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ORIGINAL ARTICLE

Global Stability of Equilibria in a Two-Sex HPV Vaccination Model

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Abstract Human papillomavirus (HPV) is the primary cause of cervical carcinoma and its precursor lesions, and is associated with a variety of other cancers and diseases. A prophylactic quadrivalent vaccine against oncogenic HPV 16/18 and warts-causing genital HPV 6/11 types is currently available in several countries. Licensure of a bivalent vaccine against oncogenic HPV 16/18 is expected in the near future. This paper presents a two-sex, deterministic model for assessing the potential impact of a prophylactic HPV vaccine with several properties. The model is based on the susceptible-infective-removed (SIR) compartmental structure. Important epidemiological thresholds such as the basic and effective reproduction numbers and a measure of vaccine impact are derived. We find that if the effective reproduction number is greater than unity, there is a locally unstable infection-free equilibrium and a unique, globally asymptotically stable endemic equilibrium. If the effective reproduction number is less than unity, the infection-free equilibrium is globally asymptotically stable, and HPV will be eliminated.

Keywords HPV · HPV disease · Cancer · Vaccine · Mathematical model · Global stability · Endemic equilibrium · Reproduction number

1. Introduction

The public health burden of human papillomavirus (HPV)-related diseases is enormous (see, e.g., Parkin et al., 2005; Insinga et al., 2004). HPV is estimated to be among the most common sexually transmitted infection. Recent national estimates from the United States suggest that overall HPV prevalence among women was high (27%), with prevalence highest among women aged 20–24 (Dunne et al., 2007). Approximately, 6.2 million new infections occur every year in the US (Centers for Disease Control and Prevention, Content Reviewed, 2004). Over 100 types of HPV have been identified, about 30 of them infect the genital areas of women and men. Although the majority of HPV infections are transient and are relatively harmless, persistent infection with certain "high-risk" HPV types can cause cervical carcinoma and its precursor lesions (Baseman and Koutsky, 2005;

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Bosch et al., 2002). HPV infection has also been linked with cancers of the anus, penis, vagina, vulva, and head and neck; benign condylomata, recurrent respiratory papillomatoses, and genital warts (see, e.g., Baseman and Koutsky, 2005).

A highly efficacious prophylactic vaccine against HPV types 6, 11, 16, and 18 is currently available for use in the US and several other countries. In large, multi-country, multi-site, human clinical trials, administration of this quadrivalent HPV (Types 6, 11, 16, 18) resulted in complete protection against disease, and near 100% efficacy against persistent infection or disease. The clinical studies also found that the quadrivalent HPV vaccine was safe and highly immunogenic (Villa et al., 2007). Another prophylactic bivalent HPV (Types 16, 18) vaccine has recently been filed for approval by the US Food and Drug Administration (FDA) (GlaxoSmithKline (GSK), 2007). A recent phase II human trial has shown high efficacy of this bivalent vaccine against incident and persistent HPV 16 and HPV 18 infections (Harper et al., 2004).

The potential epidemiologic impact of HPV vaccines has been investigated using mathematical models formulated as dynamic systems of ordinary differential equations (Hughes et al., 2002; Barnabas and Garnett, 2004; Elbasha et al., 2007). The analyses in these models were largely based on numerical simulations with few analytical results. It is known that even the simplest of dynamic models can exhibit strange behavior. For example, Kribs-Zaleta and Velasco-Hernández (2000) showed backward bifurcation exists even in a simple two-dimensional vaccination model. The phenomenon of backward bifurcation where a locally stable disease-free equilibrium coexists with multiple endemic equilibria, some of which are locally stable, has important implications for designing and assessing the impact of vaccination programs. For example, depending on the values of some parameters, the success or failure of mass vaccination programs in eliminating a disease depends on the initial distribution of individuals among the classes of susceptible, infected and removed. This should be contrasted with the situation where, regardless of the initial conditions, the success of a vaccination program in eliminating disease depends only whether the effective reproduction number, R, is below or above unity. In the presence of a vaccination program, the effective reproduction number is defined as the expected number of new HPV infections generated by a single infected individual during his/her entire period of infectiousness in a population with only susceptible or vaccinated individuals (Blower et al., 2002). It is, therefore, important to understand the global dynamic behavior in vaccination models in order to provide reliable assessment of the impact of vaccination programs.

In a previous paper (Elbasha, 2006), a simple, two-sex, epidemiologic model to assess the public health impact of vaccination against HPV infection was formulated. The vaccination model developed and analyzed there is based on the susceptible-infective-removed (SIR) compartmental structure (Hethcote, 2000) and features an imperfect vaccine that can partially protect against HPV infection with fixed duration of protection and with the ability to affect the duration and infectiousness of breakthrough infections. The expressions for the basic and effective reproduction numbers were derived and the existence, uniqueness and local stability of the infection-free and endemic equilibria were proved in Elbasha (2006). However, the global stabilities of the infection-free or endemic equilibria were not shown.

Analyzing the global stability of equilibria in epidemic models with several epidemiologic classes is not a trivial task. The global stability of the disease-free equilibrium

was analyzed in numerous epidemic models with or without vaccination (see, e.g., Hethcote, 2000; Kribs-Zaleta and Velasco-Hernández, 2000). However, the proof of the global stability of the endemic equilibrium was not provided for many of these models (see, e.g., Moreira and Yuquan, 1997; Li et al., 2001 for exceptions). In systems with three or less dimensions, a typical global stability analysis invokes the Poincaré–Bendixson theorem and applies one of the available methods to rule out existence of periodic solutions. Recently, several researchers have successfully applied the Lyapunov direct method to prove the global stability of endemic states in a variety of epidemic and virus population *in vivo* models with systems of higher dimensions (Korobeinikov, 2004a, 2004b, 2006; Korobeinikov and Maini, 2004; Korobeinikov and Wake, 2002; Iwasa et al., 2004; Guo and Li, 2006; McCluskey, 2006). The origin of the Lyapunov functions used in the analysis of these models goes back to Volterra (Harrison, 1979).

In this paper, we analyzed the global stability of equilibria in the model formulated and analyzed in Elbasha (2006). By constructing suitable Lyapunov functions, we prove that the global dynamics of this model are determined by the reproduction number R. If R is less than unity, there is a unique infection-free equilibrium which is globally asymptotically stable. For R greater than unity, the infection-free equilibrium is unstable, and there is a unique endemic equilibrium which is globally asymptotically stable. In Section 2, we outline the model. Section 3 summarizes the main results obtained in Elbasha (2006) including the expressions for the basic and effective reproduction numbers, the existence and local stability of the infection-free equilibrium and the existence and uniqueness of the endemic equilibrium. In Section 4, we prove that the infection-free equilibrium is globally stable if $R \leq 1$. In Section 5, we prove that the unique endemic equilibrium is globally stable whenever it exists. Section 6 includes the discussion and concluding remarks.

2. HPV vaccination model

The model analyzes the transmission of HPV in a heterosexually active population (Elbasha, 2006). The subscripts f and m are used to distinguish between the female and male members of this population, respectively. The model stratifies the sexually active population into several classes: susceptible to infection (X_k), infected (Y_k), immune because of recovery from infection (Z_k), vaccinated (V_k), and vaccinated with breakthrough infections (W_k) $k = f, m$ (Fig. 1). The model assumes that individuals enter the sexually active population (N) at rate Λ_k and leave (because of death or cessation of sexual activities) at rate μ_k. A proportion p_k of the new recruits into the sexually active community are vaccinated. It is assumed that the vaccine successfully takes in ε_k fraction of them. Thus, $p_k \varepsilon_k \Lambda_k$ are successfully vaccinated and move to the vaccinated class. The remainder move to the susceptible class. Susceptible individuals are infected with HPV at a per capita rate λ_k. This force of infection λ_k depends on the probability of HPV transmission from an infected individual of sex k' to a susceptible of sex k, β_k, the rate of partner acquisition, r_k, and the probability that a new sex partner from the opposite sex is infected with HPV. Upon infection, the host moves into the Y_k compartment. It is assumed that the vaccine offers a degree of protection ψ_k, where the relative risk of a vaccinated person experiencing a breakthrough infection and moving to compartment W_k is $1 - \psi_k$, with $0 \leq \psi_k \leq 1$. The relative risk of infectiousness of vaccinated individuals with breakthrough infections W_k compared to those in unvaccinated

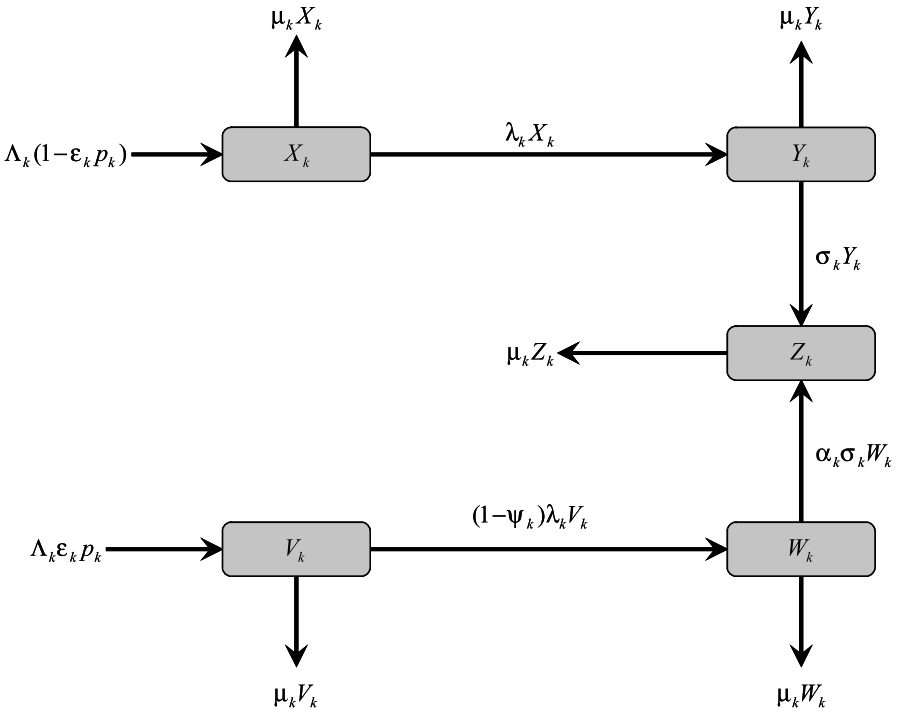

Fig. 1 Transfer diagram of the HPV model. The HPV vaccine model divides the population into five major groups according to their susceptibilities and infectiousness. The properties of the vaccine include coverage (p_k), take (ϵ_k), degree of protection (ψ_k), lower infectiousness of vaccinated infected (π_k), and faster clearance rate (α_k). $\lambda_k = r_k\beta_k(Y_{k'} + \pi_{k'}W_{k'})/N_{k'}$, $k = f, m$.

category Y_k is modeled by the parameter π_k, where $0 \leq \pi_k \leq 1$. An unvaccinated infected host can clear the infection at rate σ_k. Infected vaccinated individuals can clear infection at a rate $\alpha_k\sigma_k$, where $\alpha_k \geq 1$. We assumed that a host acquires life-long protection upon clearing infection (Hughes et al., 2002) or vaccination (Fraser et al., 2007; Villa et al., 2007). These last two assumptions regarding lack of natural or vaccine-induced waning immunity were made for the sake of simplifying the analysis. The ordinary differential equations that represent this compartmental model are

$$\begin{aligned}
dX_k/dt &= \Lambda_k(1-\varepsilon_k p_k) - \lambda_k X_k - \mu_k X_k,\\
dV_k/dt &= \Lambda_k \varepsilon_k p_k - (1-\psi_k)\lambda_k V_k - \mu_k V_k,\\
dY_k/dt &= \lambda_k X_k - (\mu_k + \sigma_k)Y_k,\\
dW_k/dt &= (1-\psi_k)\lambda_k V_k - (\mu_k + \alpha_k\sigma_k)W_k,\\
dZ_k/dt &= \sigma_k Y_k + \alpha_k\sigma_k W_k - \mu_k Z_k,
\end{aligned} \tag{1}$$

where

$$\lambda_k = r_k\beta_k(Y_{k'} + \pi_{k'}W_{k'})/N_{k'},$$

$$N_k = X_k + V_k + Y_k + W_k + Z_k, N = N_f + N_m, \quad k, k' = f, m; k \neq k'.$$

Furthermore, balancing the supply of and demand for sexual partnership requires $r_f N_f = r_m N_m$. Definitions of the variables and parameters of the model are described in Table 1.

In the limit, N_k approaches Λ_k/μ_k. Because the dynamics of (1) are qualitatively determined by those where N_k in (1) is replaced by its equilibrium value Λ_k/μ_k, we only need to analyze the limiting system (Castillo-Chavez and Thieme, 1995; Castillo-Chavez et al., 1996, 1999). Without any loss of generality, throughout the rest of the paper we let $\Lambda_k = \mu_k$, so that variables are expressed as fractions of the population of each gender. Given this, the domain of biological interest is

$$\mathfrak{D} = \left\{(X, V, Y, W, Z) \in \Re_+^{10} : X_k + V_k + Y_k + W_k + Z_k \leq 1\right\},$$

where $X = (X_f, X_m)$, $V = (V_f, V_m)$, $Y = (Y_f, Y_m)$, $W = (W_f, W_m)$, and $Z = (Z_f, Z_m)$. We will consider only the dynamics of the flow generated by (1) in this domain $\mathfrak{D}$. It can be verified that $\mathfrak{D}$ is positively invariant for system (1) and unique solutions exist in $\mathfrak{D}$ for all positive time (Simon and Jacquez, 1992). Thus, the model is epidemiologically and mathematically well posed (Hethcote, 2000). Because the behaviors of variables Z_k do not affect the rest of the system (1), we focus only on the equations of X_k, V_k, Y_k, and W_k.

Table 1 Description of variables and parameters

Symbol	Description
Subscripts	
k, k'	Gender (f = female, m = male)
Variables	
$X_k(t)$	Susceptible population
$V_k(t)$	Vaccinated population
$Y_k(t)$	Infected population
$W_k(t)$	Infected vaccinated population
$Z_k(t)$	Immune population
$\lambda_k(t)$	Force of infection
$N_k(t)$	Size of group k population
$N(t)$	Total size of sexually active population
Demographic parameters	
Λ_k	New recruits into the sexually active population
μ_k	Death or retirement rate from the sexually active population
r_k	Partner acquisition rate
Biological parameters	
β_k	Transmission probability per partnership
σ_k	Recovery from infection
Vaccine parameters	
p_k	Percentage of new recruits vaccinated
ε_k	Vaccine take
ψ_k	Vaccine degree of protection
α_k	Relative rate of recovery from breakthrough infections
π_k	Relative degree of infectiousness of breakthrough infections

3. Equilibria, reproduction numbers, and local stability

The model (1) has an infection-free equilibrium and an endemic equilibrium. The infection-free equilibrium $\mathcal{E}^\circ$ is given by

$$\mathcal{E}^\circ = (X^\circ, V^\circ, Y^\circ, W^\circ) = (1 - \varepsilon_k p_k, \varepsilon_k p_k, 0, 0), \tag{2}$$

$k = f, m$. Define the endemic equilibrium $\mathcal{E}^*$ of model (1) as

$$\mathcal{E}^* = (X^*, V^*, Y^*, W^*) = (X_k^*, V_k^*, Y_k^*, W_k^*), \quad k = f, m.$$

The *basic reproduction number* $\mathcal{R}_0$ for model (1), defined as the expected number of new HPV infections generated by a single infected individual during his/her entire period of infectiousness in a completely susceptible (without vaccination) population (see, e.g., Anderson and May, 1991; Hethcote, 2000; Diekmann et al., 1990; Simon and Jacquez, 1992), is given by Elbasha (2006):

$$\mathcal{R}_0 = \sqrt{\frac{r_f \beta_f}{\mu_f + \sigma_f} \frac{r_m \beta_m}{\mu_m + \sigma_m}}.$$

It should be noted that $\mathcal{R}_0$ for this model is given by the geometric mean of two quantities because an infected individual introduced into an entirely susceptible population generates $\mathcal{R}_{0,k} = r_k \beta_k / (\mu_k + \sigma_k)$ infections during his/her infectious period. But, starting from a single infected male, HPV has to go through a female before it can infect another new male. Therefore, the average number of secondary infections is given by the geometric mean of $\mathcal{R}_{0,f}$ and $\mathcal{R}_{0,m}$. Analogous formulae were derived for the basic reproduction numbers of vector-borne disease models (see, e.g., Esteva and Vargas, 1998). The formula for the effective reproduction number is

$$R(p_f, p_m) = \sqrt{R_f(p_f) R_m(p_m)}, \tag{3}$$

where

$$R_k(p_k) = \frac{r_k \beta_k}{\mu_k + \sigma_k} \left\{ 1 - \varepsilon_k p_k \left[1 - (1 - \psi_k) \pi_k \frac{\mu_k + \sigma_k}{\mu_k + \alpha_k \sigma_k} \right] \right\}, \tag{4}$$

$k = f, m$. From this, a gender-specific measure of vaccine impact, ϕ_k, on the "gender-specific reproduction number" (McLean and Blower, 1993) can be derived as

$$\phi_k = \varepsilon_k p_k \left[1 - (1 - \psi_k) \pi_k \frac{\mu_k + \sigma_k}{\mu_k + \alpha_k \sigma_k} \right], \quad k = f, m.$$

Thus, other things being equal, the vaccine impact (ϕ_k) on HPV transmission is greater, the higher is vaccine coverage (larger p_k), take (larger ε_k), or degree of protection (larger ψ_k); and the larger is the vaccine effect on infectiousness (smaller π_k) and clearance (larger α_k) of breakthrough cases.

A measure of vaccine impact, $\bar{\phi}$, that combines the effects of the vaccination programs pursued on each gender can be derived in a similar way. Thus,

$$\bar{\phi} = \frac{\mathcal{R}_0 - R(p_f, p_m)}{\mathcal{R}_0} = 1 - \sqrt{(1 - \phi_f)(1 - \phi_m)}.$$

The vaccine impact $\bar{\phi}$ is a monotonically increasing convex function with respect to the arguments ϕ_f and ϕ_m. An important property of this function is, for a given level of impact of vaccinating one gender, the returns from vaccinating the other gender increases as its impact increases. Thus, in the absence of constrains (e.g., inability to increase vaccine coverage on only one gender), maximum impact is achieved by expanding vaccine coverage among the gender that has the higher efficacy. However, it is unlikely that there will be no constraints on expanding vaccine coverage on one gender. These could be logistical (e.g., no established visit for vaccinating adolescent) and/or social/cultural (e.g., stigma surrounding a one-gender vaccination strategy) constraints. If constrains exist, a mono-gender vaccination program may not result in achieving the maximum public health impact.

The following results summarize the main results regarding the local stability of the infection-free equilibrium $\mathcal{E}^\circ$, and the existence and uniqueness of the endemic equilibrium $\mathcal{E}^*$. The proof of these results can be found in Elbasha (2006).

Theorem 1 *The infection-free equilibrium $\mathcal{E}^\circ$ of model (1) is locally asymptotically stable if $R(p_f, p_m) \leq 1$ and unstable if $R(p_f, p_m) > 1$.*

Theorem 2 *If $R(p_f, p_m) < 1$, there is no positive endemic equilibrium and the infection-free equilibrium is the only equilibrium. If $R(p_f, p_m) > 1$, there exists a unique positive endemic equilibrium $\mathcal{E}^*$.*

The last result indicates that if an endemic equilibrium exists, it must be unique. This is an important result because we could not make strong predictive statements about the impact of vaccination if there is more than one equilibrium. The result also rules out the possibility of backward bifurcation (multiple equilibria when $R(p_f, p_m) < 1$) that has been shown to exist in other vaccination models (e.g., Kribs-Zaleta and Velasco-Hernández, 2000). Next, we analyze the global stability of equilibria in model (1) and characterize the global dynamics of this model.

4. Stability of the infection-free equilibrium $\mathcal{E}^\circ$

In this section, we prove the global stability of the infection-free equilibrium $\mathcal{E}^\circ$ when the effective reproduction number is less than or equal to unity.

Theorem 3 *The infection-free equilibrium $\mathcal{E}^\circ$ of model (1) is globally asymptotically stable if $R(p_f, p_m) \leq 1$ and unstable if $R(p_f, p_m) > 1$.*

Proof Consider the Lyapunov function

$$
\begin{aligned}
L_1 = {} & X_f - X_f^\circ - X_f^\circ \ln \frac{X_f}{X_f^\circ} + Y_f + \frac{(\mu_f + \sigma_f)\pi_f}{\mu_f + \alpha_f \sigma_f} \left(V_f - V_f^\circ - V_f^\circ \ln \frac{V_f}{V_f^\circ} + W_f \right) \\
& + \frac{\mu_f + \sigma_f}{R_m(\mu_m + \sigma_m)} \left(X_m - X_m^\circ - X_m^\circ \ln \frac{X_m}{X_m^\circ} + Y_m \right) \\
& + \frac{(\mu_f + \sigma_f)\pi_m}{R_m(\mu_m + \alpha_m \sigma_m)} \left(V_m - V_m^\circ - V_m^\circ \ln \frac{V_m}{V_m^\circ} + W_m \right),
\end{aligned}
$$

where R_m is defined in (4). L_1 is defined, continuous and positive definite for all X_k, V_k, Y_k, $W_k > 0$, $k = f, m$. Also, the global minimum $L_1 = 0$ occurs at the infection-free equilibrium $\mathcal{E}_0$. Further, function L_1, along the trajectories of system (1), satisfies

$$\begin{aligned}
\frac{dL_1}{dt} &= \left(1 - \frac{X_f^\circ}{X_f}\right)\left[\Lambda_f(1-\varepsilon_f p_f) - r_f\beta_f X_f(Y_m + \pi_m W_m) - \mu_f X_f\right] \\
&\quad + r_f\beta_f X_f(Y_m + \pi_m W_m) - (\sigma_f + \mu_f)Y_f \\
&\quad + \frac{(\mu_f + \sigma_f)\pi_f}{\mu_f + \alpha_f\sigma_f} \\
&\quad \times \left\{\left(1 - \frac{V_f^\circ}{V_f}\right)\left[\Lambda_f\varepsilon_f p_f - (1-\psi_f)r_f\beta_f V_f(Y_m + \pi_m W_m) - \mu_f V_f\right]\right. \\
&\quad \left. + (1-\psi_f)r_f\beta_f V_f(Y_m + \pi_m W_m) - (\mu_f + \alpha_f\sigma_f)W_f\right\} \\
&\quad + \frac{\mu_f + \sigma_f}{R_m(\mu_m + \sigma_m)} \\
&\quad \times \left\{\left(1 - \frac{X_m^\circ}{X_m}\right)\left[\Lambda_m(1-\varepsilon_m p_m) - r_m\beta_m X_m(Y_f + \pi_f W_f) - \mu_m X_m\right]\right. \\
&\quad \left. + r_m\beta_m X_m(Y_f + \pi_f W_f) - (\sigma_m + \mu_m)Y_m\right\} \\
&\quad + \frac{(\mu_f + \sigma_f)\pi_m}{R_m(\mu_m + \alpha_m\sigma_m)}\left\{\left(1 - \frac{V_m^\circ}{V_m}\right)\right. \\
&\quad \times \left[\Lambda_m\varepsilon_m p_m - r_m(1-\psi_m)\beta_m V_m(Y_f + \pi_f W_f) - \mu_m V_m\right] \\
&\quad \left. + r_m(1-\psi_m)\beta_m V_m(Y_f + \pi_f W_f) - (\mu_m + \alpha_m\sigma_m)W_m\right\}.
\end{aligned}$$

Using the equilibrium conditions

$$\begin{aligned}
&\Lambda_k(1-\varepsilon_k p_k) = \mu_k X_k^\circ, \\
&\Lambda_k\varepsilon_k p_k = \mu_k V_k^\circ, \quad k = f, m,
\end{aligned}$$

and collecting terms, we obtain

$$\begin{aligned}
\frac{dL_1}{dt} &= \mu_f X_f^\circ\left(1 - \frac{X_f^\circ}{X_f}\right)\left(1 - \frac{X_f}{X_f^\circ}\right) + r_f\beta_f(Y_m + \pi_m W_m)X_f^\circ - (\sigma_f + \mu_f)Y_f \\
&\quad + \frac{\pi_f(\mu_f + \sigma_f)}{\mu_f + \alpha_f\sigma_f}\mu_f V_f^\circ\left(1 - \frac{V_f^\circ}{V_f}\right)\left(1 - \frac{V_f}{V_f^\circ}\right) \\
&\quad + \frac{\pi_f(\mu_f + \sigma_f)}{\mu_f + \alpha_f\sigma_f}(1-\psi_f)r_f\beta_f V_f^\circ(Y_m + \pi_m W_m) \\
&\quad - (\mu_f + \sigma_f)\pi_f W_f + \frac{\mu_f + \sigma_f}{R_m(\mu_m + \sigma_m)}\mu_m X_m^\circ\left(1 - \frac{X_m^\circ}{X_m}\right)\left(1 - \frac{X_m}{X_m^\circ}\right)
\end{aligned}$$

$$+\frac{\mu_f+\sigma_f}{R_m(\mu_m+\sigma_m)}r_m\beta_m X_m^\circ(Y_f+\pi_f W_f)-\frac{\mu_f+\sigma_f}{R_m}Y_m$$
$$+\frac{(\mu_f+\sigma_f)\pi_m}{R_m(\mu_m+\alpha_m\sigma_m)}\mu_m V_m^\circ\left(1-\frac{V_m^\circ}{V_m}\right)\left(1-\frac{V_m}{V_m^\circ}\right)$$
$$+\frac{(\mu_f+\sigma_f)\pi_m}{R_m(\mu_m+\alpha_m\sigma_m)}(1-\psi_m)r_m\beta_m V_m^\circ(Y_f+\pi_f W_f)-\frac{(\mu_f+\sigma_f)\pi_m}{R_m}W_m.$$

Further collecting terms, we have

$$\frac{dL_1}{dt}=\mu_f X_f^\circ\left(1-\frac{X_f^\circ}{X_f}\right)\left(1-\frac{X_f}{X_f^\circ}\right)+\frac{\pi_f(\mu_f+\sigma_f)}{\mu_f+\alpha_f\sigma_f}\mu_f V_f^\circ\left(1-\frac{V_f^\circ}{V_f}\right)\left(1-\frac{V_f}{V_f^\circ}\right)$$
$$+\frac{\mu_f+\sigma_f}{R_m(\mu_m+\sigma_m)}\mu_m X_m^\circ\left(1-\frac{X_m^\circ}{X_m}\right)\left(1-\frac{X_m}{X_m^\circ}\right)$$
$$+\frac{(\mu_f+\sigma_f)\pi_m}{R_m(\mu_m+\alpha_m\sigma_m)}\mu_m V_m^\circ\left(1-\frac{V_m^\circ}{V_m}\right)\left(1-\frac{V_m}{V_m^\circ}\right)$$
$$+\left(r_f\beta_f X_f^\circ+\frac{\pi_f(\mu_f+\sigma_f)}{\mu_f+\alpha_f\sigma_f}r_f(1-\psi_f)\beta_f V_f^\circ-\frac{\mu_f+\sigma_f}{R_m}\right)(Y_m+\pi_m W_m)$$
$$+\left(\frac{\mu_f+\sigma_f}{R_m(\mu_m+\sigma_m)}r_m\beta_m X_m^\circ+\frac{(\mu_f+\sigma_f)\pi_m}{R_m(\mu_m+\alpha_m\sigma_m)}(1-\psi_m)r_m\beta_m V_m^\circ\right.$$
$$\left.-(\sigma_f+\mu_f)\right)(Y_f+\pi_f W_f).$$

Using the definition of R_m in (4) and the values of X_m° and V_m° in (2), it can be shown that the last term is zero. Also, the first four terms are nonpositive. Thus,

$$\frac{dL_1}{dt}\le\left(r_f\beta_f X_f^\circ+\frac{\pi_f(\mu_f+\sigma_f)}{\mu_f+\alpha_f\sigma_f}(1-\psi_f)r_f\beta_f V_f^\circ-\frac{\mu_f+\sigma_f}{R_m}\right)(Y_m+\pi_m W_m)$$
$$=(R_f R_m-1)\frac{\mu_f+\sigma_f}{R_m}(Y_m+\pi_m W_m).$$

Therefore, if $R(p_f,p_m)\equiv\sqrt{R_f R_m}\le 1$, $dL_1/dt\le 0$ for all $X_k, V_k, Y_k, W_k>0, k=f,m$. The equality $dL_1/dt=0$ holds only (a) at the infection free equilibrium $\mathcal{E}_0$ or (b) when $R(p_f,p_m)=1$ and $X_k=X_k^\circ$, $V_k=V_k^\circ$. The latter case implies $Y_k=W_k=0$ since

$$1\ge X_k+V_k+Y_k+W_k+Z_k=X_k^\circ+V_k^\circ+Y_k+W_k+Z_k=1+Y_k+W_k+Z_k.$$

Therefore, the largest compact invariant subset of the set

$$M=\left\{(X,V,Y,W,Z)\in\mathfrak{D}:\frac{dL_1}{dt}=0\right\}$$

is the singleton $\{\mathcal{E}^\circ\}$. By the LaSalle's invariance principle (Khalil, 2002), the infection-free equilibrium is globally asymptotically stable if $R(p_f,p_m)\le 1$. We have shown previously that if $R(p_f,p_m)>1$, at least one of the eigenvalues of the Jacobian matrix eval-

uated at $\mathcal{E}_0$ has a positive real part (Elbasha, 2006). Therefore, the infection-free equilibrium $\mathcal{E}^\circ$ is unstable when $R(p_f, p_m) > 1$. □

5. Stability of the endemic equilibrium $\mathcal{E}^*$

In this section, we prove the global stability of endemic equilibrium $\mathcal{E}^*$ whenever it exists. We proved previously (Elbasha, 2006) that the unique endemic equilibrium exists when the effective reproduction number is greater than or equal to unity.

Theorem 4 *Assume that $R(p_f, p_m) > 1$. The endemic equilibrium $\mathcal{E}^*$ of model (1) is globally asymptotically stable.*

Proof Consider the Lyapunov function

$$\begin{aligned}
L_2 &= X_f - X_f^* - X_f^* \ln \frac{X_f}{X_f^*} + Y_f - Y_f^* - Y_f^* \ln \frac{Y_f}{Y_f^*} \\
&\quad + \frac{(\mu_f + \sigma_f)\pi_f}{\mu_f + \alpha_f \sigma_f} \left(V_f - V_f^* - V_f^* \ln \frac{V_f}{V_f^*} + W_f - W_f^* - W_f^* \ln \frac{W_f}{W_f^*} \right) \\
&\quad + d \left\{ X_m - X_m^* - X_m^* \ln \frac{X_m}{X_m^*} + Y_m - Y_m^* - Y_m^* \ln \frac{Y_m}{Y_m^*} \right. \\
&\quad \left. + \frac{(\mu_m + \sigma_m)\pi_m}{(\mu_m + \alpha_m \sigma_m)} \left(V_m - V_m^* - V_m^* \ln \frac{V_m}{V_m^*} + W_m - W_m^* - W_m^* \ln \frac{W_m}{W_m^*} \right) \right\},
\end{aligned}$$

where d is a positive constant that will be determined from the computation below. This function is defined, continuous and positive definite for all $X_k, V_k, Y_k, W_k > 0$, $k = f, m$. It can be verified that the function L_2 takes the value $L_2 = 0$ at the equilibrium point $\mathcal{E}^*$, and thus, the global minimum of L_2 occurs at the endemic equilibrium $\mathcal{E}^*$. At equilibrium we have

$$\begin{aligned}
&\Lambda_k(1 - \varepsilon_k p_k) = r_k \beta_k X_k^* (Y_{k'}^* + \pi_{k'} W_{k'}^*) + \mu_k X_k^*, \\
&\Lambda_k \varepsilon_k p_k = (1 - \psi_k) r_k \beta_k V_k^* (Y_{k'}^* + \pi_{k'} W_{k'}^*) + \mu_k V_k^*, \\
&(\mu_k + \sigma_k) Y_k^* = r_k \beta_k X_k^* (Y_{k'}^* + \pi_{k'} W_{k'}^*), \\
&(\mu_k + \alpha_k \sigma_k) W_k^* = (1 - \psi_k) r_k \beta_k V_k^* (Y_{k'}^* + \pi_{k'} W_{k'}^*).
\end{aligned} \tag{5}$$

The time derivative of L_2 along the solutions of system (1), using (5), is

$$\begin{aligned}
\frac{dL_2}{dt} &= \left(1 - \frac{X_f^*}{X_f}\right) \\
&\quad \times \left[r_f \beta_f X_f^* (Y_m^* + \pi_m W_m^*) + \mu_f X_f^* - r_f \beta_f X_f (Y_m + \pi_m W_m) - \mu_f X_f \right] \\
&\quad + \left(1 - \frac{Y_f^*}{Y_f}\right) \left[r_f \beta_f X_f (Y_m + \pi_m W_m) - r_f \beta_f X_f^* (Y_m^* + \pi_m W_m^*) \frac{Y_f}{Y_f^*} \right]
\end{aligned}$$

$$
\begin{aligned}
&+\frac{(\mu_f+\sigma_f)\pi_f}{\mu_f+\alpha_f\sigma_f}\left\{\left(1-\frac{V_f^*}{V_f}\right)\left[(1-\psi_f)\beta_f r_f V_f^*(Y_m^*+\pi_m W_m^*)+\mu_f V_f^*\right.\right.\\
&\left.-(1-\psi_f)r_f\beta_f V_f(Y_m+\pi_m W_m)-\mu_f V_f\right]+\left(1-\frac{W_f^*}{W_f}\right)\\
&\times\left[(1-\psi_f)\beta_f r_f V_f(Y_m+\pi_m W_m)\right.\\
&\left.\left.-(1-\psi_f)r_f\beta_f V_f^*(Y_m^*+\pi_m W_m^*)\frac{W_f}{W_f^*}\right]\right\}\\
&+d\left\{\left(1-\frac{X_m^*}{X_m}\right)\left[r_m\beta_m X_m^*(Y_f^*+\pi_f W_f^*)+\mu_m X_m^*\right.\right.\\
&\left.-r_m\beta_m X_m(Y_f+\pi_f W_f)-\mu_m X_m\right]\\
&\left.+\left(1-\frac{Y_m^*}{Y_m}\right)\left[r_m\beta_m X_m(Y_f+\pi_f W_f)-r_m\beta_m X_m^*(Y_f^*+\pi_f W_f^*)\frac{Y_m}{Y_m^*}\right]\right\}\\
&+\frac{(\mu_m+\sigma_m)\pi_m}{(\mu_m+\alpha_m\sigma_m)}\left\{\left(1-\frac{V_m^*}{V_m}\right)\left[(1-\psi_m)r_m\beta_m V_m^*(Y_f^*+\pi_f W_f^*)+\mu_m V_m^*\right.\right.\\
&\left.-(1-\psi_m)r_m\beta_m V_m(Y_f+\pi_f W_f)-\mu_m V_m\right]+\left(1-\frac{W_m^*}{W_m}\right)\\
&\times\left[(1-\psi_m)r_m\beta_m V_m(Y_f+\pi_f W_f)\right.\\
&\left.\left.-(1-\psi_m)r_m\beta_m V_m^*(Y_f^*+\pi_f W_f^*)\frac{W_m}{W_m^*}\right]\right\}.
\end{aligned}
$$

Collecting terms, and canceling identical terms with opposite signs, yields

$$
\begin{aligned}
\frac{dL_2}{dt}&=\mu_f X_f^*\left(1-\frac{X_f^*}{X_f}\right)\left(1-\frac{X_f}{X_f^*}\right)\\
&+r_f\beta_f X_f^* Y_m^*\left(2+\frac{Y_m}{Y_m^*}-\frac{Y_f}{Y_f^*}-\frac{X_f^*}{X_f}-\frac{Y_f^* X_f Y_m}{Y_f X_f^* Y_m^*}\right)\\
&+r_f\beta_f X_f^*\pi_m W_m^*\left(2+\frac{W_m}{W_m^*}-\frac{Y_f}{Y_f^*}-\frac{X_f^*}{X_f}-\frac{Y_f^* X_f W_m}{Y_f X_f^* W_m^*}\right)\\
&+\frac{(\mu_f+\sigma_f)\pi_f}{\mu_f+\alpha_f\sigma_f}\left\{\mu_f V_f^*\left(1-\frac{V_f^*}{V_f}\right)\left(1-\frac{V_f}{V_f^*}\right)\right.\\
&+(1-\psi_f)r_f\beta_f V_f^* Y_m^*\left(2+\frac{Y_m}{Y_m^*}-\frac{W_f}{W_f^*}-\frac{V_f^*}{V_f}-\frac{W_f^* V_f Y_m}{W_f V_f^* Y_m^*}\right)\\
&\left.+(1-\psi_f)r_f\beta_f V_f^*\pi_m W_m^*\left(2+\frac{W_m}{W_m^*}-\frac{W_f}{W_f^*}-\frac{V_f^*}{V_f}-\frac{W_f^* V_f W_m}{W_f V_f^* W_m^*}\right)\right\}
\end{aligned}
$$

$$
\begin{aligned}
&+ d\left\{\mu_m X_m^*\left(1-\frac{X_m^*}{X_m}\right)\left(1-\frac{X_m}{X_m^*}\right)\right.\\
&+ r_m\beta_m X_m^* Y_f^*\left(2+\frac{Y_f}{Y_f^*}-\frac{Y_m}{Y_m^*}-\frac{X_m^*}{X_m}-\frac{Y_m^* X_m Y_f}{Y_m X_m^* Y_f^*}\right)\\
&+ r_m\beta_m X_m^*\pi_f W_f^*\left(2+\frac{W_f}{W_f^*}-\frac{Y_m}{Y_m^*}-\frac{X_m^*}{X_m}-\frac{Y_m^* X_m W_f}{Y_m X_m^* W_f^*}\right)\\
&+ \frac{(\mu_m+\sigma_m)\pi_m}{\mu_m+\alpha_m\sigma_m}\left[\mu_m V_m^*\left(1-\frac{V_m^*}{V_m}\right)\left(1-\frac{V_m}{V_m^*}\right)\right.\\
&+ (1-\psi_m) r_m\beta_m V_m^* Y_f^*\left(2+\frac{Y_f}{Y_f^*}-\frac{W_m}{W_m^*}-\frac{V_m^*}{V_m}-\frac{W_m^* V_m Y_f}{W_m V_m^* Y_f^*}\right)\\
&\left.\left.+ (1-\psi_m) r_m\beta_m V_m^*\pi_f W_f^*\left(2+\frac{W_f}{W_f^*}-\frac{W_m}{W_m^*}-\frac{V_m^*}{V_m}-\frac{W_m^* V_m W_f}{W_m V_m^* W_f^*}\right)\right]\right\}.
\end{aligned}
$$

Let

$$d=\frac{r_f\beta_f X_f^* Y_m^*}{r_m\beta_m X_m^* Y_f^*}.$$

It can be verified, using (5), that the following is true

$$
\begin{aligned}
&d r_m\beta_m X_m^*\pi_f W_f^* = \frac{(\mu_f+\sigma_f)\pi_f}{\mu_f+\alpha_f\sigma_f}(1-\psi_f) r_f\beta_f V_f^* Y_m^*,\\
&d\frac{(\mu_m+\sigma_m)\pi_m}{\mu_m+\alpha_m\sigma_m}(1-\psi_m) r_m\beta_m V_m^*\pi_f W_f^* = \frac{(\mu_f+\sigma_f)\pi_f}{\mu_f+\alpha_f\sigma_f}(1-\psi_f) r_f\beta_f V_f^*\pi_m W_m^*,\\
&d\frac{(\mu_m+\sigma_m)\pi_m}{\mu_m+\alpha_m\sigma_m}(1-\psi_m) r_m\beta_m V_m^* Y_f^* = r_f\beta_f X_f^*\pi_m W_m^*.
\end{aligned}
$$

Using these identities, and noting that

$$
\begin{aligned}
&\mu_k X_k^*\left(1-\frac{X_k^*}{X_k}\right)\left(1-\frac{X_k}{X_k^*}\right)\le 0,\\
&\mu_k V_k^*\left(1-\frac{V_k^*}{V_k}\right)\left(1-\frac{V_k}{V_k^*}\right)\le 0,\quad k=f,m,
\end{aligned}
$$

we can rewrite the derivative of L_2 with respect to time as

$$
\begin{aligned}
\frac{dL_2}{dt} \le\ & r_f\beta_f X_f^* Y_m^*\left(4-\frac{X_f^*}{X_f}-\frac{Y_f^* X_f Y_m}{Y_f X_f^* Y_m^*}-\frac{X_m^*}{X_m}-\frac{Y_m^* X_m Y_f}{Y_m X_m^* Y_f^*}\right)\\
&+ r_f\beta_f X_f^*\pi_m W_m^*\left(4-\frac{X_f^*}{X_f}-\frac{Y_f^* X_f W_m}{Y_f X_f^* W_m^*}-\frac{V_m^*}{V_m}-\frac{W_m^* V_m Y_f}{W_m V_m^* Y_f^*}\right)\\
&+ \frac{(\mu_f+\sigma_f)\pi_f}{\mu_f+\alpha_f\sigma_f}(1-\psi_f) r_f\beta_f V_f^* Y_m^*
\end{aligned}
$$

$$\times \left(4 - \frac{V_f^*}{V_f} - \frac{W_f^* V_f Y_m}{W_f V_f^* Y_m^*} - \frac{X_m^*}{X_m} - \frac{Y_m^* X_m W_f}{Y_m X_m^* W_f^*}\right)$$

$$+ \frac{(\mu_f + \sigma_f)\pi_f}{\mu_f + \alpha_f \sigma_f}(1 - \psi_f) r_f \beta_f V_f^* \pi_m W_m^*$$

$$\times \left(4 - \frac{V_f^*}{V_f} - \frac{W_f^* V_f W_m}{W_f V_f^* W_m^*} - \frac{V_m^*}{V_m} - \frac{W_m^* V_m W_f}{W_m V_m^* W_f^*}\right)$$

$$\leq 0.$$

The terms between the larger brackets are less than or equal to zero by the inequality (the geometric mean less than or equal to the arithmetic mean)

$$\sqrt[4]{a_1 a_2 a_3 a_4} - (a_1 + a_2 + a_3 + a_4) \leq 0, \quad a_i \geq 0,\ i = 1, 2, 3, 4.$$

It should be noted that $dL_2/dt = 0$ holds if and only if (X_k, V_k, Y_k, W_k) take the equilibrium values $(X_k^*, V_k^*, Y_k^*, W_k^*)$. Therefore, the endemic equilibrium $\mathcal{E}^*$ is globally asymptotically stable. □

The fact that $\mathcal{E}^*$ is globally attractive also implies that there is no other equilibrium when $R(p_f, p_m) > 1$. The uniqueness of endemic equilibrium was proved in Elbasha (2006) using a geometric approach. In the special case where the vaccine-induced waning immunity is faster than a given minimum, we used the Poincaré–Hopf index theorem from differential topology to prove the uniqueness of endemic equilibrium.

6. Summary and discussion

Prophylactic vaccination against HPV holds promise for the control of HPV and HPV-related diseases (Jansen and Shaw, 2004; Berry and Palefsky, 2003; Lowry and Frazer, 2003; Tjalma et al., 2004). GARDASIL® [Quadrivalent HPV (Types 6, 11, 16, and 18) Recombinant Vaccine, Merck & Co., Inc., Whitehouse Station, NJ, USA], a highly efficacious prophylactic vaccine is currently licensed for use in adolescents girls and young women in the US and several other countries (Food and Drug Administration (FDA), 2006; Villa et al., 2005, 2007). The Advisory Committee for Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention (CDC) recommended that US girls and women 11 to 26 years old be vaccinated with GARDASIL® (with a provision that females as young as 9 may also be vaccinated) to prevent cervical cancer, precancerous and low-grade lesions, and genital warts caused by HPV types 6, 11, 16 and 18. Another prophylactic vaccine, CERVARIX® [Bivalent HPV (Types 16 and 18) Recombinant Vaccine, GlaxoSmithKline & Co., Inc., Brentford, Middlesex, United Kingdom], has recently been filed for approval by the US Food and Drug Administration (FDA) (GlaxoSmithKline (GSK), 2007). Both vaccines were designed to prevent the high-risk types (16 and 18) that are responsible for more than 70% of cervical cancers. GARDASIL® also prevents the low-risk types (6 and 11) which are found in over 90% of genital warts. Mathematical models play an important role in understanding the impact of prophylactic vaccination against HPV, and identifying the appropriate strategies to implement (Elbasha et al., 2007).

Assuming that the dynamic systems represented by these models are at equilibrium, the introduction of HPV vaccination will shock these systems and generate transient dynamics. Analysis of global stability is essential for gaining a full understanding of these dynamics. Without such analysis, we would not know whether the system will converge to an equilibrium, and under what conditions does a system converge to a given equilibrium.

In this paper, we analyzed a deterministic, heterosexually transmitted HPV infection model and examined the potential impact of a prophylactic HPV vaccine with several properties. We derived an explicit formula for the reproduction numbers that characterizes whether the epidemic will be contained following vaccination or not. The importance of various vaccine properties in determining the impact of vaccination programs was analyzed using a summary measure derived from the reproduction numbers.

By constructing suitable Lyapunov functions, we were able to resolve the global stability of system (1). We proved that the global dynamics of this model are determined by the reproduction number $R(p_f, p_m)$. If $R(p_f, p_m)$ is less than unity, there is a unique infection-free equilibrium which is globally asymptotically stable. For $R(p_f, p_m)$ greater than unity, the infection-free equilibrium is unstable, and there is a unique endemic equilibrium which is globally asymptotically stable.

The model could be elaborated to take into account other factors that are important for the transmission of HPV. Such risk factors include age and heterogeneity of mixing between different sexual activity groups. The model also does not incorporate some important aspects of the natural history of HPV infection and HPV-related diseases. It is well known that persistent infection with HPV leads to many diseases, including precancerous lesions; cervical, anal, penile, vaginal, vulvar, and head/neck cancers; anogenital warts; and recurrent respiratory papillomatoses (Centers for Disease Control and Prevention, Content Reviewed, 2004). Most of these diseases progress through different stages with rates of infectivity, progression, regression to normal and clearance of infection, and disease-induced mortality varying by stage. For example, it is believed that women in late stages of cancer are less infectious and have higher disease-induced mortality compared with women in early stages of cervical intraepithelial neoplasia (CIN). To simplify the analysis, it is assumed that life-long immunity is conferred following clearance of infection or vaccination. There are no studies that conclusively support the assumption that duration of protective natural immunity is permanent. Although there is strong evidence suggesting that vaccine-induced immunity is high and durable (Villa et al., 2007; Fraser et al., 2007), there will be some time before permanent efficacy is confirmed through long-term follow data. Future versions of the model that include heterogeneity in mixing between different social groups, allow for progression of infection along various disease states, and incorporate temporary immunity following recovery from infection or vaccination should be analyzed.

The model was developed specifically for HPV, but can be adapted to study the impact of vaccines against other sexually transmitted diseases (STD). For example, the vast majority of human immunodeficiency virus (HIV) cases in Africa (the global epicenter of the HIV pandemic) are transmitted through heterosexual intercourse. The current model can be adapted to analyze the impact of imperfect HIV vaccines in controlling the spread of HIV in a heterosexually mixing population. The analysis of this and other modified models will enable us to get insight into the impact of STD vaccines on the course of epidemics and help guide public policy.

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