HPV-6/11 types appear between 2 and 8 months after HPV infection. Therefore, we can expect a dramatic reduction in the occurrence of genital warts caused by HPV 6/11 types.

Yielded results are based on assumptions made in the modeling process. Vaccine coverage was assumed to be constant in the time in each scenario. French data did not specify vaccine coverage for each available vaccine; we therefore used global vaccine coverage in French females as a parameter in our model. As only one vaccine prevent HPV 6/11 infections, we were likely to overestimate vaccine coverage against HPV 6/11. French recommendations on HPV vaccination changed in 2010. Previously, quadrivalent vaccine was recommended; while since 2010 French guidelines no longer preferentially support any vaccine.

In addition, infection rates were assessed in the calibration step and depend on HPV 6/11 prevalence in males and females. In the absence of reliable French data for HPV 6/11 prevalence in males and females, we used prevalence from studies completed in the USA (Ralston *et al.*, 2009; Nielson *et al.*, 2009) which represent consistent data to model the heterosexual transmission of this infection.

In Australia a high vaccine coverage (70%) is reached due to a school-based program for HPV vaccination. They observe a dramatic reduction of the number of genital warts (approximately a reduction of 90%) in young women (under 21 years) and in heterosexual young men a few years after initiation of vaccination (Read *et al.*, 2011). This observed effect of vaccination matches with results of our modeling. In France, lower vaccine coverage was observed at the launch of the vaccination campaign and the vaccine coverage is currently decreasing (Fagot *et al.*, 2011). Thus, the reduction in HPV 6/11 and in genital warts prevalence will be expected to slow down. Our modeling suggests that in the horizon of 10 years after introduction of vaccination, HPV 6/11 prevalence in females will be halved and HPV 6/11 prevalence in males will be reduced by one quarter, assuming a sustained vaccine coverage of 30% among females (annual rate). In this case, HPV 6/11 will be eradicated within 50 years after vaccine introduction. However, these reductions will be slower if vaccine coverage is decreasing.

In our modeling, we did not assess directly the impact of vaccination on the occurrence of Recurrent Respiratory Papillomatosis (RRP). RRP is caused by HPV 6/11 and is observed usually in young children but also among adults. RRP in children is due to HPV 6/11 infection in the respiratory area due to mother-to-child transmission of HPV 6/11 during delivery (D'Souza *et al.*, 2011). Thus, if female prevalence for HPV 6/11 is decreasing due to vaccination, a reduction of RRP can be expected. However, prevalence of RRP is very low compared to genital warts (D'Souza *et al.*, 2011). To study specifically the impact of quadrivalent vaccine on RRP, a model including vertical transmission could be developed in future research.

In order to study the asymptotic behavior of the model, we did not include age structure nor sexual behavior in the model. Thus a simplest model was developed whose asymptotic behavior could be assessed. Nonetheless, the majority of HPV dynamic models take into account age or sexual behavior, in future research the vaccinated reproduction number could be assessed in more complex models including age structure.

To conclude, vaccination against HPV, using quadrivalent vaccine, represents a strong tool to prevent HPV 6/11 infections. A dramatic decrease of genital warts occurrence may be expected in France, especially among young individuals.

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Appendix: Technical proofs

Local and global stability of Disease Free Equilibrium section:

Theorem (3.1):
if $R_0 < 1$ then the DFE is locally asymptotically stable.

Proof. The Jacobian matrix of the system without vaccination ($\dot{x} = (0,0,0,0)^T$ (3.2)) is evaluated at the DFE P_0:

$$\mathcal{J}(P_0) = \begin{pmatrix} -(\delta+\mu) & \sigma_f & 0 & 0 \\ \sigma_m & -(\delta+\mu) & 0 & 0 \\ \delta & -\sigma_f & -\mu & 0 \\ -\sigma_m & -\delta & 0 & -\mu \end{pmatrix}.$$

We define:

$$A_1 = \begin{pmatrix} -(\delta+\mu) & \sigma_f \\ \sigma_m & -(\delta+\mu) \end{pmatrix}.$$

$\mathrm{Tr}(A_1) < 0$ and $\det(A_1) > 0$ if $R_0 < 1$. Thus, if $R_0 < 1$, all eigenvalues of the jacobian matrix linearized system around the DFE have strictly negative real parts, hence by the Routh-Hurwitz Criterion (Gantmacher, 1959) the DFE, P_0, is locally asymptotically stable if $R_0 < 1$.
If $R_0 > 1$, one eigenvalue has positive real part and the DFE is locally unstable. □

Theorem (3.2):
The DFE is globally asymptotically stable if and only if $R_0 \leq 1$.

Proof. Consider the Lyapunov function in D:

$$V = X_I + R_{0,f} Y_I.$$

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

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

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 $N_f = N_m = \frac{\Lambda}{\mu}$:

$$\begin{aligned} V' &\leq \left(R_{0,f}\,\sigma_m - (\delta+\mu) \right) X_I + \left(\sigma_f - R_{0,f}(\delta+\mu) \right) Y_I \\ V' &\leq (\delta+\mu)(R_0^2 - 1) X_I. \end{aligned}$$

If $R_0 \leq 1$ then $V' \leq 0$.
We denote $A = \left(R_{0,f}\sigma_m \frac{Y_S}{N_f} - (\delta+\mu) \right)$ and $B = \left(\sigma_f \frac{X_S}{N_m} - R_{0,f}(\delta+\mu) \right)$. We can rewrite $V' = AX_I + BY_I$.
We can prove that $A \leq 0$ and $B \leq 0$.
If $R_0 < 1$, then $A < 0$ and $B < 0$, the equality $V' = 0$ holds only at the DFE (when $X_I = 0$ and $Y_I = 0$).
If $R_0 = 1$, $V' = 0$ if and only if:

$$\begin{array}{cccc} & X_I = 0 & and & Y_I = 0 \\ or & A = 0 & and & Y_I = 0 \\ or & B = 0 & and & X_I = 0 \\ or & A = 0 & and & B = 0 \end{array}$$

The four cases considered lead to P_0, thus, $V' = 0$ only in P_0.
The Lasalle-Liapunov theory (Hale, 1969) implies that all paths in D approach the largest positively invariant subset of the set E where V'=0. Here, we have proved in that the only positively invariant subset is $\{P_0\}$ so P_0 is globally asymptotically stable for $R_0 \leq 1$. □

Theorem (3.3):
The endemic equilibrium is locally asymptotically stable if and only if $R_0 > 1$.

Proof. The Jacobian matrix of the system (3.1) 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 charasteristic 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:

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

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

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

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

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 $R_0 > 1$ in Lemma 6.1. Therefore, the endemic equilibrium is locally asymptotically stable if and only if $R_0 > 1$. □

LEMMA 6.1 $x_2 < 0$ if and only if $R_0 > 1$.

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

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

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 $c > 0 \Leftrightarrow R_0 > 1$.

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

$$\begin{aligned} c = {} & (\delta+\mu)^2 + (\delta+\mu)^2\left(R_{0,m} - \frac{R_{0,m}}{R_{0,f}}\frac{R_0^2+R_{0,f}}{R_0^2+R_{0,m}} + R_{0,f}\frac{R_0^2+R_{0,m}}{R_0^2+R_{0,f}} - 1\right) \\ & + (\delta+\mu)^2R_0^2\left(1-\frac{1}{R_{0,f}}\frac{R_0^2+R_{0,f}}{R_0^2+R_{0,m}}\right)\left(\frac{R_0^2+R_{0,m}}{R_0^2+R_{0,f}} - \frac{1}{R_{0,f}}\right) \\ & - (\delta+\mu)^2R_0^2\left(\frac{1}{R_{0,f}}\frac{R_0^2+R_{0,f}}{R_0^2+R_{0,m}}\left(1+\frac{1}{R_{0,f}} - \frac{R_0^2+R_{0,m}}{R_0^2+R_{0,f}}\right)\right) \end{aligned}$$

Rearranging and after simplifying

$$c = \underbrace{(\delta+\mu)^2R_0^2\frac{\left(R_{0,m}+R_{0,f}+R_0^2+1\right)}{\left(R_0^2+R_{0,m}\right)\left(R_0^2+R_{0,f}\right)})}_{>0}\left(R_0^2-1\right)$$

c is the product of a strictly positive number and $(R_0^2 - 1)$.
We conclude that: $c > 0$ iff $R_0 > 1$. □

In the model with vaccination, we prove the following results:
Theorem 3.4:
The DFE is locally asymptotically stable if and only if $R_v < 1$.

Proof. We define the system

$$(\dot{X_I}, \dot{V_I}, \dot{Y_I}, \dot{W_I}, \dot{X_S}, \dot{V_S}, \dot{Y_S}, \dot{W_S})^T = (0,0,0,0,0,0,0,0)^T \tag{6.1}$$

We compute the Jacobian matrix of the system (6.1) 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; A_2 being a square matrix of size 4; Therefore, (-μ) 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-matrix. 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:

$$C_3 = C_1C_2\left[1 - R_v^2 + R_f(\varphi_f)\frac{\sigma_m}{(\delta+\mu)}(1-\tau)\varphi_m\right]$$
$$C_4 = (\delta+\mu)^4(1-R_v^2)$$

C_3 and C_4 are positive if and only if $R_v < 1$. If $R_v < 1$, all principal minors of the Z-matrix $-A_1$ are positive, so $-A_1$ is a M-matrix (Hashimoto, 2009). 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 $R_v < 1$. Otherwise, if $R_v > 1$: $C_4 < 0$, thus $det(-A_1) < 0$, the determinant of $(-A_1)$ is equal to the product of 4 eigenvalues. Hence, at least one of the eigenvalues of the matrix $(-A_1)$ has strictly negative real part, and at least one of the eigenvalues of the matrix (A_1) has strictly positive real part. Therefore, Q_0 is locally asymptotically unstable. We proved that the DFE of the model with vaccination is locally asymptotically stable if and only if $R_v < 1$. □

Theorem 3.5:
If $R_v > 1$ the endemic equilibrium exists and is unique.
If $R_v < 1$ there isn't any endemic equilibrium.

Proof. We solve the system (2.1) in terms of λ_f and λ_m.

We obtain:

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

We define 2 level curves:

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

$$G_m(\lambda_f, \lambda_m) = -\lambda_m + \sigma_m \left[(1-\varphi_f) \frac{\lambda_f}{\lambda_f + \delta + \mu} + \varphi_f \frac{(1-\tau)\lambda_f}{(1-\tau)\lambda_f + \delta + \mu} \right].$$

The 2 levels curves go through the origin and $lim\lambda_k > 0$ when λ'_k go to infinity. 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 ($\lambda_f > 0, \lambda_m > 0$), λ_f is on the x-axis . Following the method described by Elbasha (2006), we prove that : if $R_v > 1$ the level curve G_m is above G_f around the origin, and the slopes of level curves are positive. Furthermore, each level curve intersects only once a ray from the origin. So, if $R_v > 1$, the endemic equilibrium exists.
In our modeling, we assumed that vaccination immunity is lifelong, this particular case was studied by Elbasha (2006), when $R_v > 1$, the both curves are monotically increasing in the positive quadrant, thus the two level curves intersect only once in the positive quadrant, therefore the endemic equilibrium is unique when $R_v > 1$.
If $R_v < 1$, following the proof described by Elbasha (2006), there is no positive endemic equilibrium.
□