MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **10**, Number **4**, August **2013**

doi:10.3934/mbe.2013.10.xx

pp. **x–xx**

THE IMPACT OF AN IMPERFECT VACCINE AND PAP CYTOLOGY SCREENING ON THE TRANSMISSION OF HUMAN PAPILLOMAVIRUS AND OCCURRENCE OF ASSOCIATED CERVICAL DYSPLASIA AND CANCER

Tufail Malik

Department of Applied Mathematics and Sciences
Khalifa University of Science, Technology and Research
PO Box 127788, Abu Dhabi, UAE
and
Department of Mathematics, University of Manitoba
Winnipeg, Manitoba, R3T 2N2, Canada

Jody Reimer

Mathematical Institute, University of Oxford
24-29 St Giles', Oxford OX1 3LB, UK

Abba Gumel

Department of Mathematics, University of Manitoba
Winnipeg, Manitoba, R3T 2N2, Canada

Elamin Elbasha

Merck Research Laboratories, UG1C-60, PO Box 1000
North Wales, PA 19454-1099, USA

Salaheddin Mahmud

Community Health Sciences
University of Manitoba, Winnipeg, Manitoba, Canada
and
Winnipeg Regional Health Authority
Winnipeg, Manitoba, Canada

(Communicated by Christopher M. Kribs-Zaleta)

2010 *Mathematics Subject Classification.* Primary: 92D30; Secondary: 37N25.

Key words and phrases. Human papillomavirus, cervical cancer, Pap cytology screening, vaccine, backward bifurcation, endemic equilibrium.

Abstract. A mathematical model for the natural history of human papillomavirus (HPV) is designed and used to assess the impact of a hypothetical anti-HPV vaccine and Pap cytology screening on the transmission dynamics of HPV in a population. Rigorous qualitative analysis of the model reveals that it undergoes the phenomenon of backward bifurcation. It is shown that the backward bifurcation is caused by the imperfect nature of the HPV vaccine or the HPV-induced and cancer-induced mortality in females. For the case when the disease-induced and cancer-induced mortality is negligible, it is shown that the disease-free equilibrium (i.e., equilibrium in the absence of HPV and associated dysplasia) is globally-asymptotically stable if the associated reproduction number is less than unity. The model has a unique endemic equilibrium when the reproduction threshold exceeds unity. The unique endemic equilibrium is globally-asymptotically stable for a special case, where the associated HPV-induced and cancer-induced mortality is negligible. Numerical simulations of the model, using a reasonable set of parameter values, support the recent recommendations by some medical agencies and organizations in the USA to offer Pap screening on a 3-year basis (rather than annually).

1. **Introduction.** Cervical cancer, the second most frequent form of cancer among women worldwide, is an important global public health problem [18]. In 2002, an estimated 529,000 new cases of cervical cancer occurred worldwide, representing nearly 10% of all cases of cancer among women [18]. An estimated 1,300 Canadian women were diagnosed with invasive cervical cancer in 2009, corresponding to an annual incidence rate of 7 *per* 100,000 women [6].

There is overwhelming epidemiologic and experimental evidence that cervical infection with certain "high-risk" types of the human papillomavirus (HPV) is responsible for virtually all cervical cancer cases [20, 54]. Genital HPV infection is the most common sexually-transmitted disease in the US and Canada [20]. It is estimated that up to 75% of women may eventually become infected in their lifetime [29] (some other studies, such as those reported in [31, 41, 44], show that up to 70% of sexually-active men and women acquire HPV infection at least once in their lifetime). The HPV infection is prevalent among younger women, with evidence of infection found in 5-40% of asymptomatic women in the reproductive age group. Fortunately, most of these infections are transient (last less than a year) and asymptomatic. However, persistent infection with thirteen or so high-risk (oncogenic) HPV (HR-HPV) types could lead to cancer [37].

The natural history of cervical cancer is perhaps the best understood of all malignancies. Cervical carcinogenesis is a complex stepwise process characterized by slow progression over a continuum of increasingly more severe precancerous changes known collectively as cervical intraepithelial neoplasia (CIN) [20]. Depending on the extent and severity of dysplastic features, the spectrum of CIN is traditionally divided into three histopathological categories, namely: CIN1, CIN2 and CIN3. In CIN1, cells with malignant changes are limited to the superficial layer of the cervical epithelium. Most CIN1 lesions are likely to disappear without treatment. However, a small percentage may progress to high-grade CIN (CIN2 and CIN3). This (high) grade CIN is characterized by more severe dysplastic changes and higher degree of epithelial basal cell involvement. The risk of progression to invasive cervical cancer increases significantly with worsening CIN grades [29].

In most developed countries, Pap cytology screening for the early detection of cervical neoplasia has been successful in reducing cervical cancer incidence and mortality, especially in jurisdictions with organized screening programs [10]. However,

Pap cytology, as a primary screening tool, has important limitations. A single Pap smear has both low sensitivity (approximately 51% [35]) and poor specificity which necessitates repeated screening at regular intervals throughout adulthood. In many countries, women are screened annually starting at the initiation of sexual activity [47]. The present policy in the Canadian province of Manitoba requires all women 18 years or older to undergo annual screening with conventional Pap cytology if they have ever been sexually-active. After 3 consecutive normal smears, screening is continued at 2-year intervals [43]. This policy could result in a woman undergoing 27 routine smears in her lifetime assuming full compliance and no abnormal results. Some countries offer Pap screening at a less frequent interval (see, for instance, [25, 30] for the screening guidelines in Norway). Furthermore, some agencies in the USA (such as American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology [46]) have recently recommended Pap screening to be carried out every three years.

The recent introduction of effective vaccines against HPV is expected to reduce the burden of cervical cancer substantially [23]. However, screening for cervical cancer will still be needed because about 30% of cervical cancers are caused by types other than the two high-risk HPV (HR-HPV) types targeted by the current vaccines (Types 16 and 18) [38], and because women who are already infected will continue to develop cervical cancer [19]. In the future, the cost-effectiveness of Pap screening may be significantly reduced because as the prevalence of cervical neoplasia decreases, the positive predictive value of the Pap test will also decrease, and as a result, more women will be referred for unnecessary diagnostic procedures and follow-up [19].

Mathematical modeling is a useful tool for assessing the potential impact of intervention strategies against HPV infection (and the associated cervical cancer), such as mass vaccination and Pap screening. A number of authors have reported on the use of such modeling to evaluate the impact of HPV vaccine [1, 2, 4, 9, 13, 16]. In particular, Al-arydah [2] developed a two-sex, age-structured model to describe the vaccination program for an HPV vaccine in childhood (under 13 years) and adult stages. It is shown that vaccinating a single age cohort in one gender can result in eventual control of HPV across all age groups. Furthermore, Elbasha and Galvani [13] showed that for the case of synergistic interaction between HPV types, the use of mass vaccination may reduce the prevalence of HPV types that are not included in the currently available HPV vaccines. Models for the combined impact of HPV vaccination and Pap screening have also been published in the literature (see, for instance, [15, 17, 24, 39, 40]). Myers et al. [39] proposed a model for the natural history of HPV infection and cervical carcinogenesis.

The purpose of the current study is to extend some of the aforementioned studies by designing a new and comprehensive sex-structured (male and female) model for the natural history of cervical cancer, and use the model to assess the public health impact of mass vaccination and Pap screening of sexually-active females. Although there are many oncogenic HPV types, this theoretical study only considers the dynamics and control of the two vaccine-targeted oncogenic types (Types 16 and 18). Furthermore, the only modality of screening considered in this study is Pap screening (and not HPV DNA testing). The model is formulated in Section 2 and analysed in Section 3. The impact of vaccination and screening are assessed in Section 4.

2. **Model formulation.** The model is formulated as follows. The total sexually-active female population at time t, denoted by $N_f(t)$, is split into the sub-populations of unvaccinated susceptible ($S_f(t)$), susceptible individuals vaccinated against the relevant vaccine-targeted types ($V(t)$), HPV-infected ($I_f(t)$), HPV-infected with persistent infection ($P(t)$), HPV-infected individuals with undetected CIN (three grades, $Q_i(t)$; $i = 1, 2, 3$, representing low-, medium- and high-grade squamous intraepithelial lesions, respectively), infected individuals with detected CIN (three grades, Q_{id}; $i = 1, 2, 3$), those with undetected cancer ($C(t)$), those with detected cancer ($C_d(t)$), those who recovered from infection or the CIN without developing cancer ($R_f(t)$) and those who recovered from cancer ($R_c(t)$), so that

$$N_f(t) = S_f(t) + V(t) + I_f(t) + P(t) + \sum_{i=1}^{3} Q_i(t)$$

$$+ \sum_{i=1}^{3} Q_{id}(t) + C(t) + C_d(t) + R_f(t) + R_c(t).$$

The total sexually-active male population, denoted by $N_m(t)$, is sub-divided into susceptible ($S_m(t)$), infected ($I_m(t)$) and recovered ($R_m(t)$) males. Hence,

$$N_m(t) = S_m(t) + I_m(t) + R_m(t).$$

The population of unvaccinated susceptible females (S_f) is generated by the recruitment of new sexually-active females (at a rate π_f; a fraction, ϕ, of which is vaccinated). Although this study does not explicitly model the various HPV types, it is assumed that the theoretical vaccine targets some HPV types. The vaccines currently in the market are GSK's bivalent Cervarix (which targets HPV Types 16 and 18) and Merck's quadrivalent Gardasil (which targets HPV Types 6, 11, 16, 18). These vaccines, which have been approved for use in a number of countries, including Canada [44], have 90-100% efficacy against infection with Types 16 and 18 [22, 53].

The unvaccinated susceptible female population is decreased by the acquisition of HPV infection, following effective contact with infected males, at a rate λ_m, given by

$$\lambda_m = \frac{\beta_m c_f I_m}{N_m},$$

where β_m is the proportion of potentially infectious contacts which result in the transmission of infection from males to females and c_f is the average number of contacts *per* female *per* unit time. It is also decreased due to natural death (at a rate μ_f; females in all compartments suffer natural death at this rate, μ_f).

The class of vaccinated susceptible females (V) is populated by the vaccination of new sexually-active females (at the aforementioned rate $\pi_f\phi$). It is decreased by HPV infection (at a reduced rate $(1-\epsilon_v)\lambda_m$, where $0 < \epsilon_v \leq 1$ represents the vaccine efficacy against HPV infection) and natural death. It is assumed that the vaccine does not wane during the period under consideration [16]. The population of infected females (I_f) is generated by the infection of unvaccinated and vaccinated susceptible females. It is assumed that a fraction, r_1, of the infected female population recovers (at a rate $\sigma_f r_1$), while the remaining fraction, $1 - r_1$, develops persistent infection (and moves to the class P at the rate $\sigma_f(1-r_1)$). It is assumed that recovery confers permanent immunity against re-infection with HPV. It should be mentioned that although re-infection (especially with a different HPV strain) is

possible in HPV dynamics, the model (3) does not incorporate re-infection. The reader is referred to [13] for a discussion of immunity against HPV. The class of infected females is further reduced by natural death and infection-induced death (at a rate δ_f).

The population of infected females with persistent infection (P) is generated by the fraction $(1-r_1)$ of infected females in the I_f class that develop persistent infection (at the rate $(1-r_1)\sigma_f$). It is decreased by progression to Grade 1 of undetected CIN (at a rate κ_p), recovery (at a rate ψ_0) and natural death. The population of infected females in Grade 1 of undetected CIN (CIN1) is populated by females with persistent infection (at the rate κ_p) and those regressing from CIN Grade 2 (at a rate κ_q), and is diminished by recovery (at a rate ψ_1), progression to undetected CIN Grade 2 (at a rate ζ_1), detection (at a rate α_1) and natural death. The class of infected females in Grade 2 of undetected CIN (CIN2) is generated by progression from CIN Grade 1 (at the rate ζ_1), and is decreased by remission to CIN Grade 1 (at a rate κ_q), recovery (at a rate ψ_2), progression to Grade 3 (at a rate ζ_2), detection (at a rate α_2) and natural death. Similarly, the population of those in undetected CIN Grade 3 (CIN3) is generated at the rate ζ_2, and is diminished by recovery (at a rate ψ_3), development of cervical cancer (at a rate ζ_3), detection (at a rate α_3) and natural death.

The population of females with detected CIN Grade 1 (Q_{1d}) is populated by the detection of undetected infected females in class Q_1 (at the rate α_1) and by the regression of those in Q_{2d} class (at a rate κ_d). It is decreased by progression to detected CIN Grade 2 (at the rate ζ_1), recovery (at a rate ρ_1) and natural death. The class of detected CIN Grade 2 (Q_{2d}) is generated by the detection of infected individuals in the Q_2 class (at the rate α_2) and by progression of those in the Q_{1d} class (at the rate ζ_1). It is decreased by remission to Q_{1d} class (at the rate κ_d), progression to Grade 3 (at the rate ζ_2), recovery (at a rate ρ_2) and natural death. Similarly, the population of those in detected CIN Grade 3 class (Q_{3d}) is generated at the rates α_3 (for those in Q_3 class) and ζ_2 (for those females progressing from Q_{2d} class), and is decreased by recovery (at a rate ρ_3) and natural death.

The detection rate, α_i $i=1,2,3$, is an aggregate parameter that depends on the proportion of sexually-active females screened for cervical dysplasia (χ - henceforth referred to as 'proportion screened'), the screening sensitivity of the Pap test in the respective CIN grade ($\epsilon_i,\ i=1,2,3$) and the screening frequency per year (∇). Thus for the present model, it is defined as

$$\alpha_i = \chi\epsilon_i\nabla,\ i=1,2,3$$

Van de Velde et al. [52] assume the Pap test to be 60% sensitive for the detection of CIN Grade 1 and 78% sensitive for Grades 2 and 3. They assume the proportion screened (χ) to range from a low 7% (in the age group 70-100) to 32% (in the age group 20-29) per year. The proportions screened vary from 37% in the Canadian provinces of British Columbia and Ontario to 44% in Nova Scotia [26]. As the base-case Pap test assumption, the current model assumes $\chi = 0.32$. Due to the wide range of values reported in the literature, the sensitivity of the model to the proportion screened (χ) is examined in Section 4.4.

The population of individuals with cervical cancer (C) is generated by individuals in the Q_3 class who develop cancer (at the rate ζ_3). It is decreased by cancer detection (at a rate α_c). If undetected, the population of individuals with cervical cancer suffers an additional cancer-related mortality (at a rate δ^c). The population

of females with detected cervical cancer (C_d) is populated by the detection of females in the cancer class (at the rate α_c) and decreased by recovery (at a rate γ), natural death, and cancer-related death (at a rate δ_d^c).

The population of infected females who recovered from cervical cancer (R_c) is generated by the recovery of females with detected cancer (at the rate γ) and is decreased by natural death. Similarly, the population of those who recovered from HPV infection and CIN (R_f) is generated by the recovery of infected individuals in the I_f, P, Q_{1d}, Q_{2d}, Q_{3d}, Q_1, Q_2 and Q_3 classes, and is decreased by natural death.

The population of susceptible males (S_m) is generated by the recruitment of new sexually-active males (at a rate π_m). It is decreased by infection, following effective contact with infected females (it is assumed that only infected females in the compartments I_f and P can transmit infection to males) at a rate λ_f, given by

$$\lambda_f = \frac{\beta_f c_m (I_f + \theta P)}{N_f},$$

where β_f is the proportion of potentially infectious contacts which result in the transmission of infection from females to males and c_m is the average number of contacts *per* male *per* unit time.

The modification parameter θ, $0 < \theta \leq 1$, accounts for the variability in the transmission probability of individuals in the P class in relation to those in the I_f class. It is assumed that infected females with CIN_i ($i = 1, 2, 3$) are not infectious. Males in all epidemiological compartments suffer natural death at a rate μ_m. The population of infected males is generated at the rate λ_f, and diminished by recovery (at a rate σ_m) and natural death. No persistent infection or disease-related mortality is assumed in males.

Furthermore, the following conservation law (for number of sexual contacts made by males balancing those made by females) [16] is assumed to hold:

$$c_m N_m(t) = c_f N_f(t). \tag{1}$$

Male sexual partners are assumed to be abundant, so that females can always have enough number of sexual partners per unit time. Hence, it is assumed that c_f is constant, and c_m is calculated from the relation $c_m(N_m, N_f) = \frac{c_f N_f}{N_m}$. Using (1), the infection rates λ_m and λ_f are given by

$$\lambda_m = \frac{\beta_m c_f I_m}{N_m}, \ \lambda_f = \frac{\beta_f c_f (I_f + \theta P)}{N_m}. \tag{2}$$

Based on the above formulations and assumptions, and using the conservation law (1), it follows that the model for the natural history of HPV, in the presence of an imperfect vaccine and Pap cytology screening, is given by the following deterministic system of non-linear differential equations (a flow diagram of the model is depicted in Figure 1, and the associated variables and parameters of the model are described in Tables 1 and 2, respectively):

$$\begin{aligned}
\frac{dS_f}{dt} &= \pi_f(1-\phi) - \lambda_m S_f - \mu_f S_f, \\
\frac{dV}{dt} &= \pi_f \phi - (1-\epsilon_v)\lambda_m V - \mu_f V,
\end{aligned}$$

$$
\begin{aligned}
\frac{dI_f}{dt} &= \lambda_m[S_f + (1-\epsilon_v)V] - (\sigma_f + \mu_f + \delta_f)I_f,\\
\frac{dP}{dt} &= \sigma_f(1-r_1)I_f - (\kappa_p + \psi_0 + \mu_f)P,\\
\frac{dQ_1}{dt} &= \kappa_p P + \kappa_q Q_2 - (\psi_1 + \zeta_1 + \alpha_1 + \mu_f)Q_1,\\
\frac{dQ_2}{dt} &= \zeta_1 Q_1 - (\kappa_q + \psi_2 + \zeta_2 + \alpha_2 + \mu_f)Q_2,\\
\frac{dQ_3}{dt} &= \zeta_2 Q_2 - (\psi_3 + \zeta_3 + \alpha_3 + \mu_f)Q_3,\\
\frac{dQ_{1d}}{dt} &= \alpha_1 Q_1 + \kappa_d Q_{2d} - (\zeta_1 + \rho_1 + \mu_f)Q_{1d},\\
\frac{dQ_{2d}}{dt} &= \alpha_2 Q_2 + \zeta_1 Q_{1d} - (\kappa_d + \zeta_2 + \rho_2 + \mu_f)Q_{2d},\\
\frac{dQ_{3d}}{dt} &= \alpha_3 Q_3 + \zeta_2 Q_{2d} - (\rho_3 + \mu_f)Q_{3d},\\
\frac{dC}{dt} &= \zeta_3 Q_3 - (\alpha_c + \mu_f + \delta^c)C,\\
\frac{dC_d}{dt} &= \alpha_c C - (\gamma + \mu_f + \delta_d^c)C_d,\\
\frac{dR_c}{dt} &= \gamma C_d - \mu_f R_c,\\
\frac{dR_f}{dt} &= \sigma_f r_1 I_f + \psi_0 P + \sum_{i=1}^{3}\psi_i Q_i + \sum_{i=1}^{3}\rho_i Q_{id} - \mu_f R_f,\\
\frac{dS_m}{dt} &= \pi_m - \lambda_f S_m - \mu_m S_m,\\
\frac{dI_m}{dt} &= \lambda_f S_m - (\sigma_m + \mu_m)I_m,\\
\frac{dR_m}{dt} &= \sigma_m I_m - \mu_m R_m.
\end{aligned}
\tag{3}
$$

The model (3) is a deterministic model for the natural history of the cervical cancer, inspired by the Markov model in [39], incorporating sex structure (the dynamics of sexually-active males and females) as well as a mass vaccination program (against some vaccine-targeted HPV types). Furthermore, it extends the model in [13] by incorporating sex structure and by accounting for persistent HPV infections, cervical dysplasia and cancer, and Pap screening cytology. It also extends the models in [16, 28] by incorporating the dynamics of individuals with persistent infection.

The model (3) will now be qualitatively analysed to gain insight into its dynamical features. It should be further emphasized that the model (3) only considers the vaccine-targeted HPV types.

3. Analysis of the model.

3.1. Basic properties.

The basic dynamical features of the model (3), subject to the conservation law (1), will now be explored.

Lemma 3.1. *The closed set*

$$\mathcal{D} = \{(S_f, V, I_f, P, Q_1, Q_2, Q_3, Q_{1d}, Q_{2d}, Q_{3d}, R_f, C, C_d, R_c, S_m, I_m, R_m) \in \mathbb{R}_+^{17} :$$

Variable	Description
S_f	Population of unvaccinated susceptible females
V	Population of vaccinated susceptible females
I_f	Population of infected females
P	Population of females with persistent HPV infection
$Q_i;\ i=1,2,3$	Population of infected females in Grade i of undetected CIN
$Q_{id};\ i=1,2,3$	Population of infected females in Grade i of detected CIN
C	Population of infected females with undetected cervical cancer
C_d	Population of infected females with detected cervical cancer
R_c	Population of infected females who recovered from cancer
R_f	Population of infected females who recovered from HPV infection without developing cancer
N_f	Total female population
S_m	Population of susceptible males
I_m	Population of infected males
R_m	Population of recovered males
N_m	Total male population

TABLE 1. Description of state variables of the model (3).

$$N_f \leq \pi_f/\mu_f,\ N_m \leq \pi_m/\mu_m\}.$$

is positively-invariant and attracting with respect to the model (3).

Proof. Adding the first 14 equations of the model (3) gives

$$\frac{dN_f}{dt} = \pi_f - \mu_f N_f - \delta_f I_f - \delta^c C - \delta_d^c C_d \leq \pi_f - \mu_f N_f. \tag{4}$$

Since $N_f(t) \geq 0$, it follows using a standard comparison theorem [33] that

$$N_f(t) \leq N_f(0)e^{-\mu_f t} + \frac{\pi_f}{\mu_f}(1 - e^{-\mu_f t}).$$

Therefore, $N_f(t) \leq \pi_f/\mu_f$ if $N_f(0) \leq \pi_f/\mu_f$.

Similarly, adding the last three equations of the model (3) gives:

$$\frac{dN_m}{dt} = \pi_m - \mu_m N_m, \tag{5}$$

so that,

$$N_m(t) = N_m(0)e^{-\mu_m t} + \frac{\pi_m}{\mu_m}(1 - e^{-\mu_m t}).$$

Hence $N_m(t) \leq \pi_m/\mu_m$ if $N_m(0) \leq \pi_m/\mu_m$. Thus, the positive invariance of $\mathcal{D}$ has been proved.

To prove that $\mathcal{D}$ is attracting, it is clear from (4) and (5) that (for $i = m, f$), $\frac{dN_i}{dt} < 0$, whenever $N_i(t) > \pi_i/\mu_i$. Thus, either the solution enters $\mathcal{D}$ in finite time, or $N_i(t)$ approaches π_i/μ_i, and the variables denoting infected classes approach zero. Hence, $\mathcal{D}$ is attracting and all solutions in $\mathbb{R}^{17}_+$ eventually enter $\mathcal{D}$. □

Since the region $\mathcal{D}$ is is positively-invariant and attracting, the usual existence, uniqueness, continuation results hold for the system, and the system (3) is mathematically and epidemiologically well-posed in $\mathcal{D}$ [27]. Therefore, it is sufficient to consider the dynamics of the flow generated by the model (3) in $\mathcal{D}$.

	Description	Nominal Value	Ref
π_f, π_m	Recruitment rate of new sexually-active females and males	10000/year	[42]
$1/\mu_m (1/\mu_f)$	Average duration of sexual activity for males (females)	65 years [64-69]	[5]
$\beta_m (\beta_f)$	Proportion of potentially infectious contacts resulting in transmission of infection from males to females (females to males) per contact	0.8(0.7)/contact	[13]
c_f	Average number of sexual contacts per female	2 contacts/year	[42]
c_m	Average number of sexual contacts per male	Variable ($c_m = c_f \frac{N_f}{N_m}$)	
ϕ	Fraction of new sexually-active females vaccinated (cohort vaccination)	0.7	[15]
ϵ_v	Vaccine efficacy	0.9	[17]
r_1	Fraction of infectious females who recover naturally (and do not develop persistent infection)	0.99 [0.5-1]	[39]
$\sigma_f r_1$	Recovery rate of infected females	0.495/year ($\sigma_f = 0.5$)	[13]
$\sigma_f(1-r_1)$	Rate of development of persistent infection	0.005/year ($\sigma_f = 0.5$)	[13]
σ_m	Recovery rate of infected males	0.9/year	[13]
κ_p	Progression rate from HPV to CIN1	0.1 [0.05-0.1]/year	[15]
γ	Recovery rate of individuals with cancer	0.76/year	[15]
ψ_1	Natural recovery rate for undetected CIN1	0.05 [0.05-0.13]/year	[39]
ψ_2	Natural recovery rate for undetected CIN2	0.05 [0.05-0.13]/year	[39]
ψ_3	Natural recovery rate for undetected CIN3	0.05 [0.05-0.13]/year	A
ζ_1, ζ_2	Progression rate from CIN1 to CIN2 and CIN2 to CIN3	0.02, 0.04 [0.02-.08]/year	[15]
ζ_3	Progression rate from CIN3 to cancer	0.08 [0.05-.08]/year	[15]
κ_q	Regression rate from undetected CIN2 to CIN1	0.08 [0.05-0.08]/year	[39]
κ_d	Regression rate from detected CIN2 to CIN1	0.08 [0.05-0.08]/year	[39]
$\alpha_1, \alpha_2, \alpha_3$	Detection rate for CIN1, CIN2, CIN3	[0, 1]/year	D
α_c	Detection rate for cervical cancer	[0, 1]/year	A
ϵ_1, ϵ_2, ϵ_3	Sensitivity of Pap screening for CIN1, CIN2, CIN3	0.6, 0.78, 0.78	[52]
χ	Proportion of sexually-active females screened	[7%-44%]	[26]
∇	Screening frequency	$\frac{1}{\nabla} = 1, 2, 3$ years	A
θ	Modification parameter for the infectiousness of individuals with persistent infection relative to those in the I_f class	0.9	A
δ_f	HPV infection-induced mortality rate in females	0.001/year	A
δ^c	Cancer-induced mortality rate for undetected individuals	0.01/year	A
δ_d^c	Cancer-induced mortality rate for detected individuals	0.001/year	A
ψ_0	Recovery rate of individuals with persistent infection	0.01/year	A
ρ_1, ρ_2, ρ_3	Recovery rate of detected CIN individuals	0.13 [0.05-0.13]/year	[39]

TABLE 2. Description of the parameters of the model (3).
A: Assumed. D: Derived.

3.2. **Disease-free (infection- and cancer-free) equilibrium (DFE).** The model (3) has a DFE given by

$$\mathcal{E}_0 = (S_f^*, V^*, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, S_m^*, 0, 0),$$

where,

$$S_f^* = \frac{\pi_f(1-\phi)}{\mu_f}, \; V^* = \frac{\pi_f}{\mu_f}\phi, \; S_m^* = \frac{\pi_m}{\mu_m}. \tag{6}$$

The next generation operator method [11, 51] will be used to explore the local stability of $\mathcal{E}_0$. The matrices G (for the new infection terms) and H (of the transition terms) are given, respectively, by

$$G = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_m c_m}{N_f^*}[S_f^* + (1-\epsilon_v)V^*] \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \beta_f c_f & \theta\beta_f c_f & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

and,

$$H = \begin{pmatrix} g_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_f(1-r_1) & g_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\kappa_p & g_3 & -\kappa_q & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\zeta_1 & g_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\zeta_2 & g_5 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\alpha_1 & 0 & 0 & g_6 & -\kappa_d & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\alpha_2 & 0 & -\zeta_1 & g_7 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\alpha_3 & 0 & -\zeta_2 & g_8 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\zeta_3 & 0 & 0 & 0 & g_9 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\alpha_c & g_{10} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & g_{11} \end{pmatrix},$$

where, $g_1 = \sigma_f + \mu_f + \delta_f,\; g_2 = \kappa_p + \psi_0 + \mu_f,\; g_3 = \psi_1 + \zeta_1 + \alpha_1 + \mu_f, g_4 = \kappa_q + \psi_2 + \zeta_2 + \alpha_2 + \mu_f, g_5 = \psi_3 + \zeta_3 + \alpha_3 + \mu_f,\; g_6 = \zeta_1 + \rho_1 + \mu_f, g_7 = \kappa_d + \zeta_2 + \rho_2 + \mu_f,\; g_8 = \rho_3 + \mu_f,\; g_9 = \alpha_c + \mu_f + \delta_c,\; g_{10} = \gamma + \mu_f + \delta_c^d,\; g_{11} = \sigma_m + \mu_m$.

It follows that the *reproduction number* ($\mathcal{R}_v$), associated with the model (3), is given by (where ρ is the spectral radius)

$$\mathcal{R}_v = \rho(GH^{-1}) = \sqrt{\mathcal{R}_{vm}\mathcal{R}_{vf}}, \tag{7}$$

with,

$$\mathcal{R}_{vm} = \frac{\beta_m c_f}{g_{11}}, \; \mathcal{R}_{vf} = \frac{\beta_f c_f \pi_f \mu_m}{\mu_f \pi_m g_1}\left[1 + \frac{\theta\sigma_f(1-r_1)}{g_2}\right](1-\epsilon_v\phi).$$

The threshold quantity, $\mathcal{R}_v$, measures the average number of new infections generated by a typical infected individual in a population where some susceptible females are vaccinated (and also screened). The result below follows from Theorem 2 of [51].

Lemma 3.2. *The DFE, $\mathcal{E}_0$, of the model (3), is locally-asymptotically stable (LAS) if $\mathcal{R}_v < 1$, and unstable if $\mathcal{R}_v > 1$.*

Lemma 3.2 implies that the combined use of Pap screening and an HPV vaccine can lead to the effective control of the disease in the population if the threshold quantity ($\mathcal{R}_v$) can be brought to (and maintained at) a value less than unity. Mathematically-speaking, the result implies that the vaccine-targeted HPV types can be eliminated from the population (when $\mathcal{R}_v < 1$) if the initial sizes of the sub-populations of the model (3) are in the basin of attraction of the DFE ($\mathcal{E}_0$).

3.3. **Existence of endemic equilibrium point (EEP).** Let

$$\mathcal{E}_1 := (S_f^{**}, V^{**}, I_f^{**}, P^{**}, Q_1^{**}, Q_2^{**}, Q_3^{**}, Q_{1d}^{**}, Q_{2d}^{**}, Q_{3d}^{**},$$
$$C^{**}, C_d^{**}, R_c^{**}, R_f^{**}, S_m^{**}, I_m^{**}, R_m^{**})$$

represents an arbitrary endemic equilibrium of the model (3) (i.e., equilibria for which at least one of the infected components of the model (3) is non-zero). Furthermore, let

$$\lambda_m^{**} = \frac{\beta_m c_f I_m^{**}}{N_m^{**}} \text{ and } \lambda_f^{**} = \frac{\beta_f c_f (I_f^{**} + \theta P^{**})}{N_m^{**}}, \tag{8}$$

be the *forces of infection* for males and females at steady-state, respectively.

Solving the equations of the model (3) at steady-state gives:

$$\begin{aligned}
S_f^{**} &= \frac{\pi_f(1-\phi)}{\lambda_m^{**}+\mu_f},\ V^{**} = \frac{\pi_f \phi}{[(1-\epsilon_v)\lambda_m^{**}+\mu_f]},\\
I_f^{**} &= \frac{\lambda_m^{**}\pi_f[(1-\epsilon_v)\lambda_m^{**}+(1-\epsilon_v\phi)\mu_f]}{g_1[(1-\epsilon_v)\lambda_m^{**}+\mu_f](\lambda_m^{**}+\mu_f)},\\
P^{**} &= \frac{\sigma_f(1-r_1)I_f^{**}}{g_2},\ Q_1^{**} = \frac{g_4\kappa_p\sigma_f(1-r_1)\lambda_m^{**}\pi_f[(1-\epsilon_v)\lambda_m^{**}+(1-\epsilon_v\phi)\mu_f]}{g_1g_2(g_3g_4-\zeta_1\kappa_q)[(1-\epsilon_v)\lambda_m^{**}+\mu_f](\lambda_m^{**}+\mu_f)},\\
Q_2^{**} &= \frac{\zeta_1 Q_1^{**}}{g_4},\ Q_3^{**} = \frac{\zeta_2 Q_2^{**}}{g_5},\\
Q_{1d}^{**} &= \frac{\kappa_p\sigma_f(1-r_1)\lambda_m^{**}\pi_f[(1-\epsilon_v)\lambda_m^{**}+(1-\epsilon_v\phi)\mu_f](\alpha_1 g_4 g_7+\alpha_2\zeta_1\kappa_d)}{g_1g_2(g_3g_4-\zeta_1\kappa_q)(g_6g_7-\zeta_1\kappa_d)(\lambda_m^{**}+\mu_f)[(1-\epsilon_v)\lambda_m^{**}+\mu_f]},\\
Q_{2d}^{**} &= \frac{\alpha_2 Q_2^{**}+\zeta_1 Q_{1d}^{**}}{g_7},\ Q_{3d}^{**} = \frac{\alpha_3 Q_3^{**}+\zeta_2 Q_{2d}^{**}}{g_8},\\
C^{**} &= \frac{\zeta_3 Q_3^{**}}{g_9},\ C_d^{**} = \frac{\alpha_c C^{**}}{g_{10}},\ R_c^{**} = \frac{\gamma C_d^{**}}{\mu_f},\\
R_f^{**} &= \frac{\sigma_f r_1 I_f^{**}(\lambda_m^{**}) + \psi_0 P^{**}(\lambda_m^{**}) + \sum_{i=1}^{3}\psi_i Q_i^{**}(\lambda_m^{**}) + \sum_{i=1}^{3}\rho_i Q_{id}^{**}(\lambda_m^{**})}{\mu_f},\\
S_m^{**} &= \frac{\pi_m}{\lambda_f^{**}+\mu_m},\ I_m^{**} = \frac{\pi_m\lambda_f^{**}}{g_{11}(\lambda_f^{**}+\mu_m)},\ R_m^{**} = \frac{\sigma_m\pi_m\lambda_f^{**}}{g_{11}\mu_m(\lambda_f^{**}+\mu_m)}.
\end{aligned} \tag{9}$$

Substituting (9) in (8), and simplifying, gives, respectively,

$$\lambda_m^{**} = \frac{\mu_m\lambda_f^{**}c_f\beta_m}{g_{11}(\lambda_f^{**}+\mu_m)}, \tag{10}$$

and,

$$\lambda_f^{**} = \frac{\beta_f c_f \lambda_m^{**} \pi_f [(1-\epsilon_v)\lambda_m^{**} + (1-\epsilon_v\phi)\mu_f][g_2 + \theta\sigma_f(1-r_1)]\mu_m}{g_1 g_2 \pi_m [(1-\epsilon_v)\lambda_m^{**} + \mu_f](\lambda_m^{**} + \mu_f)}. \tag{11}$$

It follows, by substituting (11) into (10), that the positive (endemic) equilibria of the model (3) satisfy the following quadratic (in terms of λ_m^{**}):

$$a_0(\lambda_m^{**})^2 + b_0\lambda_m^{**} + c_0 = 0, \tag{12}$$

where,

$$\begin{aligned} a_0 =& g_{11}(1-\epsilon_v)\left\{g_1 g_2 \pi_m + \pi_f c_f \beta_f [g_2 + \theta\sigma_f(1-r_1)]\right\}, \\ b_0 =& 2g_1 g_2 g_{11}\mu_f \pi_m (1-\epsilon_v) + \beta_f c_f \pi_f [g_2 + \theta\sigma_f(1-r_1)] \\ & \{g_{11}(1-\epsilon_v\phi)\mu_f - (1-\epsilon_v)\mu_m \beta_m c_f\}, \\ c_0 =& g_1 g_2 g_{11}\mu_m \mu_f^2 [1-(R_v)^2]. \end{aligned}$$

The components of the positive endemic equilibria of the model (3) are then obtained by solving the quadratic (12) for λ_m^{**} and substituting the results in (9) and (11). It should be observed that (11) gives λ_f^{**} as a rational function of λ_m^{**}, so that a fixed value of λ_m^{**} corresponds to a unique value of λ_f^{**}. Clearly, the coefficient a_0 of (12) is always positive (since $0 < \epsilon_v \leq 1$), and c_0 is positive (negative) if $\mathcal{R}_v$ is less than (greater than) unity. Thus, the following result is established.

Theorem 3.3. *The model (3) has:*

1. *a unique endemic equilibrium if $c_0 < 0 \Leftrightarrow \mathcal{R}_v > 1$;*
2. *a unique endemic equilibrium if $b_0 < 0$, and $c = 0$ or $b_0^2 - 4a_0c_0 = 0$;*
3. *two endemic equilibria if $c_0 > 0, b_0 < 0$ and $b_0^2 - 4a_0c_0 > 0$;*
4. *no endemic equilibrium otherwise.*

It is clear from Case 1 of Theorem 3.3 that the model has a unique endemic equilibrium whenever $\mathcal{R}_v > 1$. Numerical simulation results, depicted in Figure 2, show convergence of solutions to this EEP when $\mathcal{R}_v > 1$ suggesting that the EEP is asymptotically-stable when it exists. Furthermore, Case 3 indicates the possibility of backward bifurcation (where the locally-asymptotically stable DFE co-exists with a locally-asymptotically stable endemic equilibrium when $\mathcal{R}_v < 1$ [3, 14, 32, 48]). The existence of backward bifurcation in vaccination models, such as (3), has been established in a number of epidemiological settings (see, for instance, [3, 12, 14, 21, 36, 48, 49]). We claim the following (the proof, based on using Centre Manifold Theory [7, 8, 51], is given in Appendix A).

Theorem 3.4. *The model (3) undergoes a backward bifurcation at $\mathcal{R}_v = 1$ whenever the inequality in (24) is satisfied.*

The epidemiological implication of the backward bifurcation phenomenon of the model (3) is that having $\mathcal{R}_v < 1$ is not sufficient (albeit necessary) to effectively control the spread of HPV and the associated dysplasia in the population. In other words, the combined use of mass vaccination and Pap cytology screening may fail to lead to effective control of HPV and the associated dysplasia even when $\mathcal{R}_v < 1$ (due to the phenomenon of backward bifurcation). In such a backward bifurcation scenario, effective disease control, when $\mathcal{R}_v < 1$, is dependent on the initial sizes of the populations of the model. Clearly, this (backward bifurcation) phenomenon makes effective control of HPV and the associated dysplasia difficult. It is worth stating that with the realistic parameter values in Table 2, the associated backward

bifurcation parameter, a, is given by $a = -1.14 \times 10^{-5} < 0$ (so that backward bifurcation cannot occur). In other words, this study shows that the phenomenon of backward bifurcation is not feasible in HPV dynamics using a realistic set of parameter values.

It is worth noting that for the case when the vaccine is perfect (i.e., $\epsilon_v = 1$), the coefficient a_0 of the quadratic (12) is zero, and $b_0 > 0$. Hence, the quadratic (12) has a unique root, given by $\lambda_m^{**} = -c_0/b_0$, with $c_0 \leq 0$. The case $c_0 = 0$ implies $\lambda_m^{**} = 0$, which corresponds to the DFE. On the other hand, $c_0 < 0$ corresponds to Case 1 of Theorem 3.3, which shows the existence of a unique endemic equilibrium, only when $\mathcal{R}_v > 1$.

Corollary 1. *The model (3) with perfect vaccine ($\epsilon_v = 1$) does not undergo a backward bifurcation at $\mathcal{R}_v = 1$.*

Thus, this study shows that the imperfect nature of the HPV vaccine ($0 < \epsilon_v < 1$) causes the phenomenon of backward bifurcation in the model (3).

3.4. **Global stability of equilibria: Special case.** Consider the model (3) with the associated disease-induced and cancer-induced mortality set to zero (i.e., $\delta := \delta_f = \delta^c = \delta_d^c = 0$). When $\delta = 0$, it follows from (4) and (5) that $dN_f/dt = \pi - \mu_f N_f$ and $dN_m/dt = \pi - \mu_m N_m$, so that $N_f \to \pi_f/\mu_f$ as $t \to \infty$ and $N_m \to \pi_m/\mu_m$ as $t \to \infty$.

Let $\beta_0 = \dfrac{\beta_m c_f \mu_m}{\pi_m}$, $\beta_1 = \dfrac{\beta_f c_m \mu_f}{\pi_f}$ and $\beta_2 = \dfrac{\beta_f c_m \mu_f \theta}{\pi_f}$. Hence,

$$\lambda_m = \beta_0 I_m \text{ and } \lambda_f = \beta_1 I_f + \beta_2 P.$$

It is convenient to write

$$W = Q_1 + Q_2 + Q_3 + Q_{1d} + Q_{2d} + Q_{3d} + C + C_d + R_c + R_f.$$

Thus the system (3) can now be re-written as:

$$\begin{aligned}
\frac{dS_f}{dt} &= \pi_f(1-\phi) - \beta_0 I_m S_f - \mu_f S_f,\\
\frac{dV}{dt} &= \pi_f \phi - (1-\epsilon_v)\beta_0 I_m V - \mu_f V,\\
\frac{dI_f}{dt} &= \beta_0 I_m [S_f + (1-\epsilon_v)V] - \tilde{g}_1 I_f,\\
\frac{dP}{dt} &= \sigma_f(1-r_1)I_f - g_2 P,\\
\frac{dW}{dt} &= (\kappa_p + \psi_0)P + \sigma_f r_1 I_f - \mu_f W,\\
\frac{dS_m}{dt} &= \pi_m - (\beta_1 I_f + \beta_2 P)S_m - \mu_m S_m,\\
\frac{dI_m}{dt} &= (\beta_1 I_f + \beta_2 P)S_m - g_{11} I_m,\\
\frac{dR_m}{dt} &= \sigma_m I_m - \mu_m R_m,
\end{aligned} \tag{13}$$

where, $\tilde{g}_1 = g_1|_{\delta=0} = \sigma_f + \mu_f$.

Since the variable W does not feature in any of the other equations of the model (13), it is removed from the analysis. The invariant region of the reduced system (13) is

$$\tilde{\mathcal{D}} = \{(S_f, V, I_f, P, W, S_m, I_m, R_m) \in \mathbb{R}_+^8 : \ N_f \leq \pi_f/\mu_f, \ N_m \leq \pi_m/\mu_m\},$$

and the associated DFE is given by

$$\tilde{\mathcal{E}}_0 = (S_f^*, V^*, 0, 0, 0, S_m^*, 0, 0),$$

where, S_f^*, V^* and S_m^* are given by (6). Furthermore, the reproduction number of the reduced model (13) is

$$\tilde{\mathcal{R}}_v = \mathcal{R}_v|_{\delta=0} = \sqrt{\frac{\beta_m \beta_f c_f^2 \pi_f \mu_m}{\pi_m \mu_f \tilde{g}_1 g_{11}} \left[1 + \frac{\theta \sigma_f (1-r_1)}{g_2}\right] (1-\epsilon_v \phi)}. \tag{14}$$

It is worth noting that the associated backward bifurcation parameter, a, for the reduced model (13) is given by

$$a = -\frac{2\beta_f \beta_m^2 c_f^3 \mu_m^3 v_7 w_7^2 S_m^* [\alpha + m u_f + \theta \sigma_f (1-r_1)]}{\pi_m^3 (\sigma_f + \mu_f)(\alpha + \mu_f)} \left\{ \frac{S_f^* + (1-\epsilon_v)^2 V^*}{\mu_f} + \frac{[S_f^* + (1-\epsilon_v)^2 V^*]^2}{\pi_m (\sigma_f + \mu_f)} + \frac{\theta \sigma_f (1-r_1) c_f [S_f^* + (1-\epsilon_v) V^*]}{\pi_m (\sigma_f + \mu_f)(\alpha + \mu_f)} \right\} < 0,$$

so that the reduced model (13) will not undergo backward bifurcation (by Theorem 4.1 of [8]). To further confirm the absence of backward bifurcation in the reduced model (13), a global-asymptotic stability proof is given below for the DFE of the model (13).

3.4.1. *Global stability of DFE.*

Theorem 3.5. *The DFE, $\tilde{\mathcal{E}}_0$, of the reduced model (13), is GAS in $\tilde{\mathcal{D}}$ whenever $\tilde{\mathcal{R}}_v < 1$.*

Proof. Consider the non-linear Lyapunov function

$$\mathcal{F} = S_f - S_f^* - S_f^* \ln \frac{S_f}{S_f^*} + V - V^* - V^* \ln \frac{V}{V^*} + I_f + \frac{\beta_2 \tilde{g}_1}{\beta_1 g_2 + \beta_2 \sigma_f (1-r_1)} P + \frac{\tilde{g}_1 g_2}{\beta_1 g_2 + \beta_2 \sigma_f (1-r_1)} \left(S_m - S_m^* - S_m^* \ln \frac{S_m}{S_m^*} + I_m \right),$$

with the Lyapunov derivative given by (where the prime denotes differentiation with respect to t)

$$\begin{aligned}
\mathcal{F}' &= \left(1 - \frac{S_f^*}{S_f}\right) S_f' + \left(1 - \frac{V^*}{V}\right) V' + I_f' + \frac{\beta_2 \tilde{g}_1}{\beta_1 g_2 + \beta_2 \sigma_f (1-r_1)} P' \\
&\quad + \frac{\tilde{g}_1 g_2}{\beta_1 g_2 + \beta_2 \sigma_f (1-r_1)} \left[\left(1 - \frac{S_m^*}{S_m}\right) S_m' + I_m' \right] \\
&= \left(1 - \frac{S_f^*}{S_f}\right) [\mu_f S_f^* - \beta_0 I_m S_f - \mu_f S_f] \\
&+ \left(1 - \frac{V^*}{V}\right) [\mu_f V^* - (1-\epsilon_v) \beta_0 I_m V - \mu_f V] \\
&+ \beta_0 I_m [S_f + (1-\epsilon_v) V] - \tilde{g}_1 I_f + \frac{\beta_2 \tilde{g}_1}{\beta_1 g_2 + \beta_2 \sigma_f (1-r_1)} [\sigma_f (1-r_1) I_f - g_2 P] \\
&+ \frac{\tilde{g}_1 g_2}{\beta_1 g_2 + \beta_2 \sigma_f (1-r_1)} \left\{ \left(1 - \frac{S_m^*}{S_m}\right) [\mu_m S_m^* - (\beta_1 I_f + \beta_2 P) S_m - \mu_m S_m] \right. \\
&\left. + (\beta_1 I_f + \beta_2 P) S_m - g_{11} I_m \right\}
\end{aligned}$$

$$
\begin{aligned}
&= \mu_f S_f^* \left(2 - \frac{S_f^*}{S_f} - \frac{S_f}{S_f^*}\right) - \beta_0 I_m S_f + \beta_0 I_m S_f^* + \mu_f V^* \left(2 - \frac{V^*}{V} - \frac{V}{V^*}\right) \\
&- (1-\epsilon_v)\beta_0 I_m V + (1-\epsilon_v)\beta_0 I_m V^* + \beta_0 I_m [S_f + (1-\epsilon_v)V] - \tilde{g}_1 I_f \\
&+ \frac{\beta_2 \tilde{g}_1}{\beta_1 g_2 + \beta_2 \sigma_f (1-r_1)} [\sigma_f (1-r_1) I_f - g_2 P] + \frac{\tilde{g}_1 g_2}{\beta_1 g_2 S_m^* + \beta_2 \sigma_f (1-r_1) S_m^{**}} \\
&\left[\mu_m S_m^* \left(2 - \frac{S_m^*}{S_m} - \frac{S_m}{S_m^*}\right) - (\beta_1 I_f + \beta_2 P) S_m + (\beta_1 I_f + \beta_2 P) S_m^* \right. \\
&\left. + (\beta_1 I_f + \beta_2 P) S_m - g_{11} I_m \right] \\
&= \mu_f S_f^* \left(2 - \frac{S_f^*}{S_f} - \frac{S_f}{S_f^*}\right) + \mu_f V^* \left(2 - \frac{V^*}{V} - \frac{V}{V^*}\right) + \mu_m S_m^* \left(2 - \frac{S_m^*}{S_m} - \frac{S_m}{S_m^*}\right) \\
&+ \left[-\tilde{g}_1 + \frac{\beta_2 \tilde{g}_1 \sigma_f (1-r_1)}{\beta_1 g_2 + \beta_2 \sigma_f (1-r_1)} + \frac{\beta_1 \tilde{g}_1 g_2}{\beta_1 g_2 + \beta_2 \sigma_f (1-r_1)}\right] I_f \\
&+ \left[-\frac{\beta_2 \tilde{g}_1 g_2}{\beta_1 g_2 + \beta_2 \sigma_f (1-r_1)} + \frac{\beta_2 \tilde{g}_1 g_2}{\beta_1 g_2 + \beta_1 \sigma_f (1-r_1)}\right] P \\
&+ \left\{\beta_0 [S_f^* + (1-\epsilon_v) V^*] - \frac{\tilde{g}_1 g_2 g_{11}}{\beta_1 g_2 S_m^* + \beta_1 \sigma_f (1-r_1) S_m^*}\right\} I_m, \\
&= \mu_f S_f^* \left(2 - \frac{S_f^*}{S_f} - \frac{S_f}{S_f^*}\right) + \mu_f V^* \left(2 - \frac{V^*}{V} - \frac{V}{V^*}\right) + \mu_m S_m^* \left(2 - \frac{S_m^*}{S_m} - \frac{S_m}{S_m^*}\right) \\
&+ \frac{\tilde{g}_1 g_2 g_{11} \mu_m}{[\beta_1 g_2 + \beta_2 \sigma_f (1-r_1)] \pi_m} [(\tilde{\mathcal{R}}_v)^2 - 1] I_m.
\end{aligned}
$$

In the above calculations, the following DFE relations (obtained from (13) at $\mathcal{E}_0$) have been used:

$$\pi_f (1-\phi) = \mu_f S_f^*, \ \pi_f \phi = \mu_f V^*, \ \pi_m = \mu_m S_m^*.$$

Since the arithmetic mean exceeds the geometric mean (that is, $a_1 + a_2 + \cdots + a_n \geq n \sqrt[n]{a_1 \cdot a_2 \cdots a_n}$ for $a_i \geq 0, \ i = 1, \ldots, n$), it follows that

$$2 - \frac{S_f^*}{S_f} - \frac{S_f}{S_f^*} \leq 0, \ 2 - \frac{V^*}{V} - \frac{V}{V^*} \leq 0, \ 2 - \frac{S_m^*}{S_m} - \frac{S_m}{S_m^*} \leq 0.$$

Therefore, $\mathcal{F}' \leq 0$ if $\tilde{\mathcal{R}}_v \leq 1$. The equality $\mathcal{F}' = 0$ holds only (a) at the DFE $\tilde{\mathcal{E}}_0$ or (b) when $\tilde{\mathcal{R}}_v = 1$ and $S_f = S_f^*$, $V = V^*$ and $S_m = S_m^*$. In case (b),

$$
\begin{aligned}
\frac{\pi_f}{\mu_f} + \frac{\pi_m}{\mu_m} &\geq S_f + V + I_f + P + W + S_m + I_m + R_m \\
&= S_f^* + V^* + I_f + P + W + S_m^* + I_m + R_m \\
&= \frac{\pi_f}{\mu_f} + \frac{\pi_m}{\mu_m} + I_f + P + W + I_m + R_m,
\end{aligned}
$$

so that $I_f + P + I_m + R_m \leq 0$. This implies that $I_f = P = I_m = R_m = 0$. Therefore the largest compact invariant set in $\{(S_f, V, I_f, P, S_m, I_m, R_m) \in \tilde{\mathcal{D}} : \mathcal{F}' = 0\}$ is the singleton $\{\tilde{\mathcal{E}}_0\}$. It follows from the LaSalle's Invariance Principle [34] that every solution of the system (13) with initial conditions in $\tilde{\mathcal{D}}$ converges to the DFE $\tilde{\mathcal{E}}_0$ as $t \to \infty$. That is, $(I_f(t), P(t), I_m(t)) \to (0, 0, 0)$ as $t \to \infty$. Substituting $I_f = P = I_m = 0$ in the equations for the susceptible females and males of the

model (13) gives $S_f(t) \to S_f^*$ and $S_m(t) \to S_m^*$ as $t \to \infty$. Similarly, it is easy to see that (when $(I_f, P, I_m) = (0, 0, 0)$) the variable $W(t) \to 0$ as $t \to \infty$. Thus, $(S_f(t), V(t), I_f(t), P(t), W(t), I_m(t)) \to \tilde{\mathcal{E}}_0$, as $t \to \infty$ for $\tilde{\mathcal{R}}_v < 1$. Hence, the DFE $\tilde{\mathcal{E}}_0$, of the model (13), is GAS in $\tilde{\mathcal{D}}$ if $\tilde{\mathcal{R}}_v < 1$. □

The above analyses clearly show that the backward bifurcation property of the model (3) can be removed if the associated disease-induced and cancer-induced mortality is set to zero. The epidemiological implication of Theorem 3.5 is that for this special case (of the model (3) with $\delta = 0$), the vaccine-targeted HPV types and associated dysplasia will be eliminated from the community if the combined use of (cohort) vaccination and Pap screening can make $\tilde{\mathcal{R}}_v < 1$ (i.e., $\tilde{\mathcal{R}}_v < 1$ is necessary and sufficient for the elimination of the relevant HPV types). Figure 3 depicts solution profiles of the model (3) with $\delta = 0$, for various initial conditions, showing convergence to the DFE ($\tilde{\mathcal{E}}_0$) for $\tilde{\mathcal{R}}_v < 1$ (in line with Theorem 3.5).

The following result can be shown using the approach in Section 3.3.

Theorem 3.6. *The reduced model (13) has an EEP of the form*

$$\mathcal{E}_1 := (\tilde{S}_f^{**}, \tilde{V}^{**}, \tilde{I}_f^{**}, \tilde{P}^{**}, \tilde{W}^{**}, \tilde{S}_m^{**}, \tilde{I}_m^{**}, \tilde{R}_m^{**}),$$

whenever $\tilde{\mathcal{R}}_v > 1$, where

$$\tilde{S}_f^{**} = S_f^{**}|_{\delta=0},\ \tilde{V}^{**} = V^{**}|_{\delta=0},\ \tilde{I}_f^{**} = I_f^{**}|_{\delta=0},\ \tilde{P}^{**} = P^{**}|_{\delta=0},$$

$$\tilde{S}_m^{**} = S_m^{**}|_{\delta=0},\ \tilde{I}_m^{**} = I_m^{**}|_{\delta=0},\ \tilde{R}_m^{**} = R_m^{**}|_{\delta=0},$$

and,

$$\tilde{W}^{**} = \frac{(\kappa_p + \psi_0)\tilde{P}^{**} + \sigma_f r_1 \tilde{I}_f^{**}}{\mu_f}.$$

3.4.2. *Global stability of EEP.* In this section, the global stability of the EEP of the reduced model (13) is established. Define:

$$\mathcal{D}_0 = \{(S_f, V, I_f, P, W, S_m, I_m, R_m) \in \tilde{\mathcal{D}} : I_f = P = W = I_m = R_m = 0\}.$$

Theorem 3.7. *The EEP, $\tilde{\mathcal{E}}_1$, of the reduced model (13), is GAS in $\tilde{\mathcal{D}} \setminus \mathcal{D}_0$ whenever $\tilde{\mathcal{R}}_v > 1$.*

Proof. Let $\tilde{\mathcal{R}}_v > 1$, so that the unique EEP of the model (13), $\tilde{\mathcal{E}}_1$, exists (Theorem 3.6). Here, too, the variable W of the model (13) is not included in the analysis.

Consider the non-linear Lyapunov function

$$\mathcal{F} = S_f - \tilde{S}_f^{**} - \tilde{S}_f^{**} \ln \frac{S_f}{\tilde{S}_f^{**}} + V - \tilde{V}^{**} - \tilde{V}^{**} \ln \frac{V}{\tilde{V}^{**}} + I_f - \tilde{I}_f^{**} - \tilde{I}_f^{**} \ln \frac{I_f}{\tilde{I}_f^{**}}$$
$$+ \frac{\beta_0 \tilde{I}_m^{**} \left[\tilde{S}_f^{**} + (1-\epsilon_v)\tilde{V}^{**}\right]}{\beta_1 \tilde{I}_f^{**} + \beta_2 \tilde{P}^{**}} \left[\frac{\beta_2 \tilde{P}^{**}}{\sigma_f (1-r_1) \tilde{I}_f^{**}} \left(P - \tilde{P}^{**} - \tilde{P}^{**} \ln \frac{P}{\tilde{P}^{**}} \right) \right.$$
$$\left. + \frac{1}{\tilde{S}_m^{**}} \left(S_m - \tilde{S}_m^{**} - \tilde{S}_m^{**} \ln \frac{S_m}{\tilde{S}_m^{**}} + I_m - \tilde{I}_m^{**} - \tilde{I}_m^{**} \ln \frac{I_m}{\tilde{I}_m^{**}} \right) \right],$$

with Lyapunov derivative

$$\mathcal{F}' = \left(1 - \frac{\tilde{S}_f^{**}}{S_f}\right) S_f' + \left(1 - \frac{\tilde{V}^{**}}{V}\right) V' + \left(1 - \frac{\tilde{I}_f^{**}}{I_f}\right) I_f'$$

$$
\begin{aligned}
&+\frac{\beta_0\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]}{\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}}\left\{\frac{\beta_2\tilde{P}^{**}}{\sigma_f(1-r_1)\tilde{I}_f^{**}}\left(1-\frac{\tilde{P}^{**}}{P}\right)P'\right.\\
&\left.+\frac{1}{\tilde{S}_m^{**}}\left[\left(1-\frac{\tilde{S}_m^{**}}{S_m}\right)S_m'+\left(1-\frac{\tilde{I}_m^{**}}{I_m}\right)I_m'\right]\right\}\\
&=\left(1-\frac{\tilde{S}_f^{**}}{S_f}\right)\left[\pi_f(1-\phi)-\beta_0 I_m S_f-\mu_f S_f\right]\\
&+\left(1-\frac{\tilde{V}^{**}}{V}\right)\left[\pi_f\phi-(1-\epsilon_v)\beta_0 I_m V-\mu_f V\right]\\
&+\left(1-\frac{\tilde{I}_f^{**}}{I_f}\right)\left\{\beta_0 I_m[S_f+(1-\epsilon_v)V]-\tilde{g}_1 I_f\right\}\\
&+\frac{\beta_0\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]}{\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}}\left\{\frac{\beta_2\tilde{P}^{**}}{\sigma_f(1-r_1)\tilde{I}_f^{**}}\left(1-\frac{\tilde{P}^{**}}{P}\right)[\sigma_f(1-r_1)I_f-g_2P]\right.\\
&+\frac{1}{\tilde{S}_m^{**}}\left\{\left(1-\frac{\tilde{S}_m^{**}}{S_m}\right)[\pi_m-(\beta_1 I_f+\beta_2 P)S_m-\mu_m S_m]\right.\\
&\left.\left.+\left(1-\frac{\tilde{I}_m^{**}}{I_m}\right)[(\beta_1 I_f+\beta_2 P)S_m-g_{11}I_m]\right\}\right\}.
\end{aligned}
$$

The above can be simplified using the following endemic equilibrium conditions

$$\pi_f(1-\phi)=\beta_0\tilde{I}_m^{**}\tilde{S}_f^{**}+\mu_f\tilde{S}_f^{**},\ \pi_f\phi=(1-\epsilon_v)\beta_0\tilde{I}_m^{**}\tilde{V}^{**}+\mu_f\tilde{V}^{**},$$

$$\tilde{g}_1\tilde{I}_f^{**}=\beta_0\tilde{I}_m^{**}[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}],\ g_2\tilde{P}^{**}=\sigma_f(1-r_1)\tilde{I}_f^{**},$$

$$\pi_m=(\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**})\tilde{S}_m^{**}+\mu_m\tilde{S}_m^{**},\ g_{11}\tilde{I}_m^{**}=(\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**})\tilde{S}_m^{**}.$$

This gives:

$$
\begin{aligned}
\mathcal{F}'=&\left(1-\frac{\tilde{S}_f^{**}}{S_f}\right)\left[\beta_0\tilde{I}_m^{**}\tilde{S}_f^{**}+\mu_f\tilde{S}_f^{**}-\beta_0 I_m S_f-\mu_f S_f\right]\\
&+\left(1-\frac{\tilde{V}^{**}}{V}\right)\left[(1-\epsilon_v)\beta_0\tilde{I}_m^{**}\tilde{V}^{**}+\mu_f\tilde{V}^{**}-(1-\epsilon_v)\beta_0 I_m V-\mu_f V\right]\\
&+\left(1-\frac{\tilde{I}_f^{**}}{I_f}\right)\left\{\beta_0 I_m\left[S_f+(1-\epsilon_v)V\right]-\beta_0\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]\frac{I_f}{\tilde{I}_f^{**}}\right\}\\
&+\frac{\beta_0\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]}{\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}}\\
&\left\{\frac{\beta_2\tilde{P}^{**}}{\sigma_f(1-r_1)\tilde{I}_f^{**}}\left(1-\frac{\tilde{P}^{**}}{P}\right)\left[\sigma_f(1-r_1)I_f-\sigma_f(1-r_1)\frac{\tilde{I}_f^{**}}{\tilde{P}^{**}}\right]\right.\\
&\left.+\frac{1}{\tilde{S}_m^{**}}\left\{\left(1-\frac{\tilde{S}_m^{**}}{S_m}\right)\left[\left(\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}\right)\tilde{S}_m^{**}+\mu_m\tilde{S}_m^{**}\right.\right.\right.
\end{aligned}
$$

$$
\begin{aligned}
&-(\beta_1 I_f+\beta_2 P)S_m-\mu_m S_m \quad \Big] \\
&+\left(1-\frac{\tilde{I}_m^{**}}{I_m}\right)\left[(\beta_1 I_f+\beta_2 P)S_m-\left(\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}\right)\tilde{S}_m^{**}\frac{I_m}{\tilde{I}_m^{**}}\right]\Bigg\}\Bigg\} \\
&=\mu_f\left(2-\frac{\tilde{S}_f^{**}}{S_f}-\frac{S_f}{\tilde{S}_f^{**}}\right)+\beta_0\left[\tilde{I}_m^{**}\tilde{S}_f^{**}-I_m S_f-\tilde{I}_m^{**}\frac{(\tilde{S}_f^{**})^2}{S_f}+I_m\tilde{S}_f^{**}\right] \\
&+(1-\epsilon_v)\mu_f\left(2-\frac{\tilde{V}^{**}}{V}-\frac{V}{\tilde{V}^{**}}\right) \\
&+(1-\epsilon_v)\beta_0\left[\tilde{I}_m^{**}\tilde{V}^{**}-I_m V-\tilde{I}_m^{**}\frac{(\tilde{V}^{**})^2}{V}+I_m\tilde{V}^{**}\right] \\
&+\beta_0\Bigg\{I_m[S_f+(1-\epsilon_v)V]-\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]\frac{I_f}{\tilde{I}_f^{**}} \\
&-I_m[S_f+(1-\epsilon_v)V]\frac{\tilde{I}_f^{**}}{I_f}+\tilde{I}_f^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]\Bigg\} \\
&+\frac{\beta_0\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]}{\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}}\Bigg\{\frac{\beta_2\tilde{P}^{**}}{\tilde{I}_f^{**}}\left(I_f-\tilde{I}_f^{**}\frac{P}{\tilde{P}^{**}}-I_f\frac{\tilde{P}^{**}}{P}+\tilde{I}_f^{**}\right) \\
&+\frac{1}{\tilde{S}_m^{**}}\Bigg[\left(\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}\right)\tilde{S}_m^{**}-(\beta_1 I_f+\beta_2 P)S_m \\
&-\left(\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}\right)\frac{(\tilde{S}_m^{**})^2}{S_m}+(\beta_1 I_f+\beta_2 P)\tilde{S}_m^{**} \\
&+(\beta_1 I_f+\beta_2 P)S_m-\left(\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}\right)\tilde{S}_m^{**}\frac{I_m}{\tilde{I}_m^{**}} \\
&-(\beta_1 I_f+\beta_2 P)S_m\frac{\tilde{I}_m^{**}}{I_m}+\left(\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}\right)\tilde{S}_m^{**}\Bigg]\Bigg\}.
\end{aligned}
\tag{15}
$$

It follows, using Proposition 1 (Appendix B) in (15), that

$$
\begin{aligned}
\mathcal{F}' \leq\ &\mu_f\left(2-\frac{\tilde{S}_f^{**}}{S_f}-\frac{S_f}{\tilde{S}_f^{**}}\right)+\beta_0\Bigg\{\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right] \\
&-\tilde{I}_m^{**}\frac{\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]^2}{[S_f+(1-\epsilon_v)V]}+I_m\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]\Bigg\} \\
&+(1-\epsilon_v)\mu_f\left(2-\frac{\tilde{V}^{**}}{V}-\frac{V}{\tilde{V}^{**}}\right)+\beta_0\Bigg\{-\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]\frac{I_f}{\tilde{I}_f^{**}} \\
&-I_m[S_f+(1-\epsilon_v)V]\frac{\tilde{I}_f^{**}}{I_f}+\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]\Bigg\} \\
&+\frac{\beta_0\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]}{\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}}\left\{\frac{\beta_2\tilde{P}^{**}}{\tilde{I}_f^{**}}\left(I_f-\tilde{I}_f^{**}\frac{P}{\tilde{P}^{**}}-I_f\frac{\tilde{P}^{**}}{P}+\tilde{I}_f^{**}\right)\right.
\end{aligned}
$$

$$
\begin{aligned}
&+\frac{1}{\tilde{S}_m^{**}}\left[\left(\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}\right)\tilde{S}_m^{**}-\left(\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}\right)\frac{(\tilde{S}_m^{**})^2}{S_m}+(\beta_1 I_f+\beta_2 P)\tilde{S}_m^{**}\right.\\
&\left.-\left(\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}\right)\tilde{S}_m^{**}\frac{I_m}{\tilde{I}_m^{**}}-(\beta_1 I_f+\beta_2 P)S_m\frac{\tilde{I}_m^{**}}{I_m}+\left(\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}\right)\tilde{S}_m^{**}\right]\Bigg\}\\
&=\mu_f\left(2-\frac{\tilde{S}_f^{**}}{S_f}-\frac{S_f}{\tilde{S}_f^{**}}\right)+(1-\epsilon_v)\mu_f\left(2-\frac{\tilde{V}^{**}}{V}-\frac{V}{\tilde{V}^{**}}\right)\\
&+\beta_0\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]\\
&\left\{\left\{2-\frac{\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}}{S_f+(1-\epsilon_v)V}+\frac{I_m}{\tilde{I}_m^{**}}-\frac{I_f}{\tilde{I}_f^{**}}-\frac{I_m[S_f+(1-\epsilon_v)V]\tilde{I}_f^{**}}{\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]I_f}\right\}\right.\\
&+\frac{1}{\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}}\left[\beta_2 P^{**}\left(3+\frac{I_f}{\tilde{I}_f^{**}}-\frac{I_f\tilde{P}^{**}}{\tilde{I}_f^{**}P}-\frac{\tilde{S}_m^{**}}{S_m}-\frac{I_m}{\tilde{I}_m^{**}}-\frac{PS_m\tilde{I}_m^{**}}{\tilde{P}^{**}\tilde{S}_m^{**}I_m}\right)\right.\\
&\left.\left.+\beta_1\tilde{I}_f^{**}\left(2-\frac{\tilde{S}_m^{**}}{S_m}+\frac{I_f}{\tilde{I}_f^{**}}-\frac{I_m}{\tilde{I}_m^{**}}-\frac{I_fS_m\tilde{I}_m^{**}}{\tilde{I}_f^{**}\tilde{S}_m^{**}I_m}\right)\right]\right\}\\
&=\mu_f\left(2-\frac{\tilde{S}_f^{**}}{S_f}-\frac{S_f}{\tilde{S}_f^{**}}\right)+(1-\epsilon_v)\mu_f\left(2-\frac{\tilde{V}^{**}}{V}-\frac{V}{\tilde{V}^{**}}\right)\\
&+\frac{\beta_0\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]}{\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}}\\
&\left\{\beta_1\tilde{I}_f^{**}\left\{2-\frac{\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}}{S_f+(1-\epsilon_v)V}-\frac{I_m[S_f+(1-\epsilon_v)V]\tilde{I}_f^{**}}{\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]I_f}\right\}\right.\\
&+\beta_2\tilde{P}^{**}\left\{2-\frac{\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}}{S_f+(1-\epsilon_v)V}-\frac{I_m[S_f+(1-\epsilon_v)V]\tilde{I}_f^{**}}{\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]I_f}\right\}\\
&\left.+\beta_1\tilde{I}_f^{**}\left(2-\frac{\tilde{S}_m^{**}}{S_m}-\frac{I_fS_m\tilde{I}_m^{**}}{\tilde{I}_f^{**}\tilde{S}_m^{**}I_m}\right)+\beta_2\tilde{P}^{**}\left(3-\frac{I_f\tilde{P}^{**}}{\tilde{I}_f^{**}P}-\frac{\tilde{S}_m^{**}}{S_m}-\frac{PS_m\tilde{I}_m^{**}}{\tilde{P}^{**}\tilde{S}_m^{**}I_m}\right)\right\}\\
&=\mu_f\left(2-\frac{\tilde{S}_f^{**}}{S_f}-\frac{S_f}{\tilde{S}_f^{**}}\right)+(1-\epsilon_v)\mu_f\left(2-\frac{\tilde{V}^{**}}{V}-\frac{V}{\tilde{V}^{**}}\right)\\
&+\frac{\beta_0\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]}{\beta_1\tilde{I}_f^{**}+\beta_2\tilde{P}^{**}}\left\{\beta_1\tilde{I}_f^{**}\left\{4-\frac{\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}}{S_f+(1-\epsilon_v)V}-\frac{\tilde{S}_m^{**}}{S_m}\right.\right.\\
&\left.-\frac{I_m[S_f+(1-\epsilon_v)V]\tilde{I}_f^{**}}{\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]I_f}-\frac{I_fS_m\tilde{I}_m^{**}}{\tilde{I}_f^{**}\tilde{S}_m^{**}I_m}\right\}\\
&+\beta_2\tilde{P}^{**}\left\{5-\frac{\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}}{S_f+(1-\epsilon_v)V}-\frac{\tilde{S}_m^{**}}{S_m}-\frac{I_f\tilde{P}^{**}}{\tilde{I}_f^{**}P}\right.
\end{aligned}
$$

$$-\frac{I_m[S_f+(1-\epsilon_v)V]\tilde{I}_f^{**}}{\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]I_f}-\frac{PS_m\tilde{I}_m^{**}}{\tilde{P}^{**}\tilde{S}_m^{**}I_m}\Bigg\}\Bigg\}.$$

Since the arithmetic mean exceeds the geometric mean, the following inequalities hold:

$$\begin{aligned}
&2-\frac{\tilde{S}_f^{**}}{S_f}-\frac{S_f}{\tilde{S}_f^{**}}\leq 0,\ 2-\frac{\tilde{V}^{**}}{V}-\frac{V}{\tilde{V}^{**}}\leq 0,\\
&4-\frac{\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}}{S_f+(1-\epsilon_v)V}-\frac{\tilde{S}_m^{**}}{S_m}-\frac{I_m[S_f+(1-\epsilon_v)V]\tilde{I}_f^{**}}{\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]I_f}-\frac{I_fS_m\tilde{I}_m^{**}}{\tilde{I}_f^{**}\tilde{S}_m^{**}I_m}\leq 0,\\
&5-\frac{\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}}{S_f+(1-\epsilon_v)V}-\frac{\tilde{S}_m^{**}}{S_m}-\frac{I_f\tilde{P}^{**}}{\tilde{I}_f^{**}P}-\frac{I_m[S_f+(1-\epsilon_v)V]\tilde{I}_f^{**}}{\tilde{I}_m^{**}\left[\tilde{S}_f^{**}+(1-\epsilon_v)\tilde{V}^{**}\right]I_f}\\
&-\frac{PS_m\tilde{I}_m^{**}}{\tilde{P}^{**}\tilde{S}_m^{**}I_m}\leq 0.
\end{aligned}\tag{16}$$

Hence $\mathcal{F}'\leq 0$, with equality if and only if equality holds in each of the inequalities in (16). Thus, $(S_f,V,I_f,P,S_m,I_m)\to(\tilde{S}_f^{**},\tilde{V}^{**},\tilde{I}_f^{**},\tilde{P}^{**},\tilde{S}_m^{**},\tilde{I}_m^{**})$. Substituting these (endemic equilibrium) values in the equation for W in (13) shows that $W\to\tilde{W}^{**}$ as $t\to\infty$. Hence, $(S_f,V,I_f,P,W,S_m,I_m)\to(\tilde{S}_f^{**},\tilde{V}^{**},\tilde{I}_f^{**},\tilde{P}^{**},\tilde{W}^{**},\tilde{S}_m^{**},\tilde{I}_m^{**})$, so that the EEP $(\tilde{E}_1)$ of (13) is GAS in $\tilde{\mathcal{D}}\setminus\mathcal{D}_0$. □

4. **Assessment of vaccine and screening impact.** In this section, the community-wide impact of mass vaccination and Pap cytology screening will be assessed using the model (3) with $\delta=0$ (or, equivalently, (13)).

4.1. **Vaccine impact.** Let $x=V^*/N_f^*$ represents the fraction of females vaccinated at the disease-free steady state. It follows from (14) that

$$\tilde{\mathcal{R}}_v=\mathcal{R}_0\sqrt{1-\epsilon_v x},\tag{17}$$

where,

$$\mathcal{R}_0=\tilde{\mathcal{R}}_v|_{\phi=0}=\sqrt{\frac{\beta_m\beta_f c_f^2\pi_f\mu_m}{\pi_m\mu_f\tilde{g}_1 g_{11}}\left[1+\frac{\theta\sigma_f(1-r_1)}{g_2}\right]}.\tag{18}$$

is the basic reproduction number (the average number of new HPV cases generated by a typical infected individual in a completely susceptible population) associated with the model (3).

Considering $\tilde{\mathcal{R}}_v$ as a function of x (i.e., $\tilde{\mathcal{R}}_v=\tilde{\mathcal{R}}_v(x)$), it can be shown that

$$\frac{\partial\tilde{\mathcal{R}}_v}{\partial x}=-\frac{\mathcal{R}_0\epsilon_v}{2\sqrt{1-\epsilon_v x}}.$$

Since $0<\epsilon_v<1$, it follows that $\frac{\partial\tilde{\mathcal{R}}_v}{\partial x}<0$ for $0\leq x<1$. Thus, $\tilde{\mathcal{R}}_v$ is a decreasing function of x. Since, in general, a reduction in the reproduction number signifies a reduction in disease burden (measured in terms of number of infections, HPV-related morbidity, hospitalization, mortality etc.), the above analysis shows that an imperfect HPV vaccine will have a positive impact (in reducing HPV burden) for any $x>0$ and $\epsilon_v>0$ (that is, for a given vaccine efficacy, $\epsilon_v>0$, vaccinating any fraction of susceptible females at steady-state will result in a decrease in HPV burden).

Furthermore, there is a unique x_c such that $\tilde{\mathcal{R}}_v(x) = 1$, given by

$$x_c = \frac{1}{\epsilon_v}\left(1 - \frac{1}{\mathcal{R}_0}\right).$$

Lemma 4.1. *The DFE of the reduced model (13), $\tilde{\mathcal{E}}_0$, is GAS in $\tilde{\mathcal{D}}$ if $x > x_c$.*

Proof. Since $\tilde{\mathcal{R}}_v$ is a decreasing function of x, it follows that $\tilde{\mathcal{R}}_v < 1$ whenever $x > x_c$. Thus, it follows from Theorem 3.5 that the DFE of the model (13) is GAS in $\tilde{\mathcal{D}}$ in this case (with $x > x_c$). □

The above result implies that if the fraction of vaccinated susceptible females exceeds the threshold level x_c, then the DFE of the model (3) with $\delta = 0$ is GAS (and the vaccine-targeted types will be eliminated from the community). A contour plot of $\tilde{\mathcal{R}}_v$ as a function of vaccine efficacy and coverage rate, depicted in Figure 4, shows that with the assumed vaccine efficacy of 90%, the relevant HPV types can be eliminated from the community if at least 88% of the susceptible females are vaccinated at steady-state (it should be recalled from Theorem 3.5 that the disease dies out when $\tilde{\mathcal{R}}_v < 1$).

It should be noted that the above analyses also hold for the case where only (cohort) vaccination is used (i.e., for the case where Pap screening is not also used in the community). In other words, the singular use of a vaccination program can lead to the elimination of the relevant (vaccine-targeted) HPV types from the community if the vaccine efficacy and coverage rate are high enough. Figure 5 shows that the prevalence of the vaccine-targeted HPV types can be reduced by about 97.14% in 50 years.

4.2. **Screening impact.** To assess the singular impact of Pap cytology screening, the model (3) is simulated in the absence of vaccination ($\phi = 0$) and no disease-induced and cancer-induced mortality ($\delta = 0$). Thus, this case models the situation where Pap cytology screening is the only intervention strategy adopted. Figure 6 depicts the cumulative number of females detected with cervical cancer or CIN (in the absence of vaccination) using various screening intervals (1, 2, and 3 years). It is evident from Figure 6 that the use of annual screening results in the detection of about 534 cases of females with cancer or CIN over 10 years. Furthermore, this figure shows that extending the screening interval from 2 to 3 years has marginal impact on the cumulative number of cases detected (while 2-year screening detects about 320 cases over 10 years, 3-year screening leads to the detection of about 228 cases over the same time period).

4.3. **Combined impact of vaccination and screening.** The combined impact of Pap screening and mass vaccination is assessed by simulating the model (3) using the parameter values in Table 2 with $\delta = 0$. It is shown that, unlike in the case of the vaccine-only control strategy (which reduces the prevalence of the vaccine-targeted HPV types and dysplasia by 97.14% in 50 years) (Figure 5), the combined vaccination-screening strategy (with 2-year or 3-year screening interval) achieved the same reduction in about 35 years (Figure 7). It is worth noting from Figure 7 that the 2-year and 3-year screening strategies resulted in essentially the same reduction (over the same time period).

4.4. **Model sensitivity to the proportion screened.** As noted, a wide range of values of the proportion screened (χ) are cited in the literature (7% to 44%). Therefore the sensitivity of the model to this parameter is analyzed in this section. Under the base-case Pap test assumptions (with $\chi = 32\%$), the model predicts a total of 534, 320 and 228 cases in 10 years with the annual, 2-year and 3-year screening (Figure 6). Low proportion (7%) screened results in 157, 82 and 56 cases, respectively (Figure 6 top inset) and the high proportion (44%) screened results in 650, 410 and 298 cases detected, respectively (Figure 6 bottom inset). Whereas χ is an influential parameter in determining the number of detected cumulative cervical cancer and CIN cases, a comparison of the cumulative number of cases under annual and the 2-year screening respectively, relative to the 3-year screening reveals that the model is not much sensitive to the proportion screened; while the base-case value of the proportion screened (χ) results in the detection of 2.4 and 1.4 times more cases respectively relative to the 3-year screening, low proportion screened results in the detection of 2.8 and 1.5 times more cases with annual and 2-year screening respectively and the high proportion screened results in the detection of 2.2 and 1.4 times more cases. The comparison also signifies that (i) 3-year (rather than 2-year) screening is reasonable, and (ii) with low proportions screened, a higher screening frequency is more desirable.

Comparing the reduction in the prevalence of HPV infection and associated dysplasia leads to similar conclusions. The base-case value of the proportion screened results in 97.14% reduction in 35 years (Figure 7). The same reduction takes 41 years with a low proportion screened (Figure 7 top inset) and 33 years with a high proportion screened (Figure 7 bottom inset). As under the base-case scenario, the annual, 2-year and 3-year screening with low or high proportions screened makes no significant difference in providing the same amount of reduction in prevalence (hence the solid, dashed and dotted lines are indistinguishable in the inset figures).

Conclusions. A two-sex deterministic model is designed and used to study the transmission dynamics of HPV in the presence of Pap cytology screening and mass vaccination against some vaccine-targeted HPV types. The main theoretical results shown are summarized below:

(i) The model exhibits the phenomenon of backward bifurcation where the stable disease-free equilibrium coexists with two endemic equilibria (one of which is suggested to be stable, by numerical simulations) when the associated reproduction number ($\mathcal{R}_v$) is less than unity. The epidemiological implication of this result is that having the reproduction number less than unity, while necessary, is no longer sufficient for eliminating the HPV-infection and associated dysplasia from the community;

(ii) The backward bifurcation phenomenon of the model is caused by any of the following mechanisms:
   (a) imperfect nature of the vaccine in preventing infection ($0 < \epsilon_v < 1$)
   (b) HPV- and cancer-induced mortality in the female population ($\delta_f > 0$, $\delta^c > 0$ or $\delta_d^c > 0$);

(iii) For the case when the HPV-induced and cancer-induced mortality is negligible ($\delta = 0$), it is shown that the disease-free (HPV-infection- and dysplasia-free) equilibrium of the model is globally-asymptotically stable when the associated reproduction number ($\tilde{\mathcal{R}}_v$) is less than unity;

(iv) The model has a unique endemic equilibrium when the reproduction number ($\mathcal{R}_v$) exceeds unity. This equilibrium is shown to be globally-asymptotically stable for the special case when the HPV-induced and cancer-induced mortality is negligible.

Numerical simulations of the model suggest the following:

(v) Pap screening every three years is reasonable. This result is consistent with the empirical findings [45, 46];

(vi) The use of mass vaccination alone (with a vaccine efficacy of 90%) can lead to the elimination of the vaccine-targeted HPV types and associated dysplasia from the community if at least 88% of the susceptible female population is vaccinated at steady-state;

(vii) Mass vaccination alone (without Pap screening) could result in 97.14% reduction in the prevalence of the vaccine-targeted HPV types and the associated dysplasia in about 50 years;

(viii) If Pap screening (2-year or 3-year) is implemented in addition to mass vaccination, the time required to achieve the same amount of reduction in the prevalence of HPV infection and the associated dysplasia is reduced to about 35 years.

Acknowledgments. One of the authors (A.B.G.) acknowledges, with thanks, the support in part of the Natural Science and Engineering Research Council (NSERC) and Mathematics of Information Technology and Complex Systems (MITACS) of Canada.

REFERENCES

[1] M. Llamazares and R. J. Smith, *Evaluating human papillomavirus vaccination programs in Canada: Should provincial healthcare pay for voluntary adult vaccination?*, BMC Public Health, **8** (2008), 1–12.

[2] M. Al-arydah and R. J. Smith, *An age-structured model of human papillomavirus vaccination*, Mathematics and Computers in Simulation, **82** (2011), 629–652.

[3] F. Brauer, *Backward bifurcations in simple vaccination models*, J. Math. Anal. Appl., **298** (2004), 418–431.

[4] M. Brisson, N. Van de Velde and M. C. Boily, *Different population-level vaccination effectiveness for HPV types 16, 18, 6 and 11*, Sex. Transm. Infect., **87** (2011), 41–43.

[5] V. Brown and K. A. J. White, *The HPV vaccination strategy: Could male vaccination have a significant impact?*, Comput. Math. Methods. Med., **11** (2010), 223–237.

[6] Canadian Cancer Society's Steering Committee, "Cancer Statistics 2009," (2009). Available from: `http://www.cancer.ca`.

[7] J. Carr, "Applications of Centre Manifold Theory," Springer-Verlag, New York, 1981.

[8] C. Castillo-Chavez and B. Song, *Dynamical models of tuberculosis and their applications*, Math. Biosci. Engrg., **1** (2004), 361–404.

[9] B. Crawford and C. M. Kribs Zaleta, *The impact of vaccination and coinfection on HPV and cervical cancer*, Discrete Contin. Dyn. Syst. Ser. B., **12** (2009), 279–304.

[10] L. A. Denny and J. T. C. Wright, *Human papillomavirus testing and screening*, Best Practice & Research Clinical Obstetrics and Gynaecology, **19** (2005), 501–515.

[11] O. Diekmann, J. A. P. Heesterbeek and J. A. J. Metz, *On the definition and computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations*, J. Math. Biol., **28** (1990), 365–382.

[12] J. Dushoff, H. Wenzhang and C. Castillo-Chavez, *Backward bifurcations and catastrophe in simple models of fatal diseases*, J. Math. Biol., **36** (1998), 227–248.

[13] E. H. Elbasha and A. P. Galvani, *Vaccination against multiple HPV types*, Math. Biosci., **197** (2005), 88–117.

[14] E. H. Elbasha and A. B. Gumel, *Theoretical assesment of public health impact of imperfect prophylactic HIV-1 vaccines with therapeutic benefits*, Bull. Math. Biol., **68** (2006), 577–614.

[15] E. H. Elbasha, E. J.Dasbach and R. P. Insinga, *Model for assessing human papillomavirus vaccination strategies*, Emerg. Infect. Dis., **13** (2007), 28–41.

[16] E. H. Elbasha, *Global stability of equilibria in a two-sex HPV vaccination model*, Bull. Math. Biol., **70** (2008), 894–909.

[17] E. H. Elbasha, E. J. Dasbach and R. P. Insinga, *A multi-type HPV transmission model*, Bull. Math. Biol., **70** (2008), 2126–2176.

[18] J. Ferlay, H. R. Shin, F. Bray, D. Forman, C. Mathers and D. M. Parkin, *Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008*, Int. J. Cancer., **127** (2010), 2893–2917.

[19] E. L. Franco, S. M. Mahmud, J. Tota, A. Ferenczy and F. Coutle, *The expected impact of HPV vaccination on the accuracy of cervical cancer screening: The need for a paradigm change*, Arch. Med. Res., **40** (2009), 478–485.

[20] E. L. Franco, E. Duarte-Franco and A. Ferenczy, *Cervical cancer: Epidemiology, prevention and the role of human papillomavirus infection*, CMAJ., **164** (2001), 1017–1025.

[21] S. M. Garba, A. B. Gumel and M. R. Abu Bakar, *Backward bifurcations in dengue transmission dynamics*, Math. Biosci., **215** (2008), 11–25.

[22] The GlaxoSmithKline Vaccine HPV-007 Study Group, *Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/17 ASO4-adjuvanted vaccine: Analysis of a randomised placebo-controlled trial up to 6.4 years*, Lancet., **374** (2009), 1975–1985.

[23] S. J. Goldie et al., *Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine*, Journal of the National Cancer Institute, **96** (2004), 604–615.

[24] O. P. Günther et al., *Protecting the next generation: What is the role of the duration of Human Papillomavirus vaccine-related immunity?*, J. Infect. Dis., **197** (2008), 1653–1661.

[25] B. T. Hansen et al., *Factors associated with non-attendance, opportunistic attendance and reminded attendance to cervical screening in an organized screening program: A cross-sectional study of 12,058 Norwegian women*, BMC Public Health, **11** (2011), 1–13.

[26] Health Canada, "Cervical Cancer Screening Activities in Canada," (2012). Available from: `http://www.phac-aspc.gc.ca`.

[27] H. W. Hethcote, *The mathematics of infectious diseases*, SIAM Rev., **42** (2000), 599–653.

[28] J. Hughes, G. Garnett and L. Koutsky, *The theoretical population level impact of a prophylactic human papillomavirus vaccine*, Epidemiology, **13** (2002), 631–639.

[29] "International Agency for Research on Cancer" Working Group. *Human papillomaviruses*, IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans, (1995). Lyon, France.

[30] O. Klungsøyr, M. Nygård, G. Skare, T. Eriksen and J. F Nygård, *Validity of self-reported Pap smear history in Norwegian women*, J. Med. Screen, **16** (2009), 91–97.

[31] L. Koutsky, *Epidemiology of genital human papillomavirus infection*, American Journal of Medicine, **102** (1997), 3–8.

[32] C. Kribs-Zaleta and J. Velasco-Hernandez, *A simple vaccination model with multiple endemic states*, Math Biosci., **164** (2000), 183–201.

[33] V. Lakshmikantham, S. Leela and A. A. Martynyuk, "Stability Analysis of Nonlinear Systems," Marcel Dekker, Inc., New York and Basel, 1989.

[34] J. P. LaSalle, "The Stability of Dynamical Systems," Regional Conference Series in Applied Mathematics, SIAM, Philadelphia, 1976.

[35] D. C. McCrory and D. B. Matchar, *Evaluation of Cervical Cytology. Evidence Report/Technology Assessment No. 5;*, AHCPR Pub; No 99-E 010 1999.

[36] Z. Mukandavire, A. B. Gumel, W. Garira and J. M. Tchuenche, *Mathematical analysis of a model for HIV-malaria co-infection*, Math. Biosci. Engrg., **6** (2009), 333–362.

[37] N. Munoz, F. X. Bosch, S. de Sanjose et al., *Epidemiologic classification of human papillomavirus types associated with cervical cancer*, N. Engl. J. Med., **348** (2003), 518–527.

[38] N. Munoz et al., *Against which human papillomavirus types shall we vaccinate and screen? The international perspective*, International Journal of Cancer, **111** (2004), 278–285.

[39] E. R. Myers et al., *Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis*, Am. J. Epidemiol., **151** (2000), 1158–1171.

[40] S. L. Kulasingam and E. R. Myers, *Potential health and economic impact of adding a human papillomavirus vaccine to screening programs*, JAMA., **290** (2003), 781–789.

[41] J. M. Palefsky, *Human papillomavirus-related disease in men: Not just a women's issue*, Journal of Adolescent Health, **46** (2010), S12–S19.

[42] C. N. Podder and A. B. Gumel, *Transmission dynamics of a two-sex model for Herpes Simplex Virus type 2*, Can. Appl. Math. Quarterly, **17** (2009), 339–386.

[43] Public Health Agency of Canada, "Cervical Cancer Screening in Canada," (2013). Available from: http://www.phac-aspc.gc.ca/publicat/ccsic-dccuac/pdf/chap_3_e.pdf.

[44] Public Health Agency of Canada, "Human Papillomavirus. HPV Purple Paper (bds)," (2010). Available from: http://www.phac-aspc.gc.ca.

[45] P. Sasieni and A. Castanon, *Call and recall cervical screening programme: Screening interval and age limits*, Curr. Diagn. Pathol., **12** (2006), 114–126.

[46] D. Saslow et al., *American cancer society, American society for colposcopy and cervical pathology, and American society for clinical pathology screening guidelines for the prevention and early detection of cervical cancer*, Am. J. Clin. Pathol., **137** (2012), 516–542.

[47] M. Schiffman and P. E. Castle, *When to test women for human papillomavirus*, BMJ., **332** (2006), 61–62.

[48] O. Sharomi, C. N. Podder, A. B. Gumel, E. H. Elbasha and J. Watmough, *Role of incidence function in vaccine-induced backward bifurcation in some HIV models*, Math. Biosci., **210** (2007), 436–463.

[49] O. Sharomi, C. N. Podder, A. B. Gumel and B. Song, *Mathematical analysis of the transmission dynamics of HIV/TB co-infection in the presence of treatment*, Math. Biosci. Engrg., **5** (2008), 145–174.

[50] H. L. Smith and P. Waltman, "The Theory of the Chemostat," Cambridge University Press, 1995.

[51] P. van den Driessche and J. Watmough, *Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission*, Math. Biosci., **180** (2002), 29–48.

[52] N. Van de Velde, M. Brisson and M. C. Boily, *Modeling human papillomavirus vaccine effectiveness: Quantifying the impact of parameter uncertainty*, Am. J. Epidemiol., **165** (2007), 762–775.

[53] L. L. Villa et al., *High sustained efficacy of a prophylactic quadrivalent human Papillomavirus types 6/11/16/18 virus-like particle vaccine through 5 years of follow-up*, British Journal of Cancer, **95** (2006), 1459–1466.

[54] J. M. M. Walboomers, *Human papillomavirus is a necessary cause of invasive cervical cancer worldwide*, J. Pathol., **189** (1999), 12–19.

Received April 09, 2012; revised February 24, 2013.

E-mail address: tufail.malik@kustar.ac.ae
E-mail address: jody_reimer@hotmail.com
E-mail address: Abba.Gumel@ad.umanitoba.ca
E-mail address: elamin_elbasha@merck.com
E-mail address: smahmud@wrha.mb.ca

Appendix A: Proof of Theorem 3.4.

Proof. It is convenient to use the change of variables:

$$\begin{aligned} &S_f = x_1, V = x_2, I_f = x_3, P = x_4, Q_1 = x_5, Q_2 = x_6, Q_3 = x_7, Q_{1d} = x_8, Q_{2d} = x_9, \\ &Q_{3d} = x_{10}, C = x_{11}, C_d = x_{12}, R_c = x_{13}, R_f = x_{14}, S_m = x_{15}, I_m = x_{16}, R_m = x_{17}. \end{aligned} \tag{19}$$

Let $\hat{f} = [f_1, \cdots, f_{17}]$ denote the vector field of (3) in the notation (19), so that the model (3), with the conservation law (1), is re-written in the form:

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \pi_f(1-\phi) - \frac{\beta_m c_f}{x_{15}+x_{16}+x_{17}} x_{16} x_1 - \mu_f x_1, \\
\frac{dx_2}{dt} &= f_2 = \pi_f \phi - (1-\epsilon_v)\frac{\beta_m c_f}{x_{15}+x_{16}+x_{17}} x_{16} x_2 - \mu_f x_2, \\
\frac{dx_3}{dt} &= f_3 = \frac{\beta_m c_f}{x_{15}+x_{16}+x_{17}} x_{16}[x_1 + (1-\epsilon_v)x_2] - g_1 x_3, \\
\frac{dx_4}{dt} &= f_4 = \sigma_f(1-r_1)x_3 - g_2 x_4, \\
\frac{dx_5}{dt} &= f_5 = \kappa_p x_4 + \kappa_q x_6 - g_3 x_5, \\
\frac{dx_6}{dt} &= f_6 = \zeta_1 x_5 - g_4 x_6, \\
\frac{dx_7}{dt} &= f_7 = \zeta_2 x_6 - g_5 x_7, \\
\frac{dx_8}{dt} &= f_8 = \alpha_1 x_5 + \kappa_d x_9 - g_6 x_8, \\
\frac{dx_9}{dt} &= f_9 = \alpha_2 x_6 + \zeta_1 x_8 - g_7 x_9, \\
\frac{dx_{10}}{dt} &= f_{10} = \alpha_3 x_7 + \zeta_2 x_9 - g_8 x_{10}, \\
\frac{dx_{11}}{dt} &= f_{11} = \zeta_3 x_7 - g_9 x_{11}, \\
\frac{dx_{12}}{dt} &= f_{12} = \alpha_c x_{11} - g_{10} x_{12}, \\
\frac{dx_{13}}{dt} &= f_{13} = \gamma x_{12} - \mu_f x_{13}, \\
\frac{dx_{14}}{dt} &= f_{14} = \sigma_f r_1 x_3 + \psi_0 x_4 + \sum_{i=1}^{3} \psi_i x_{i+4} + \sum_{i=1}^{3} \rho_i x_{i+7} - \mu_f x_{14}, \\
\frac{dx_{15}}{dt} &= f_{15} = \pi_m - \frac{\beta_f c_f}{x_{15}+x_{16}+x_{17}}(x_3 + \theta x_4) x_{15} - \mu_m x_{15}, \\
\frac{dx_{16}}{dt} &= f_{16} = \frac{\beta_f c_f}{x_{15}+x_{16}+x_{17}}(x_3 + \theta x_4) x_{15} - g_{11} x_{16}, \\
\frac{dx_{17}}{dt} &= f_{17} = \sigma_m x_{16} - \mu_m x_{17}.
\end{aligned} \tag{20}$$

The Jacobian of the system (20), at the DFE $\mathcal{E}_0$, is given by

$$J(\mathcal{E}_0) = \begin{pmatrix}
-\mu_f & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -\mu_f & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & -g_1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \sigma_f(1-r_1) & -g_2 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \kappa_p & -g_3 & \kappa_q & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & \zeta_1 & -g_4 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & \zeta_2 & -g_5 & 0 & 0 \\
0 & 0 & 0 & 0 & \alpha_1 & 0 & 0 & -g_6 & \kappa_d \\
0 & 0 & 0 & 0 & 0 & \alpha_2 & 0 & \zeta_1 & -g_7 \\
0 & 0 & 0 & 0 & 0 & 0 & \alpha_3 & 0 & \zeta_2 \\
0 & 0 & 0 & 0 & 0 & 0 & \zeta_3 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \sigma_f r_1 & \psi_0 & \psi_1 & \psi_2 & \psi_3 & \rho_1 & \rho_2 \\
0 & 0 & -j_3 & -\theta j_3 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & j_3 & \theta j_3 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{pmatrix}$$

$$\begin{pmatrix}
0 & 0 & 0 & 0 & 0 & 0 & -j_1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & -j_2 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & j_1+j_2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-g_8 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -g_9 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & \alpha_c & -g_{10} & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \gamma & -\mu_f & 0 & 0 & 0 & 0 \\
\rho_3 & 0 & 0 & 0 & -\mu_f & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & -\mu_m & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & -g_{11} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & \sigma_m & -\mu_m
\end{pmatrix},$$

where, $j_1 = \dfrac{\beta_m c_f \pi_f \mu_m (1-\phi)}{\pi_m \mu_f}$, $j_2 = \dfrac{(1-\epsilon_v)\beta_m c_f \pi_f \mu_m \phi}{\pi_m \mu_f}$ and $j_3 = \dfrac{\beta_m c_f x_1}{x_{15}}$. It can be shown, from the Jacobian $J(\mathcal{E}_0)$, that (as in 7)),

$$\mathcal{R}_v^2 = \frac{\beta_f \beta_m c_f^2 \pi_f \mu_m [g_2 + \theta\sigma_f(1-r_1)](1-\epsilon_v\phi)}{g_1 g_2 g_{11} \pi_m \mu_f}. \tag{21}$$

Consider the case when $\mathcal{R}_v = 1$. Suppose, further, that β_f is chosen as a bifurcation parameter. Solving for β_f from $\mathcal{R}_v = 1$ in (21) gives

$$\beta_f = \beta^* = \frac{g_1 g_2 g_{11} \pi_m \mu_f}{\beta_m c_f^2 \pi_f \mu_m [g_2 + \theta\sigma_f(1-r_1)](1-\epsilon_v\phi)}. \tag{22}$$

It is easy to verify that the transformed system (20), with $\beta_f = \beta^*$ has a simple eigenvalue with zero real part, and all other eigenvalues have negative real parts. Hence, the centre manifold theory can be used to analyse the dynamics of (20) near

$\beta_f = \beta^*$. In particular, Theorem 4.1 in [8] will be used. The application of this theorem entails the following computations.

Eigenvectors of $J(\mathcal{E}_0)|_{\beta_f=\beta^*}$. The Jacobian of (20) at $\beta_f = \beta^*$, denoted by J_{β^*}, has a right eigenvector (corresponding to the zero eigenvalue) given by $\mathbf{w} = [w_1, \cdots, w_{17}]^T$, where

$$
\begin{aligned}
&w_1 = -\frac{\beta_m S_f^* c_f}{S_m^* \mu_f} w_{16},\ w_2 = -\frac{\beta_m c_f (1-\epsilon_v) V^*]}{S_m^* \mu_f} w_{16},\\
&w_3 = \frac{\beta_m [S_f^* + (1-\epsilon_v) V^*] c_f}{g_1 S_m^*} w_{16},\ w_4 = \frac{\sigma_f (1-r_1) \beta_m [S_f^* + (1-\epsilon_v) V^*] c_f}{g_1 g_2 S_m^*} w_{16},\\
&w_5 = \frac{\kappa_p g_4}{g_3 g_4 - \kappa_q \zeta_1} w_4,\ w_6 = \frac{\kappa_p \zeta_1}{g_3 g_4 - \kappa_q \zeta_1} w_4,\ w_7 = \frac{\kappa_p \zeta_1 \zeta_2}{g_5 (g_3 g_4 - \kappa_q \zeta_1)} w_4,\\
&w_8 = \frac{\kappa_p (g_4 g_7 \alpha_1 + \alpha_2 \kappa_d \zeta_1)}{(g_6 g_7 - \kappa_d \zeta_1)(g_3 g_4 - \kappa_q \zeta_1)} w_4,\ w_9 = \frac{\zeta_1 [\kappa_p \alpha_2 w_4 + (g_3 g_4 - \kappa_q \zeta_1) w_8]}{g_7 (g_3 g_4 - \kappa_q \zeta_1)},\\
&w_{10} = \frac{\zeta_1 \zeta_2 (g_5 \alpha_2 + \alpha_3 g_7) \kappa_p w_4 + (g_3 g_4 - \kappa_q \zeta_1) g_5 w_8}{g_8 g_7 g_5 (g_4 g_3 - \kappa_q \zeta_1)},\ w_{11} = \frac{\zeta_1 \zeta_2 \zeta_3 \kappa_p}{g_5 g_9 (g_3 g_4 - \kappa_q \zeta_1)} w_4,\\
&w_{12} = \frac{\alpha_c}{g_{10}} w_{11},\ w_{13} = \frac{\gamma}{\mu_f} w_{12},\\
&w_{14} = \frac{\sigma_f r_1 w_3 + \psi_0 w_4 + \psi_1 w_5 + \psi_2 w_6 + \psi_3 w_7 + \rho_1 w_8 + \rho_2 w_9 + \rho_3 w_{10}}{\mu},\\
&w_{15} = -\frac{\beta^* c_f (w_3 + \theta w_4)}{\mu_m},\ w_{16} = w_{16} > 0,\ w_{17} = \frac{\sigma_m}{\mu_m} w_{16},
\end{aligned}
$$

where, $g_3 g_4 - \kappa_q \zeta_1 > 0$, and $g_6 g_7 - \kappa_d \zeta_1 > 0$. Further, the Jacobian J_{β^*} has a left eigenvector (associated with the zero eigenvalue) given by $\mathbf{v} = [v_1, \cdots, v_{17}]$, where

$$
\begin{aligned}
&v_1 = 0,\ v_2 = 0,\ v_3 = \frac{\beta_f c_f [g_2 + \theta \sigma (1-r_1)]}{g_1 g_2} v_{16},\ v_4 = \frac{\beta^* c_f \theta}{g_2} v_{16},\\
&v_5 = \cdots v_{15} = 0,\ v_{16} = v_{16} > 0,\ v_{17} = 0.
\end{aligned}
$$

Computations of bifurcation coefficients a and b: For the system (20), the associated non-zero partial derivatives of $\hat{f}$ (at the DFE $\mathcal{E}_0$) are given by

$$
\begin{aligned}
&\frac{\partial^2 f_3}{\partial x_1 \partial x_{16}}(0,0) = \frac{\beta_m c_f}{S_m^*},\ \frac{\partial^2 f_3}{\partial x_2 \partial x_{16}}(0,0) = \frac{(1-\epsilon_v) \beta_m c_f}{S_m^*},\\
&\frac{\partial^2 f_3}{\partial x_{15} \partial x_{16}}(0,0) = \frac{\partial^2 f_3}{\partial x_{16} \partial x_{17}}(0,0) = -\frac{\beta_m c_f [S_f^* + (1-\epsilon_v) V^*]}{(S_m^*)^2},\\
&\frac{\partial^2 f_3}{\partial x_{16}^2}(0,0) = -\frac{2\beta_m [S_f^* + (1-\epsilon_v) V^*] c_f}{(S_m^*)^2},\ \frac{\partial^2 f_{16}}{\partial x_3 \partial x_{16}}(0,0) = \frac{\partial^2 f_{16}}{\partial x_3 \partial x_{17}}(0,0) = -\frac{\beta^* c_f}{S_m^*},\\
&\frac{\partial^2 f_{16}}{\partial x_4 \partial x_{16}}(0,0) = \frac{\partial^2 f_{16}}{\partial x_4 \partial x_{17}}(0,0) = -\frac{\beta^* c_f \theta}{S_m^*}.
\end{aligned}
$$

so that,

$$\begin{aligned} a &= \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \\ &= \frac{2v_{16}w_{16}^2\beta^*\beta_m c_f^2\pi_f\mu_m^2[g_2+\theta\sigma_f(1-r_1)]}{g_1 g_2 \pi_m^2} \\ &\quad \left\{ \frac{\beta^*\beta_m c_f^2\pi_f(1-\epsilon_v\phi)^2[g_2+\theta\sigma_f(1-r_1)]}{g_1 g_2^2 \pi_m \mu_f} \right. \\ &\quad \left. -\frac{\beta_m c_f}{g_2\mu_f}[(1-\phi)+(1-\epsilon_v)^2\phi] - \frac{2(1-\epsilon_v\phi)g_{11}}{\mu_m} \right\} \end{aligned} \tag{23}$$

The bifurcation coefficient b is similarly given by

$$b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*}(0,0) = v_{16}w_{16}\beta_m c_f^2 A_2 \frac{[S_f^* + (1-\epsilon_v)V^*]}{g_1 g_2 S_m^*} > 0.$$

Thus, it follows from Theorem 4.1 of [8] that the model (3) undergoes backward bifurcation whenever the bifurcation coefficient, a, given in (23), is positive. The inequality $a > 0$ can be expressed in terms of the model parameters as below.

$$\begin{aligned} & \frac{\beta^*\beta_m c_f^2\pi_f(1-\epsilon_v\phi)^2[g_2+\theta\sigma_f(1-r_1)]}{g_1 g_2^2 \pi_m \mu_f} \\ > \quad & \frac{\beta_m c_f}{g_2\mu_f}[(1-\phi)+(1-\epsilon_v)^2\phi] + \frac{2(1-\epsilon_v\phi)g_{11}}{\mu_m}. \end{aligned} \tag{24}$$

□

Remark 1. If $\epsilon_v = 1$, then

$$a = -\frac{2v_{16}w_{16}^2\beta^*\beta_m c_f^2\pi_f\mu_m^2[g_2+\theta\sigma_f(1-r_1)]}{g_1 g_2 \pi_m^2}\left\{\frac{c_f\beta_m(1-\phi)}{\mu_f} + \frac{(1-\phi)g_{11}}{\mu_m}\right\} < 0.$$

Thus the model (3) with perfect vaccine does not undergo a backward bifurcation at $\mathcal{R}_v = 1$, in line with Corollary 1.

Appendix B: Proposition 1.

Proposition 1. $-\frac{(\tilde{S}_f^{**})^2}{S_f} - (1-\epsilon_v)\frac{(\tilde{V}^{**})^2}{V} \leq -\frac{[\tilde{S}_f^{**} + (1-\epsilon_v)\tilde{V}^{**}]^2}{S_f + (1-\epsilon_v)V}.$

Proof. Suppose the proposition is false. Hence,

$$\frac{(\tilde{S}_f^{**})^2}{S_f} + (1-\epsilon_v)\frac{(\tilde{V}^{**})^2}{V} < \frac{[\tilde{S}_f^{**} + (1-\epsilon_v)\tilde{V}^{**}]^2}{S_f + (1-\epsilon_v)V}$$

so that,

$$\frac{\tilde{S}_f^{**})^2 V + (1-\epsilon_v)(\tilde{V}^{**})^2 S_f}{S_f V} < \frac{(\tilde{S}_f^{**})^2 + \epsilon_v^2(\tilde{V}^{**})^2 + 2\epsilon_v\tilde{S}_f^{**}\tilde{V}^{**}}{S_f + \epsilon_v V}$$

which can be simplified to:

$$(\tilde{S}_f^{**})^2 V S_f + \epsilon_v (\tilde{S}_f^{**})^2 V^2 + \epsilon_v S_f^2 (\tilde{V}^{**})^2 + \epsilon_v^2 S_f V (\tilde{V}^{**})^2$$
$$< S_f (\tilde{S}_f^{**})^2 V + \epsilon_v^2 S_f V (\tilde{V}^{**})^2 + 2\epsilon_v S_f \tilde{S}_f^{**} V \tilde{V}^{**}$$
$$\text{or } \epsilon_v (\tilde{S}_f^{**})^2 V^2 + \epsilon_v S_f^2 (\tilde{V}^{**})^2 - 2\epsilon_v S_f \tilde{S}_f^{**} V \tilde{V}^{**} < 0$$
$$\text{or } (\tilde{S}_f^{**} V - S_f \tilde{V}^{**})^2 < 0,$$

which is a contradiction. Hence, $-\frac{(\tilde{S}_f^{**})^2}{S_f} - (1-\epsilon_v)\frac{(\tilde{V}^{**})^2}{V} \leq -\frac{[\tilde{S}_f^{**} + (1-\epsilon_v)\tilde{V}^{**}]^2}{S_f + (1-\epsilon_v)V}$. □

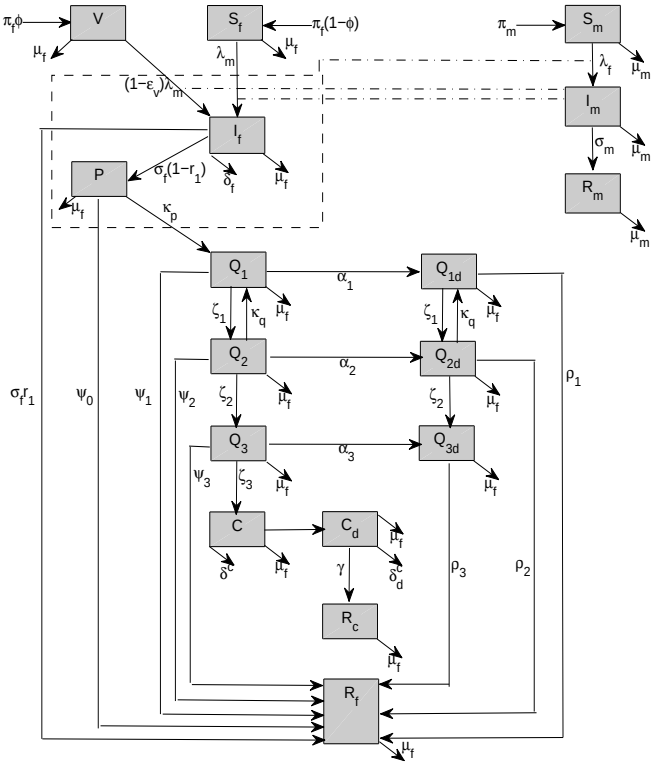

FIGURE 1. Schematic diagram of the model (3).

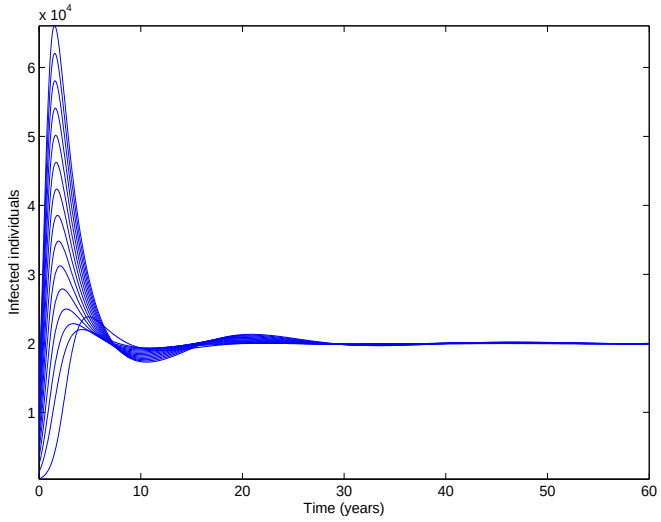

FIGURE 2. Simulations of the model (3) showing the number of infected individuals (males and females) as a function of time, using various initial conditions. Parameter values used are as given in Table 2, with $\phi = 0.3$ and $c_f = 4$ (so that, $\mathcal{R}_v = 3.7897 > 1$).

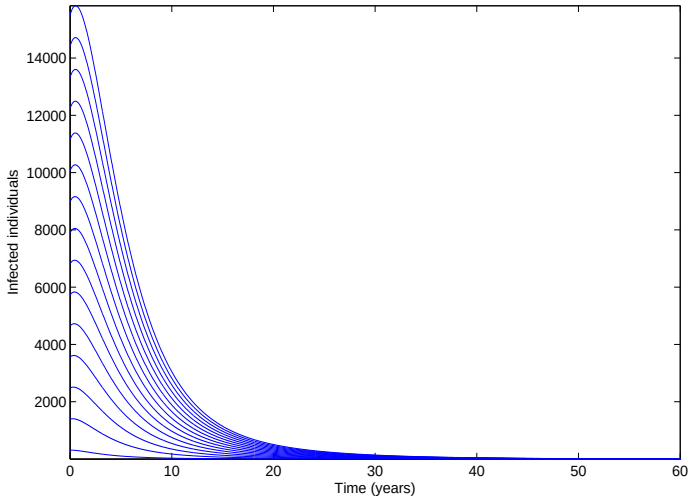

FIGURE 3. Simulations of the model (3) showing the number of infected individuals (males and females) as a function of time, using various initial conditions. Parameter values used are as given in Table 2 with $\delta = 0$, $\phi = 0.9$ and $c_f = 1$ (so that, $\tilde{\mathcal{R}}_v = 0.4833 < 1$).

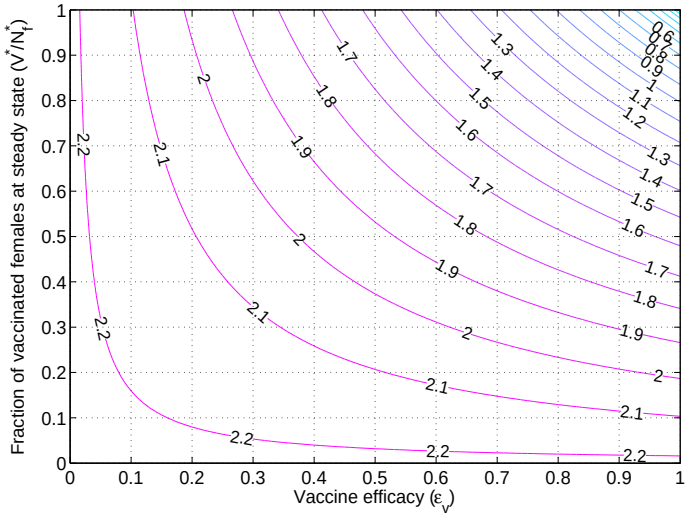

FIGURE 4. Simulation of the model (3) showing the contour plot of $\tilde{\mathcal{R}}_v$ as a function of vaccine efficacy (ϵ_v) and the fraction of susceptible females vaccinated at steady-state (V^*/N_f^*). Parameter values used are as in Table 2, with $\delta = 0$.

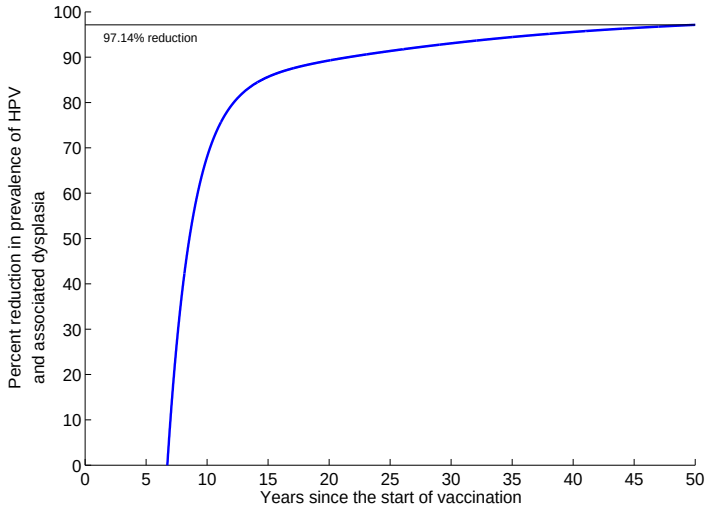

FIGURE 5. Simulation of the model (3) showing the percentage reduction in prevalence of the HPV infection and the associated dysplasia as a function of time, in the absence of Pap screening. Parameter values used are the same as those used to generate Figure 4.

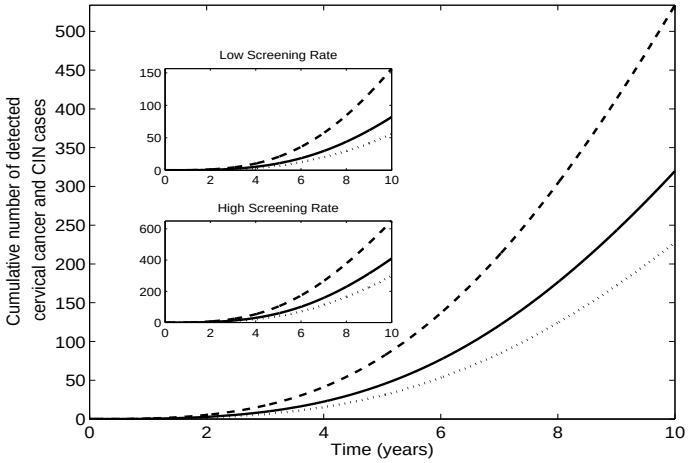

FIGURE 6. Cumulative number of detected cervical cancer and CIN cases as a function of time. The dotted line represents 3-year screening, solid line represents 2-year screening, and dashed line represents annual screening. Parameter values used are as in Table 2, with $\delta = \phi = 0$. The inset plots show the same corresponding to low screening rate due to low proportion screened ($\chi = 7\%$) and high screening rate due to high proportion screened ($\chi = 44\%$).

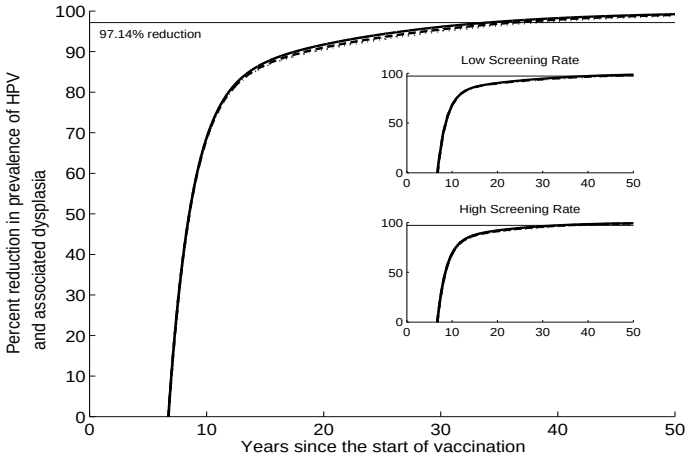

FIGURE 7. Simulation of the model (3) with $\delta = 0$ showing the percentage reduction in prevalence of the HPV infection and the associated dysplasia as a function of time, with Pap screening. The solid curve represents annual screening, dashed line represents 2-year screening and the dotted line represents 3-year screening. Parameter values used are the same as those used to generate Figure 4. The inset plots show the same corresponding to low screening rate due to low proportion screened ($\chi = 7\%$) and high screening rate due to high proportion screened ($\chi = 44\%$).