Mathematical Biosciences and Engineering

MBE, 17(5): 5449−5476.
DOI: 10.3934/mbe.2020294
Received: 21 April 2020
Accepted: 03 August 2020
Published: 12 August 2020

http://www.aimspress.com/journal/MBE

Research article

Mathematical analysis of a human papillomavirus transmission model with vaccination and screening

Kai Zhang[1], Xinwei Wang[2], Hua Liu[1,*], Yunpeng Ji[3,4,5], Qiuwei Pan[3,4], Yumei Wei[6] and Ming Ma[1]

[1] School of Mathematics and Computer Science, Northwest Minzu University, Lanzhou 730030, China
[2] Department of Engineering Mechanics, State Key Laboratory of Structural Analysis for Industrial Equipment, Dalian University of Technology, Dalian 116024, China
[3] Biomedical Research Center, Northwest Minzu University, Lanzhou 730030, China
[4] Department of Gastroenterology and Hepatology, Erasmus MC-University Medical Center, Rotterdam, Netherlands
[5] Department of Genetics, Inner Mongolia Maternal and Child Care Hospital, Hohhot 010020, China
[6] Experimental Teaching Department, Northwest Minzu University, Lanzhou 730030, China

*** Correspondence:** Email: jslh@xbmu.edu.cn.

Abstract: We formulate a mathematical model to explore the transmission dynamics of human papillomavirus (HPV). In our model, infected individuals can recover with a limited immunity that results in a lower probability of being infected again. In practice, it is necessary to revaccinate individuals within a period after the first vaccination to ensure immunity to HPV infection. Accordingly, we include vaccination and revaccination in our model. The model exhibits backward bifurcation as a result of imperfect protection after recovery and because the basic reproduction number is less than one. We conduct sensitivity analysis to identify the factors that markedly affect HPV infection rates and propose an optimal control problem that minimizes vaccination and screening cost. The optimal controls are characterized according to Pontryagin's maximum principle and numerically solved by the symplectic pseudospectral method.

Keywords: infectious disease; global stability; sensitivity analysis; optimal control

1. Introduction

Uterine cervical cancer is a worldwide health problem but it is especially concerning in developing countries. It is the first or second most common cancer in women [1]. It is estimated that the probability of a person being infected with human papillomavirus (HPV) in their lifetime reaches 70 to 80% [2], and the total infection rate in the global population is as high as 11.7% [3]. An estimated 233,000 deaths were attributed to HPV infection in the year 2000 [4]. There were approximately 500,000 cases and 275,000 deaths due to cervical cancer worldwide in 2002, equivalent to about a tenth of all deaths in women due to cancer [5]. The burden of cervical cancer is disproportionately high (> 80%) in the developing world [6].

HPV was discovered to be the causative agent of cervical cancer in the 1970s by the Zur Hausen group [7]. Usually, the infecting papillomavirus is eliminated from individuals; however, some individuals retain the virus. Persistent infection with oncogenic HPV is recognized as the major cause of uterine cervical cancer [8]. Cervical carcinogenesis is a complex stepwise process over a continuum of increasingly severe precancerous changes known collectively as cervical intraepithelial neoplasia (CIN) [9]. The spectrum of CIN is traditionally divided into three histopathological categories: 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 CINs (i.e., CIN2 and CIN3). The risk of progression to invasive cervical cancer increases significantly with worsening CIN grades [10–11].

Pap cytology screening for the early detection of cervical neoplasia has been successful in reducing cervical cancer incidence and mortality [12]. In unscreened populations, the risk of invasive cervical cancer occurs earlier than of most adult cancers, peaking or reaching a plateau between about 35 and 55 years of age [13]. This distribution is because cervical cancers originate mainly from HPV infections transmitted sexually in late adolescence and early adulthood [14]. HPV transmission can be reduced through the use of condoms [15]. Some studies have reported that smoking [16], multiparity [17], and long-term use of oral contraceptives [18] can double or triple the risk of precancer and cancer among women infected with carcinogenic types of HPV. There are two major kinds of anti-HPV vaccines approved for use to protect newly sexually active individuals against some of the most common HPV types and boost immunity, namely, therapeutic vaccines and prophylactic vaccines [7]. A few years after receiving a prophylactic vaccine, the individual must be revaccinated because the vaccine loses its preventive effect. Progress in the development of therapeutic vaccines for HPV has been slow [7]. In summary, there is currently no specific treatment for HPV infection [19]. There are three major treatments for cervical cancer: surgery (such as total hysterectomy and subtotal hysterectomy), radiotherapy, and chemotherapy. Among these, surgery and radiotherapy are the main treatment methods [19].

Mathematical modeling is a useful tool for assessing the potential impact of intervention strategies against HPV spread among humans [20−24]. A number of authors have reported the use of mathematical modeling to evaluate the impact of HPV vaccination. Al-arydah [20] developed a two-sex, age-structured model to describe a vaccination program for the administration of an HPV vaccine. Malik et al. [11] presented an age-structured mathematical model that incorporated sex structure and Pap screening cytology. Sharomi and Malik [21] developed a two-sex HPV vaccination model to study the effect of vaccine compliance on HPV infection and cervical cancer. Omame [22] developed a two-sex deterministic model for HPV that assessed the impact of treatment and

vaccination. Elbasha [23] presented a two-sex, deterministic model for assessing the potential impact of a prophylactic HPV vaccine with several properties.

Based on the above research and understanding of HPV pathology, we develop an ordinary differential equation model with precautionary measures such as screening, which are rarely considered in previous studies, and analyze the potential effects of multiple factors on HPV transmission. The model is formulated in section 2. In section 3, the equilibria, basic reproduction number, and global stability are analyzed. We report the sensitivity analysis of the model through the partial rank correlation coefficient (PRCC) method and identify the key factors in the model in section 4. In section 5, we set the vaccination rate and screening rate as control variables and analyze an optimal control problem that minimizes vaccination and screening cost. Section 6 concludes the article. Through extensive numerical simulations with MATLAB, we obtained results to verify our conclusions.

2. An HPV model with vaccination and screening

The total individual population at time *t* is divided into 10 mutually exclusive subpopulations of susceptible individuals *S(t)*, vaccinated individuals *V(t)*, infectious individuals without disease symptoms *E(t)*, infectious individuals with disease symptoms *H(t)*, individuals with persistent HPV infection *P(t)*, CIN1 symptomatic individuals $I_1(t)$, CIN2 symptomatic individuals $I_2(t)$, CIN3 symptomatic individuals $I_3(t)$, cancer-infected individuals *A(t)* and recovered individuals *R(t)*. As such, the total population is

$$N(t)=V(t)+S(t)+E(t)+H(t)+P(t)+I_1(t)+I_2(t)+I_3(t)+A(t)+R(t).$$

Susceptible individuals acquire HPV infection, following effective contact with infected individuals (i.e., those in the E, H, P, I_1, I_2 and I_3 classes) at the rate α_1 as follows

$$\alpha_1(t)=\frac{\beta\alpha c_n c_k\left(1-c_c c_a\right)\left(E+\theta_1 H+\theta_2 P+\theta_3 I_1+\theta_4 I_2+\theta_5 I_3\right)}{N}. \tag{1}$$

It follows that the model for the transmission of HPV is given by the following system of differential equations.

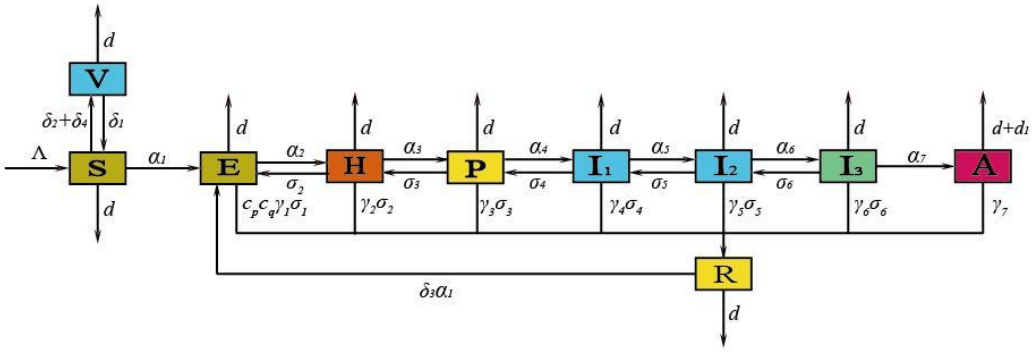

Figure 1. Flow diagram of model (2).

$$
\begin{aligned}
&\text{(2a)}\ \frac{dV}{dt} = \delta_2 S(t) + \delta_4 S(t) - (d+\delta_1)V(t),\\
&\text{(2b)}\ \frac{dS}{dt} = \Lambda + \delta_1 V(t) - (\delta_2 + \delta_4 + \alpha_1(t) + d)S(t),\\
&\text{(2c)}\ \frac{dE}{dt} = \alpha_1(t)S(t) + \delta_3\alpha_1(t)R(t) + \sigma_2 H(t) - (\alpha_2 + c_p c_q \gamma_1 \sigma_1 + d)E(t),\\
&\text{(2d)}\ \frac{dH}{dt} = \alpha_2 E(t) + \sigma_3 P(t) - (\sigma_2 + \gamma_2\sigma_2 + \alpha_3 + d)H(t),\\
&\text{(2e)}\ \frac{dP}{dt} = \alpha_3 H(t) + \sigma_4 I_1(t) - (\alpha_4 + \gamma_3\sigma_3 + \sigma_3 + d)P(t),\\
&\text{(2f)}\ \frac{dI_1}{dt} = \alpha_4 P(t) + \sigma_5 I_2(t) - (\alpha_5 + \gamma_4\sigma_4 + \sigma_4 + d)I_1(t),\\
&\text{(2g)}\ \frac{dI_2}{dt} = \alpha_5 I_1(t) + \sigma_6 I_3(t) - (\sigma_5 + \gamma_5\sigma_5 + \alpha_6 + d)I_2(t),\\
&\text{(2h)}\ \frac{dI_3}{dt} = \alpha_6 I_2(t) - (\sigma_6 + \gamma_6\sigma_6 + \alpha_7 + d)I_3(t),\\
&\text{(2i)}\ \frac{dA}{dt} = \alpha_7 I_3(t) - (\gamma_7 + d + d_1)A(t),\\
&\text{(2j)}\ \frac{dR}{dt} = c_p c_q \gamma_1 \sigma_1 E(t) + \gamma_2\sigma_2 H(t) + \gamma_3\sigma_3 P(t) + \gamma_4\sigma_4 I_1(t) + \gamma_5\sigma_5 I_2(t) + \gamma_6\sigma_6 I_3(t) + \gamma_7 A(t)\\
&\qquad\qquad - (\delta_3\alpha_1(t) + d)R(t).
\end{aligned}
\tag{2}
$$

Table 1. Description of variables in model (2).

Variable	Description
$V(t)$	Vaccinated individuals
$S(t)$	Susceptible individuals
$E(t)$	Infectious individuals with no symptoms
$H(t)$	Infectious individuals with symptoms
$P(t)$	Infectious individuals with persistent infection
$I_1(t)$	Cervical intraepithelial neoplasia grade 1 (CIN1)
$I_2(t)$	Cervical intraepithelial neoplasia grade 2 (CIN2)
$I_3(t)$	Cervical intraepithelial neoplasia grade 3 (CIN3)
$A(t)$	Cancer-infected individuals
$R(t)$	Recovered individuals

Tables 1 and 2 list the associated state variables and parameters of model (2). Figure 1 shows the flow diagram of the model. We emphasize that the vaccine mentioned in model (2) is a prophylactic vaccine. In the following section, model (2) is qualitatively analyzed to derive insights into its dynamical features.

Table 2. Description of the parameters in model (2).

Parameter	Description
Λ	Recruitment rate into the susceptible population (per year)
d	Natural death rate (per year)
d_1	Disease-induced mortality for individuals (per year)
α_1	Effective contact rate
δ_1	Vaccine failure rate (per year)
δ_2, δ_4	Vaccination rate and revaccination rate (per year)
δ_3	The modification parameter for the probability of R being infected relative to S
c_p	The effect of screening by HPV testing
c_q	Screening frequency (per year)
c_n	Rate at which females (males) acquire new sexual partners (per year)
c_k	The probability of transmitting HPV from female (male) to male (female)
c_c	Condom efficacy
c_a	Condom compliance (per year)
α	The negative effects of contraceptive drugs
β	The negative effects of smoking
$\alpha_2, \alpha_3, \alpha_4, \alpha_5, \alpha_6, \alpha_7$	Progression rate of infectious individuals from E to H, H to P, P to I_1, I_1 to I_2, I_2 to I_3, I_3 to A (per year)
$\sigma_1, \sigma_2, \sigma_3, \sigma_4, \sigma_5, \sigma_6$	Recovery rates of infectious individuals from E to R, H to E, P to H, I_1 to P, I_2 to I_1, I_3 to I_2 (per year)
$\gamma_1, \gamma_2, \gamma_3, \gamma_4, \gamma_5, \gamma_6, \gamma_7$	Effect of drugs on infectious individuals' recovery
$\theta_1, \theta_2, \theta_3, \theta_4, \theta_5$	Modification parameter that accounts for the infectiousness of individuals in the H, P, I_1, I_2, I_3 classes relative to those in the E class for females (males)

3. Analysis of the model

3.1. Basic properties

3.1.1. Positivity and boundedness of solutions

Model (2) is epidemiologically and mathematically well-posed in the epidemiologically valid domain

$$D = \{(V,S,E,H,P,I_1,I_2,I_3,A,R) \in R^{10} \mid V \geq 0, S \geq 0, E \geq 0, H \geq 0, P \geq 0, I_1 \geq 0, I_2 \geq 0, I_3 \geq 0, A \geq 0, R \geq 0\}.$$

Theorem 3.1 Assuming that the initial condition lies in domain D, then the solutions $(V,S,E,H,P,I_1,I_2,I_3,A,R)$ of model (2) remain in *D* for all time $t \geq 0$. Furthermore

$$\limsup_{t\to\infty} N(t) \leq \frac{\Lambda}{d}, \text{ with } N = V + S + E + H + P + I_1 + I_2 + I_3 + A + R.$$

Proof. We note that along the edges of *D*, the time derivatives all lead the solution into the invariant domain [25]

$$V = 0 \Rightarrow V' \geq 0 \quad (2a),$$
$$S = 0 \Rightarrow S' \geq 0 \quad (2b),$$
$$E = 0 \Rightarrow E' \geq 0 \quad (2c),$$
$$H = 0 \Rightarrow H' \geq 0 \quad (2d),$$
$$P = 0 \Rightarrow P' \geq 0 \quad (2e),$$
$$I_1 = 0 \Rightarrow I_1' \geq 0 \quad (2f),$$
$$I_2 = 0 \Rightarrow I_2' \geq 0 \quad (2g),$$
$$I_3 = 0 \Rightarrow I_3' \geq 0 \quad (2h),$$
$$A = 0 \Rightarrow A' \geq 0 \quad (2i),$$
$$R = 0 \Rightarrow R' \geq 0 \quad (2j).$$

Furthermore, adding all the equations in the differential equation system of model (2) gives

$$\frac{dN}{dt} = \Lambda - dV - dS - dE - dH - dP - dI_1 - dI_2 - dI_3 - dA - dR - d_1 A. \quad (3)$$

It follows from Eq (3) that

$$\Lambda - (d + d_1) N \leq \frac{dN}{dt} \leq \Lambda - dN.$$

Therefore

$$\frac{\Lambda}{d + d_1} \leq \liminf_{t\to\infty} N(t) \leq \limsup_{t\to\infty} N(t) \leq \frac{\Lambda}{d},$$

and

$$\limsup_{t\to\infty} N(t) \leq \frac{\Lambda}{d},$$

as required.

3.1.2. Invariant regions

Model (2) is analyzed in a biologically-feasible region as follows [26]. We first show that model (2)

is dissipative (i.e., all feasible solutions are uniformly bounded in a proper subset $\Omega \subset R_+^{10}$). Consider the region

$$\Omega = \left\{ (V,S,E,H,P,I_1,I_2,I_3,A,R) \in R^{10} : \right.$$
$$\left. V+S+E+H+P+I_1+I_2+I_3+A+R \le \frac{\Lambda}{d} \right\}.$$

The following steps establish the positive invariance of Ω (i.e., solutions in Ω remain in Ω $t \ge 0$). It follows from Eq (3) that

$$\frac{dN}{dt} \le \Lambda - dN .$$

A standard comparison theorem can then be used to show that

$$N(t) \le N(0)e^{-dt} + \frac{\Lambda}{d}\left(1-e^{-dt}\right).$$

In particular

$$N(t) \le \frac{\Lambda}{d} \text{ if } N(0) \le \frac{\Lambda}{d}.$$

Thus, the region Ω is positively invariant. Hence, it is sufficient to consider the dynamics of the flow generated by model (2) in Ω. In this region, the model can be considered as being epidemiologically and mathematically well-posed [27]. Thus, every solution of model (2) with initial conditions in Ω remains in Ω for all $t > 0$. Therefore, the ω-limit sets of model (2) are contained in Ω. This result is summarized below.

Lemma 3.1 The region Ω is positively invariant for model (2) with initial conditions in R_+^{10}.

3.2. Local stability of the disease-free equilibrium (DFE)

Model (2) has a DFE, which is obtained by setting the right-hand sides of the equations in the model to zero, given by

$$\begin{aligned} \varepsilon_0 &= \left(V^0,S^0,E^0,H^0,P^0,I_1{}^0,I_2{}^0,I_3{}^0,A^0,R^0\right) \\ &= \left(\frac{\Lambda(\delta_2+\delta_4)}{a_1a_2-\delta_1(\delta_2+\delta_4)}, \frac{\Lambda a_1}{a_1a_2-\delta_1(\delta_2+\delta_4)}, 0,0,0,0,0,0,0 \right). \end{aligned} \tag{4}$$

Let $\mathrm{X} = (V,S,E,H,P,I_1,I_2,I_3,A,R)^T$. Using the notation from [28], the model consists of nonnegative initial conditions together with the following system of equations:

$$\frac{dX}{dt} = \Phi(X) - \Gamma(X),$$

where

$$\Phi(X)=\begin{pmatrix}\alpha_1 S\\0\\0\\0\\0\\0\\0\\0\\0\\0\end{pmatrix},\ \Gamma(X)=\begin{pmatrix}-\delta_3\alpha_1 R-\sigma_2 H+(\alpha_2+c_p c_q\gamma_1\sigma_1+d)E\\-\alpha_2 E-\sigma_3 P+(\sigma_2+\gamma_2\sigma_2+\alpha_3+d)H\\-\alpha_3 H-\sigma_4 I_1+(\alpha_4+\gamma_3\sigma_3+\sigma_3+d)P\\-\alpha_4 P-\sigma_5 I_2+(\alpha_5+\gamma_4\sigma_4+\sigma_4+d)I_1\\-\alpha_5 I_1-\sigma_6 I_3+(\sigma_5+\gamma_5\sigma_5+\alpha_6+d)I_2\\-\alpha_6 I_2+(\sigma_6+\gamma_6\sigma_6+\alpha_7+d)I_3\\-\alpha_7 I_3+(\gamma_7+d+d_1)A\\-\Lambda-\delta_1 V+(\delta_2+\delta_4+\alpha_1+d)S\\-c_p c_q\gamma_1\sigma_1 E-\gamma_2\sigma_2 H-\gamma_3\sigma_3 P-\gamma_4\sigma_4 I_1-\gamma_5\sigma_5 I_2-\gamma_6\sigma_6 I_3-\gamma_7 A\\+(\delta_3\alpha_1+d)R\\-\delta_2 S-\delta_4 S+(d+\delta_1)V\end{pmatrix},$$

and it follows that

$$D\Phi(X)=\begin{pmatrix}F&0\\0&0\end{pmatrix},\ D\Gamma(X)=\begin{pmatrix}V_\Delta&0\\J_3&J_4\end{pmatrix}.$$

The matrices F and V_Δ for the new infection terms and the remaining transfer terms are respectively given by

$$F=a_{10}\begin{bmatrix}1&\theta_1&\theta_2&\theta_5&\theta_4&\theta_3\\0&0&0&0&0&0\\0&0&0&0&0&0\\0&0&0&0&0&0\\0&0&0&0&0&0\\0&0&0&0&0&0\end{bmatrix},\ V_\Delta=\begin{bmatrix}a_3&-\sigma_2&0&0&0&0\\-\alpha_2&a_4&-\sigma_3&0&0&0\\0&-\alpha_3&a_5&0&0&-\sigma_4\\0&0&0&a_8&-\alpha_6&0\\0&0&0&-\sigma_6&a_7&-\alpha_5\\0&0&-\alpha_4&0&-\sigma_5&a_6\end{bmatrix},$$

$$J_3=\begin{bmatrix}0&0&0&-\alpha_7&0&0\\-c_p c_q\gamma_1\sigma_1&-\gamma_2\sigma_2&-\gamma_3\sigma_3&-\gamma_6\sigma_6&-\gamma_5\sigma_5&-\gamma_4\sigma_4\\a_{10}&a_{10}\theta_1&a_{10}\theta_2&a_{10}\theta_5&a_{10}\theta_4&a_{10}\theta_3\\0&0&0&0&0&0\end{bmatrix},\ J_4=\begin{bmatrix}a_9&0&0&0\\-\gamma_7&d&0&0\\0&0&a_2&-\delta_1\\0&0&-\delta_2-\delta_4&a_1\end{bmatrix},$$

where

$a_1=d+\delta_1$, $a_2=\delta_2+\delta_4+d$, $a_3=\alpha_2+c_p c_q\gamma_1\sigma_1+d$,

$a_4=\sigma_2+\gamma_2\sigma_2+\alpha_3+d$, $a_5=\alpha_4+\gamma_3\sigma_3+\sigma_3+d$, $a_6=\alpha_5+\gamma_4\sigma_4+\sigma_4+d$,

$a_7=\sigma_5+\gamma_5\sigma_5+\alpha_6+d$, $a_8=\sigma_6+\gamma_6\sigma_6+\alpha_7+d$, $a_9=\gamma_7+d+d_1$,

$a_{10}=\dfrac{Ma_1}{a_1+\delta_2+\delta_3}$, $M=\beta\alpha c_n c_k(1-c_c c_a)$.

We obtain

$$R_0=\rho\left(FV_\Delta^{-1}\right)=\frac{a_1 MM_1}{(a_3D_6-\sigma_2D_5)(a_1+\delta_2+\delta_4)},\tag{5}$$

where

$$M_1 = D_6 + \theta_1 D_5 + \theta_2 D_4 + \theta_3 D_3 + \theta_4 D_2 + \theta_5,\ \ D_1 = \frac{\alpha_7}{a_9},\ \ D_2 = \frac{a_8}{\alpha_6},$$

$$D_3 = \frac{a_7 D_2 - \sigma_6}{\alpha_5} > 0,\ \ D_4 = \frac{a_6 D_3 - \sigma_5 D_2}{\alpha_4} > 0,\ \ D_5 = \frac{a_5 D_4 - \sigma_4 D_3}{\alpha_3} > 0,$$

$$D_6 = \frac{a_4 D_5 - \sigma_3 D_4}{\alpha_2} > 0.$$

Consequently, it follows from Theorem 2 of [28].

Lemma 3.2 The DFE of model (2), given by (4), is locally asymptotically stable (LAS) when $R_0 < 1$ and unstable if $R_0 > 1$.

3.3. Backward bifurcation

The epidemiological significance of forward bifurcation is that the disease will eventually disappear if the basic reproduction number is less than one. The public health significance of backward bifurcation is that the classical requirement of $R_0 < 1$ although necessary is no longer sufficient for effective disease control. Therefore, the presence of backward bifurcation in HPV transmission dynamics makes its effective control more difficult.

3.3.1. Existence of backward bifurcation

First, the possible equilibrium solutions that model (2) can have are determined as follows. Let

$$\varepsilon_1 = \left(V_*, S_*, E_*, H_*, P_*, I_{1*}, I_{2*}, I_{3*}, A_*, R_*\right),$$

be any arbitrary equilibrium of model (2). Further, let

$$\alpha_{1*} = \frac{\beta\alpha c_n c_k \left(1 - c_c c_a\right)\left(E_* + \theta_1 H_* + \theta_2 P_* + \theta_3 I_{1*} + \theta_4 I_{2*} + \theta_5 I_{3*}\right)}{N_*}, \tag{6}$$

be the associated force of infection at a steady state.

Setting the right-hand sides of model (2) to zero (steady state) gives

$$A_* = D_1 I_{3*},\ \ I_{2*} = D_2 I_{3*},\ \ I_{1*} = D_3 I_{3*},\ \ P_* = D_4 I_{3*},\ \ H_* = D_5 I_{3*},\ \ E_* = D_6 I_{3*},$$

$$R_* = \frac{D_7}{d + \delta_3 \alpha_{1*}} I_{3*},\ \ S_* = \left(\frac{a_3 D_6}{\alpha_{1*}} - \frac{\sigma_3 D_7}{d + \delta_3 \alpha_{1*}} - \frac{\sigma_2 D_5}{\alpha_{1*}}\right) I_{3*}, \tag{7}$$

$$V_* = \frac{\delta_2 + \delta_4}{a_1}\left(\frac{a_3 D_6}{\alpha_{1*}} - \frac{\sigma_3 D_7}{d + \delta_3 \alpha_{1*}} - \frac{\sigma_2 D_5}{\alpha_{1*}}\right) I_{3*},$$

where

$$D_7 = c_p c_q \gamma_1 \sigma_1 D_6 + \gamma_2 \sigma_2 D_5 + \gamma_3 \sigma_3 D_4 + \gamma_4 \sigma_4 D_3 + \gamma_5 \sigma_5 D_2 + \gamma_6 \sigma_6 + \gamma_7 D_1.$$

Substituting (7) into the expressions for α_{1*} in (6) gives

$$\alpha_{1^*}=\frac{M\left(D_6+\theta_1 D_5+\theta_2 D_4+\theta_3 D_3+\theta_4 D_2+\theta_5\right)I_{3^*}}{\left(\frac{a_3 D_6}{\alpha_{1^*}}-\frac{\sigma_3 D_7}{d+\delta_3\alpha_{1^*}}-\frac{\sigma_2 D_5}{\alpha_{1^*}}\right)\left(1+\frac{\delta_2+\delta_4}{a_1}\right)I_{3^*}+D_8 I_{3^*}+\frac{D_7}{d+\delta_3\alpha_{1^*}}I_{3^*}}, \tag{8}$$

so

$$a\alpha_{1^*}^2+b\alpha_{1^*}+c=0, \tag{9}$$

where

$a=D_8\delta_3 a_1$,

$b=\delta_3\left(1-R_0\right)\left(a_3D_6-\sigma_2D_5\right)\left(a_1+\delta_2+\delta_4\right)+D_7a_1+D_8a_1d-D_7\delta_3\left(a_1+\delta_2+\delta_4\right)$,

$c=d\left(1-R_0\right)\left(a_3D_6-\sigma_2D_5\right)\left(a_1+\delta_2+\delta_4\right)$,

and

$$D_8=D_6+D_5+D_4+D_3+D_2+D_1+1.$$

Quadratic Eq (9) can be analyzed for the possibility of multiple endemic equilibria. It is worth noting that the coefficient a is always positive, and c is positive (negative) if R_0 is less than (greater than) one. Hence, the following result is established.

Theorem 3.2 Model (2) (details in Appendix A (Table A1)) has the following.

i. A unique endemic equilibrium if $c<0\Leftrightarrow R_0>1$;

ii. A unique endemic equilibrium if $b<0$, and $c=0$ or $b^2-4ac=0$;

iii. Two endemic equilibria if $c>0$, $b<0$ and $b^2-4ac>0$;

iv. No endemic equilibrium otherwise.

Case (iii) of Theorem 3.2 indicates the possibility of backward bifurcation in model (2) when $R_0<1$. To check for this, by setting

$$R_1=1-\frac{b^2}{d\left(a_3D_6-\sigma_2D_5\right)\left(a_1+\delta_2+\delta_4\right)},$$

it can be shown that backward bifurcation occurs for values of $R_1<R_0<1$. This phenomenon is illustrated by simulating model (2). The parameter values are presented in Table 3. Let $M\in[0.35,0.5]$. It should be mentioned that the aforementioned parameter values may not all be epidemiologically realistic.

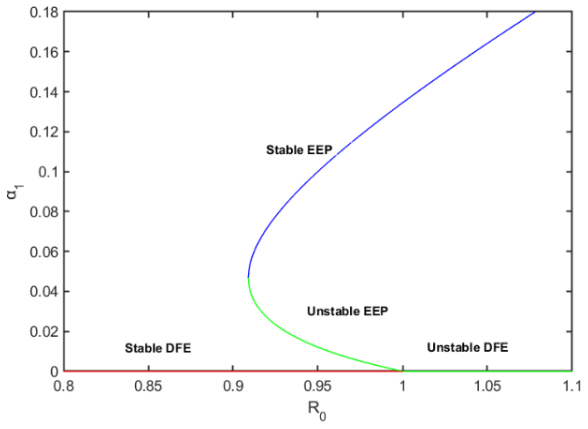

Figure 2. Backward bifurcation diagram of model (2).

Table 3. Parameter values used in Figure 2 (A: Assumed).

Parameter	Value	Source	Parameter	Value	Source	Parameter	Value	Source
Λ	288802	[22]	α_3	0.005	[11]	γ_1	1.5	A
d	0.0162	[22]	α_4	0.1	[11]	γ_2	1.5	A
d_1	0.01	[11]	α_5	0.02	[11]	γ_3	1.2	A
δ_1	0.1	[11]	α_6	0.04	[11]	γ_4	1.1	A
δ_2	0.87	[22]	α_7	0.08	[11]	γ_5	1.05	A
δ_3	0.3	[22]	σ_1	0.99	[11]	γ_6	1.03	A
δ_4	0.27	A	σ_2	$9e-4$	[22]	γ_7	1.01	A
c_p	0.9	A	σ_3	0.5	[22]	θ_4	0.6	A
c_q	0.4	A	σ_4	$1.9e-7$	A	θ_5	0.5	A
σ_5	$1.9e-7$	A	θ_1	1	A	θ_2	0.8	[22]
α_2	0.5	[22]	σ_6	$1.9e-7$	A	θ_3	0.7	A

The associated backward bifurcation diagram, depicted in Figure 2, shows that the model has a DFE (corresponding to Figure 3) and two endemic equilibria: One of the endemic equilibria is LAS (corresponding to Figure 4a); the other is unstable (a saddle); and the disease-free equilibrium is LAS. This clearly shows the coexistence of two stable equilibria when $R_0 < 1$, confirming that the model exhibits backward bifurcation for $R_1 < R_0 < 1$. This result is summarized below for model (2) (a more rigorous proof of the backward bifurcation phenomenon of the model, using the center manifold theory is given in Appendix B).

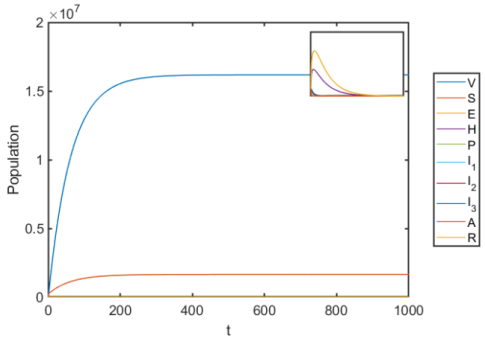

Figure 3. Variation in population with $R_0 = 0.6659$ and $R_1 = 0.9976$.

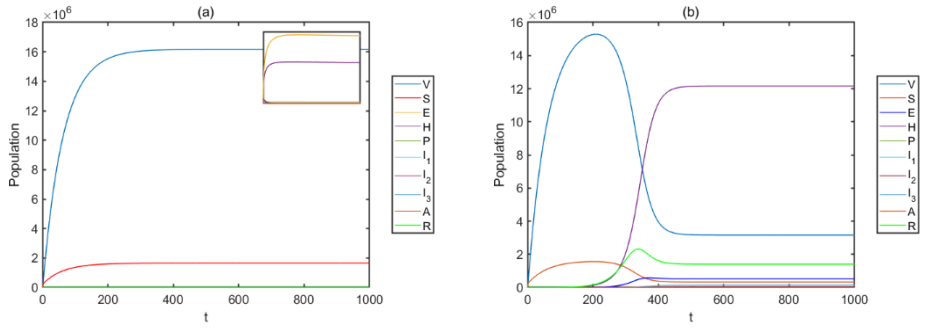

Figure 4. Variation in population with (a) $R_0 = 0.9988$, $R_1 = 0.8144$; (b) $R_0 = 2.2196$.

Theorem 3.3 Model (2) exhibits backward bifurcation when Case (iii) of Theorem 3.2 holds and $R_1 < R_0 < 1$.

3.3.2. Effect of perfect protection after recovery on backward bifurcation

Consider model (2) with perfect protection after recovery (that is, $\delta_3 = 0$). In such a case, the basic reproduction number is $R_0' = R_0\big|_{\delta_3=0}$. It follows from Eq (9) that if $\delta_3 = 0$, the coefficients $a = 0$ and $b > 0$, so quadratic Eq (9) reduces to a linear equation in α_{1*} (with $\alpha_{1*} = -c/b$). In this case, model (2) has a unique endemic equilibrium if $c < 0$ (i.e., $R_0' > 1$), ruling out backward bifurcation in the model for this case (the presence of two endemic equilibria when $R_0' < 1$ is necessary for the existence of backward bifurcation). Furthermore, it follows that $c = 0$ when $R_0' = 1$. Thus, in such a case (with $a = c = 0$), quadratic Eq (9) has only the trivial solution $\alpha_{1*} = 0$ (which corresponds to the DFE ε_0). This result is summarized below.

Lemma 3.3 Consider the case where the protection after recovery is perfect ($\delta_3 = 0$). Model (2) has a unique endemic equilibrium whenever $R_0' > 1$ and no endemic equilibrium otherwise.

3.4. Global stability of the DFE

Theorem 3.4 In the first quadrant, there is no limit cycle in model (2).

Proof We consider the Dulac function as $B(S,E) = \dfrac{1}{SE}$. Let

$$Q = E + \theta_1 H + \theta_2 P + \theta_3 I_1 + \theta_4 I_2 + \theta_5 I_3.$$

Hence $Q \geq E$ and $N \geq R$. Therefore,

$$\frac{MQ}{N} - \frac{MQR}{N^2} \geq 0, \quad \frac{EM}{E^2 N} - \frac{MQ}{E^2 N} \leq 0.$$

Then,

$$\Theta = \frac{\partial(BV)}{\partial V} + \frac{\partial(BS)}{\partial S} + \frac{\partial(BE)}{\partial E} + \frac{\partial(BH)}{\partial H} + \frac{\partial(BP)}{\partial P} + \frac{\partial(BI_1)}{\partial I_1} + \frac{\partial(BI_2)}{\partial I_2} + \frac{\partial(BI_3)}{\partial I_3} + \frac{\partial(BA)}{\partial A} + \frac{\partial(BR)}{\partial R}$$

$$= -\frac{a_1}{SE} - \frac{\Lambda + \delta_1 V}{S^2 E} + \frac{MQ}{EN^2} + \left[\frac{EM}{E^2 N} - \frac{MQ}{EN^2} - \frac{MQ}{E^2 N}\right] + \frac{\delta_3 R}{S}\left[\frac{EM}{E^2 N} - \frac{MQ}{EN^2} - \frac{MQ}{E^2 N}\right] - \frac{\sigma_2 H}{SE^2}$$

$$- \frac{a_4}{SE} - \frac{a_5}{SE} - \frac{a_5}{SE} - \frac{a_6}{SE} - \frac{a_7}{SE} - \frac{a_8}{SE} - \frac{a_9}{SE} - \frac{d}{SE} - \frac{\delta_3}{SE}\left(\frac{MQ}{N} - \frac{MQR}{N^2}\right)$$

$$< 0.$$

Therefore, by the Dulac−Bendixson theorem [29], there is no periodic orbit for model (2). Moreover, ε_0 is the unique positive equilibrium point in R_+^{10} if $\delta_3 = 0$, and it is also locally asymptotically stable for $R_0 < 1$. Hence, every positive solution actually approaches ε_0. Thus, ε_0 is globally asymptotically stable if $\delta_3 = 0$ and $R_0 < 1$.

4. Efficacy of interventions and sensitivity analysis

In this section, we performed a numerical simulation to enhance the understanding of model (2).

4.1. Efficacy of interventions

To examine the possible impact of interventions on disease infections we plot the number of infected individuals (E) with various vaccination rates and revaccination rates.

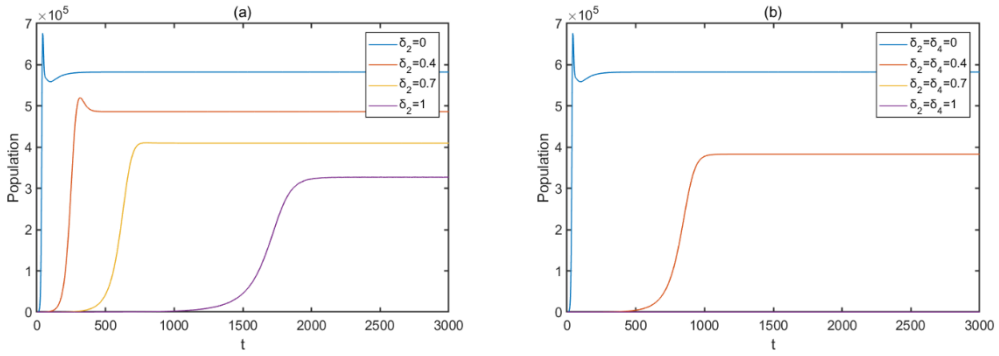

Figure 5. Variation in population E with different parameters (a) δ_2; (b) $\delta_2 + \delta_4$.

This analysis shows that an increasing vaccination rate persistently decreases the peak value, as shown in Figure 5. Increasing the vaccination rate δ_2 by 1.75 times (increase from 0.4 to 0.7) or 1.43 times (increased from 0.7 to 1) will lead to a reduction in the peak value in the number of E by 20.21% or by 15.67%, respectively. In addition, the peak value of the number of people infected with $\delta_2 = 1$ decreased by 43.82% compared with the number of people infected with $\delta_2 = 0$.

On the premise that the vaccine's protective effect will end after a few years, we consider the situation of vaccination and revaccination. Figure 5b indicates that increasing δ_2 and δ_4 from 0 to 0.4 will lead to a reduction in the peak value in the number of E by 34.16%. In addition, the peak value of the number of people infected with $\delta_2 = \delta_4 = 0.7$ decreased by 100% compared with the

number of people infected with $\delta_2 = \delta_4 = 0$.

4.2. Sensitivity analysis of R_0 to parameters

To identify the factors associated with a certain intervention that markedly affect the rate of new infections, we performed sensitivity analysis of the basic reproduction number.

LHS belongs to the MC class of sampling methods; it was introduced by Mckay et al. [30]. LHS allows an unbiased estimate of the average model output and has the advantage that it requires fewer samples than simple random sampling to achieve the same accuracy. For nonlinear but monotonic relationships between outputs and inputs, measures that work well are based on rank transforms such as the partial rank correlation coefficient, and standardized rank regression coefficient.

Model (2) has 39 parameters. To identify the key factors, following [30], we performed a Latin hypercube sampling on the parameters that appear in R_0 and calculated the PRCC. The parameters of the model were set as input variables, and R_0 was the output variable. Generally, in PRCC analysis, the parameters with large PRCC values and corresponding small p values are deemed to be the most influential parameters in the model.

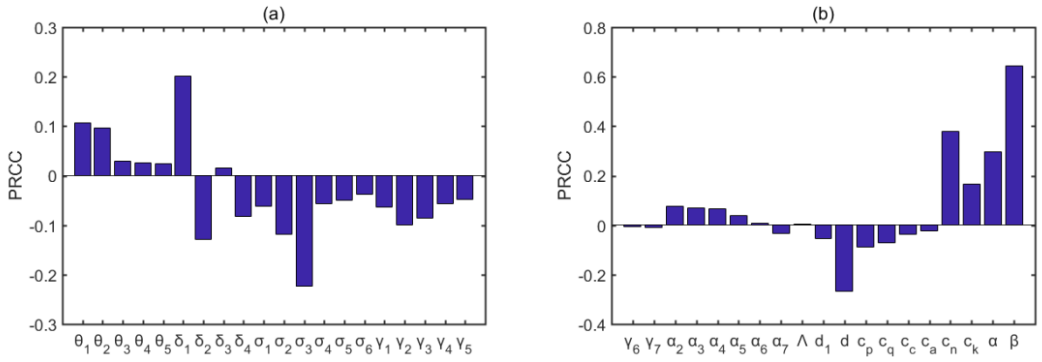

Figure 6. Significance test of model parameters and PRCC results for R_0.

Detailed inspection of Table C1 (Appendix C) and Figure 6 indicates that in terms of reducing the value of R_0, except σ_3 (control the disease and reduce the number of persistent infections) and d, the vaccination rate δ_2 is the most sensitive parameter with a leading PRCC value, followed by γ_2, γ_3, σ_2, δ_4. This implies that enhancing the vaccination rate is the most effective intervention for lowering HPV new infections. Moreover, in the treatment of patients in stages H, P, I_1, I_2 and I_3, the effect of treatments γ_2, γ_3, γ_4, γ_5 and γ_6 on R_0 decreases successively. That is, the same treatment intervention is more effective in the earlier stages. This means that more attention should be paid to patients in the early stages of infection. As asymptomatic patients are unable to diagnose themselves, regular screening for HPV should be strengthened. Smoking, overuse of contraceptive drugs, and unsafe sexual life will increase the value of R_0, thus promoting the spread of HPV.

5. Optimal control in an extended model

In this section, an optimal control model for the transmission dynamics of HPV is formulated by extending model (2) to include control functions. Our goal here is to study the optimal control strategies to curtail the epidemic and minimize cost.

5.1. An extended HPV model

The optimal vaccination and screening strategy can be formulated as the following optimal control problem (P) with inequality constraints and free terminal states defined over the prescribed interval $\left[0, t_f\right]$ [31]:

$$\min J = \int_0^{t_f} \left(C_1E^2 + C_2H^2 + C_3P^2 + C_4I_1^{\,2} + C_5I_2^{\,2} + C_6I_3^{\,2} + B_1u_1^2 + B_2u_2^2\right)dt,$$

s.t.

$$V' = u_1(t)S + \delta_4 S - \left(d + \delta_1\right)V,$$

$$S' = \Lambda + \delta_1 V - \left(u_1(t) + \delta_4 + \alpha_1 + d\right)S,$$

$$E' = \alpha_1 S + \delta_3\alpha_1 R + \sigma_2 H - \left(\alpha_2 + c_p u_2(t)\gamma_1\sigma_1 + d\right)E,$$

$$H' = \alpha_2 E + \sigma_3 P - \left(\sigma_2 + \gamma_2\sigma_2 + \alpha_3 + d\right)H,$$

$$P' = \alpha_3 H + \sigma_4 I_1 - \left(\alpha_4 + \gamma_3\sigma_3 + \sigma_3 + d\right)P,$$

$$I_1' = \alpha_4 P + \sigma_5 I_2 - \left(\alpha_5 + \gamma_4\sigma_4 + \sigma_4 + d\right)I_1, \tag{10}$$

$$I_2' = \alpha_5 I_1 + \sigma_6 I_3 - \left(\sigma_5 + \gamma_5\sigma_5 + \alpha_6 + d\right)I_2,$$

$$I_3' = \alpha_6 I_2 - \left(\sigma_6 + \gamma_6\sigma_6 + \alpha_7 + d\right)I_3,$$

$$A' = \alpha_7 I_3 - \left(\gamma_7 + d + d_1\right)A,$$

$$R' = c_p u_2(t)\gamma_1\sigma_1 E + \gamma_2\sigma_2 H + \gamma_3\sigma_3 P + \gamma_4\sigma_4 I_1 + \gamma_5\sigma_5 I_2 + \gamma_6\sigma_6 I_3 + \gamma_7 A - \left(\delta_3\alpha_1 + d\right)R,$$

$$V(0) = V_s,\ S(0) = S_s,\ E(0) = E_s,\ H(0) = H_s,\ P(0) = P_s,\ I_1(0) = I_{1s}, I_2(0) = I_{2s},\ I_3(0) = I_{3s},$$

$$A(0) = A_s,\ R(0) = R_s,$$

$$0 \le u_1(t) \le u_{1\max},\ 0 \le u_2(t) \le u_{2\max},$$

where $t_f \in R^+$ is the fixed terminal time, the coefficients C_1, C_2, C_3, C_4, C_5, C_6, B_1 and B_2 represent the corresponding weight constants, and these weights are balancing cost factors related to the size and importance of the parts of the objective function. The control function $u_1(t)$ is the fraction of the population of susceptible individuals who enters the vaccination compartment. The control function $u_2(t)$ is the fraction of the population of infectious individuals with no symptoms who undergo HPV screening, and they are Lebesgue integrable.

5.2. Characterization of optimal control

The inequality constraints in problem (P) can be transformed into equality ones with the help of

some non-negative parametric parameters, that is, $\eta_i\,(i=1,2,3,4)$, as

$$\begin{cases} -u_1+\eta_1=0, \\ u_1-u_{1\max}+\eta_2=0, \\ -u_2+\eta_3=0, \\ u_2-u_{2\max}+\eta_4=0. \end{cases} \tag{11}$$

Hence, the Hamiltonian function for problem (P) is obtained as follows:

$$\begin{aligned} H_\Delta &= C_1E^2+C_2H^2+C_3P^2+C_4I_1^{\,2}+C_5I_2^{\,2}+C_6I_3^{\,2}+B_1u_1^2+B_2u_2^2 \\ &+\lambda_V\left[u_1S+\delta_4S-(d+\delta_1)V\right]+\lambda_S\left[\Lambda+\delta_1V-(u_1+\delta_4+\alpha_1+d)S\right] \\ &+\lambda_E\left[\alpha_1S+\delta_3\alpha_1R+\sigma_2H-(\alpha_2+c_pu_2\gamma_1\sigma_1+d)E\right]+\lambda_H\left[\alpha_2E+\sigma_3P-(\sigma_2+\gamma_2\sigma_2+\alpha_3+d)H\right] \\ &+\lambda_{I_1}\left[\alpha_4P+\sigma_5I_2-(\alpha_5+\gamma_4\sigma_4+\sigma_4+d)I_1\right]+\lambda_{I_2}\left[\alpha_5I_1+\sigma_6I_3-(\sigma_5+\gamma_5\sigma_5+\alpha_6+d)I_2\right] \\ &+\lambda_{I_3}\left[\alpha_6I_2-(\sigma_6+\gamma_6\sigma_6+\alpha_7+d)I_3\right]+\lambda_A\left[\alpha_7I_3-(\gamma_7+d+d_1)A\right] \\ &+\lambda_R\left[c_pu_2\gamma_1\sigma_1E+\gamma_2\sigma_2H+\gamma_3\sigma_3P+\gamma_4\sigma_4I_1+\gamma_5\sigma_5I_2+\gamma_6\sigma_6I_3+\gamma_7A-(\delta_3\alpha_1+d)R\right] \\ &+\mu_1(-u_1+\eta_1)+\mu_2(u_1-u_{1\max}+\eta_2)+\mu_3(-u_2+\eta_3)+\mu_4(u_2-u_{2\max}+\eta_4), \end{aligned} \tag{12}$$

where $\lambda=\left[\lambda_V,\lambda_S,\lambda_E,\lambda_H,\lambda_P,\lambda_{I_1},\lambda_{I_2},\lambda_{I_3},\lambda_A,\lambda_R\right]^T$ are adjoint variables, and $\mu=\left[\mu_1,\mu_2,\mu_3,\mu_4\right]^T$ are non-negative penalty multipliers [32].

Theorem 5.1 There exists an optimal control $\left(u_1^*(t),u_2^*(t)\right)$ and corresponding solution V, S, E, H, P, I_1, I_2, I_3, A, and R that minimize $J\left(u_1(t),u_2(t)\right)$ over Ω. Furthermore, there exist adjoint functions λ_V, λ_S, λ_E, λ_H, λ_P, λ_{I_1}, λ_{I_2}, λ_{I_3}, λ_A and λ_R, such that

$$\lambda_V'=-\lambda_S\left(\delta_1+\frac{\alpha_1S}{N}\right)+\lambda_E\frac{\alpha_1S+\alpha_1\delta_3R}{N}+\lambda_Va_1-\lambda_R\frac{\alpha_1\delta_3R}{N},$$

$$\lambda_S'=\lambda_S\left(d+\alpha_1+\delta_4+u_1-\frac{\alpha_1S}{N}\right)+\lambda_E\left(\frac{\alpha_1S+\alpha_1\delta_3R}{N}-\alpha_1\right)-\lambda_R\frac{\alpha_1\delta_3R}{N}-\lambda_V(u_1+\delta_4),$$

$$\begin{aligned} \lambda_E' &= -2C_1E-\lambda_H\alpha_2+\lambda_E\left(a_3+\frac{\alpha_1S+\delta_3R-MS-MR\delta_3}{N}\right)+\lambda_S\frac{S(M-\alpha_1)}{N} \\ &\quad-\lambda_R\left(c_pu_2\gamma_1\sigma_1+\frac{\alpha_1\delta_3R-\alpha_1\delta_3}{N}\right), \end{aligned}$$

$$\begin{aligned} \lambda_H' &= -2C_2H-\lambda_P\alpha_3-\lambda_E\left(\sigma_2+\frac{MS\theta_1+MR\delta_3\theta_1-\alpha_1\delta_3R-\alpha_1S}{N}\right)+\lambda_Ha_4+\lambda_S\frac{S(M\theta_1-\alpha_1)}{N} \\ &\quad-\lambda_R\left(\gamma_2\sigma_2+\frac{\alpha_1\delta_3R-MR\delta_3\theta_1}{N}\right), \end{aligned}$$

$$\begin{aligned} \lambda_P' &= -2C_3P-\lambda_{I_1}\alpha_4-\lambda_H\sigma_3+\lambda_Pa_5-\lambda_E\left(\sigma_2+\frac{MS\theta_2+MR\delta_3\theta_2-\alpha_1\delta_3R-\alpha_1S}{N}\right) \\ &\quad+\lambda_S\frac{S(M\theta_2-\alpha_1)}{N}-\lambda_R\left(\gamma_3\sigma_3+\frac{\alpha_1\delta_3R-MR\delta_3\theta_2}{N}\right), \end{aligned}$$

$$\lambda_{I_1}' = -2C_4 I_1 - \lambda_{I_2}\alpha_5 - \lambda_P\sigma_4 + \lambda_S\frac{S\left(M\theta_3-\alpha_1\right)}{N} - \lambda_E\frac{MS\theta_3 + MR\delta_3\theta_3 - \alpha_1\delta_3 R - \alpha_1 S}{N}$$
$$+ \lambda_{I_1}a_6 - \lambda_R\left(\gamma_4\sigma_4 + \frac{\alpha_1\delta_3 R - MR\delta_3\theta_3}{N}\right),$$

$$\lambda_{I_2}' = -2C_5 I_2 - \lambda_{I_3}\alpha_6 - \lambda_{I_1}\sigma_5 + \lambda_{I_2}a_7 - \lambda_E\frac{MS\theta_4 + MR\delta_3\theta_4 - \alpha_1\delta_3 R - \alpha_1 S}{N}$$
$$- \lambda_R\left(\gamma_5\sigma_5 + \frac{\alpha_1\delta_3 R - MR\delta_3\theta_4}{N}\right) + \lambda_S\frac{S\left(M\theta_4-\alpha_1\right)}{N},$$

$$\lambda_{I_3}' = -2C_6 I_3 - \lambda_A\alpha_7 - \lambda_{I_2}\sigma_6 + \lambda_{I_3}a_8 - \lambda_E\frac{MS\theta_5 + MR\delta_3\theta_5 - \alpha_1\delta_3 R - \alpha_1 S}{N}$$
$$- \lambda_R\left(\gamma_6\sigma_6 + \frac{\alpha_1\delta_3 R - MR\delta_3\theta_5}{N}\right) + \lambda_S\frac{S\left(M\theta_5-\alpha_1\right)}{N},$$

$$\lambda_A' = -\lambda_R\left(\gamma_7 + \frac{\alpha_1\delta_3 R}{N}\right) + \lambda_E\frac{\alpha_1\delta_3 R + \alpha_1 S}{N} + \lambda_A a_9 - \lambda_S\frac{S\alpha_1}{N},$$

$$\lambda_R' = \lambda_R\left(d + \delta_3\alpha_1 - \frac{\alpha_1\delta_3 R}{N}\right) - \lambda_S\frac{S\alpha_1}{N} + \lambda_E\left(\frac{\alpha_1\delta_3 R + \alpha_1 S}{N} - \delta_3\alpha_1\right), \tag{13}$$

with transversality conditions

$$\lambda_V\left(t_f\right) = \lambda_S\left(t_f\right) = \text{L} = \lambda_A\left(t_f\right) = \lambda_R\left(t_f\right) = 0. \tag{14}$$

The following characterization holds

$$\begin{cases} u_1^*(t) = \max\left\{0, \min\left\{\dfrac{S\left(\lambda_S - \lambda_V\right)}{2B_1}, u_{1\max}\right\}\right\}, \\ u_2^*(t) = \max\left\{0, \min\left\{\dfrac{Ec_p\gamma_1\sigma_1\left(\lambda_E - \lambda_R\right)}{2B_2}, u_{2\max}\right\}\right\}. \end{cases} \tag{15}$$

Proof. The existence of an optimal control can be obtained owing to the convexity of the integrand of $J\left(u_1(t), u_2(t)\right)$ with respect to $\left(u_1(t), u_2(t)\right)$ [33], a priori boundedness of the state solutions, and the Lipschitz property of the state system with respect to the state variables.

By Pontryagin's maximum principle [34], the optimal conditions with respect to the state, costate, and parametric variables result in a two-point boundary value problem coupled with a nonlinear complementarity problem as follows:

$$\lambda_V{}' = -\frac{\partial H_\Delta}{\partial V},\ \lambda_S' = -\frac{\partial H_\Delta}{\partial S},\ \text{L},\ \lambda_A' = -\frac{\partial H_\Delta}{\partial A},\ \lambda_R' = -\frac{\partial H_\Delta}{\partial R}, \tag{16}$$

and

$$\lambda_V\left(t_f\right) = \lambda_S\left(t_f\right) = \text{L} = \lambda_A\left(t_f\right) = \lambda_R\left(t_f\right) = 0,$$

evaluated at the optimal control and corresponding states results in the stated adjoint system (13) with transversality (14).

The optimality conditions with respect to the control variables are

$$\frac{\partial H_\Delta}{\partial u_1}=0,\ \frac{\partial H_\Delta}{\partial u_2}=0. \tag{17}$$

By solving Eq (17), the optimal control can be expressed as

$$u_1^*(t)=\frac{S(\lambda_S-\lambda_V)+\mu_1-\mu_2}{2B_1}.$$

To determine an explicit expression of the optimal control without μ_1, we consider the following three cases:

i. On the set $\left\{t\middle|0<u_1^*<u_{1\max}\right\}$, we have $\mu_1=\mu_2=0$. Hence, $u_1^*(t)=\frac{S(\lambda_S-\lambda_V)}{2B_1}$.

ii. On the set $\left\{t\middle|u_1^*=u_{1\max}\right\}$, we have $\mu_2=0$. Hence, $u_1^*(t)=u_{1\max}=\frac{S(\lambda_S-\lambda_V)+\mu_1}{2B_1}$. As $\mu_1\geq 0$, it is determined that $u_{1\max}\geq\frac{S(\lambda_S-\lambda_V)}{2B_1}$.

iii. On the set $\left\{t\middle|u_1^*=0\right\}$, we have $\mu_1=0$. Hence, $u_1^*(t)=0=\frac{S(\lambda_S-\lambda_V)-\mu_2}{2B_1}$. As $\mu_2\geq 0$, it is determined that $\frac{S(\lambda_S-\lambda_V)}{2B_1}\geq 0$.

Combining the above three cases, the optimal control u_1^* is characterized as

$$u_1^*(t)=\max\left\{0,\min\left\{\frac{S(\lambda_S-\lambda_V)}{2B_1},u_{1\max}\right\}\right\}. \tag{18}$$

Using similar arguments, we can characterize the optimal control u_2^* as

$$u_2^*(t)=\max\left\{0,\min\left\{\frac{Ec_p\gamma_1\sigma_1(\lambda_E-\lambda_R)}{2B_2},u_{2\max}\right\}\right\}. \tag{19}$$

5.3. Numerical simulations

An analytical expression of the optimal vaccination rate and screening rate was derived in Eq (15). However, an effective algorithm is still required to solve the nonlinear constrained optimal control problem numerically. Based on the generating function method, Peng et al. developed a series of symplectic methods for nonlinear optimal control problems [35−38]. Such symplectic methods have good precision and efficiency because of the structure-preserved property. Recently, Wang et al. improved the symplectic methods by incorporating the local pseudospectral discretization scheme [39−42]. Such symplectic pseudospectral methods (SPMs) have been successfully applied to solve optimal control problems in various mechanical systems [43−44]. In this paper, the SPM developed in [45] was adopted.

In the following simulation, the weights in the objective function (meaning the minimization of

the number of patients at each stage has different importance) are $C_1 = 4.5e-2$, $C_2 = 1e-7$, $C_3 = 1e-4$, $C_4 = 1e-5$, $C_5 = 2e-4$, and $C_6 = 1e-4$. Let $M = 1$. The initial values for the states and other parameters are listed in Table 4. Unless otherwise stated, the parameters used in each case were as listed in Table 3.

Table 4. Parameter values used in Figure 7.

Parameter	Value	Parameter	Value
V_s	3.2607*e*6	I_{2s}	4.15*e*4
S_s	3.2212*e*5	I_{3s}	1.68*e*4
E_s	4.2204*e*4	A_s	1.29*e*3
H_s	1.1162*e*7	R_s	6.3*e*3
P_s	4*e*4	t_f	50
I_{1s}	1.15*e*5	$u_{1\max}$	1
$u_{2\max}$	2		

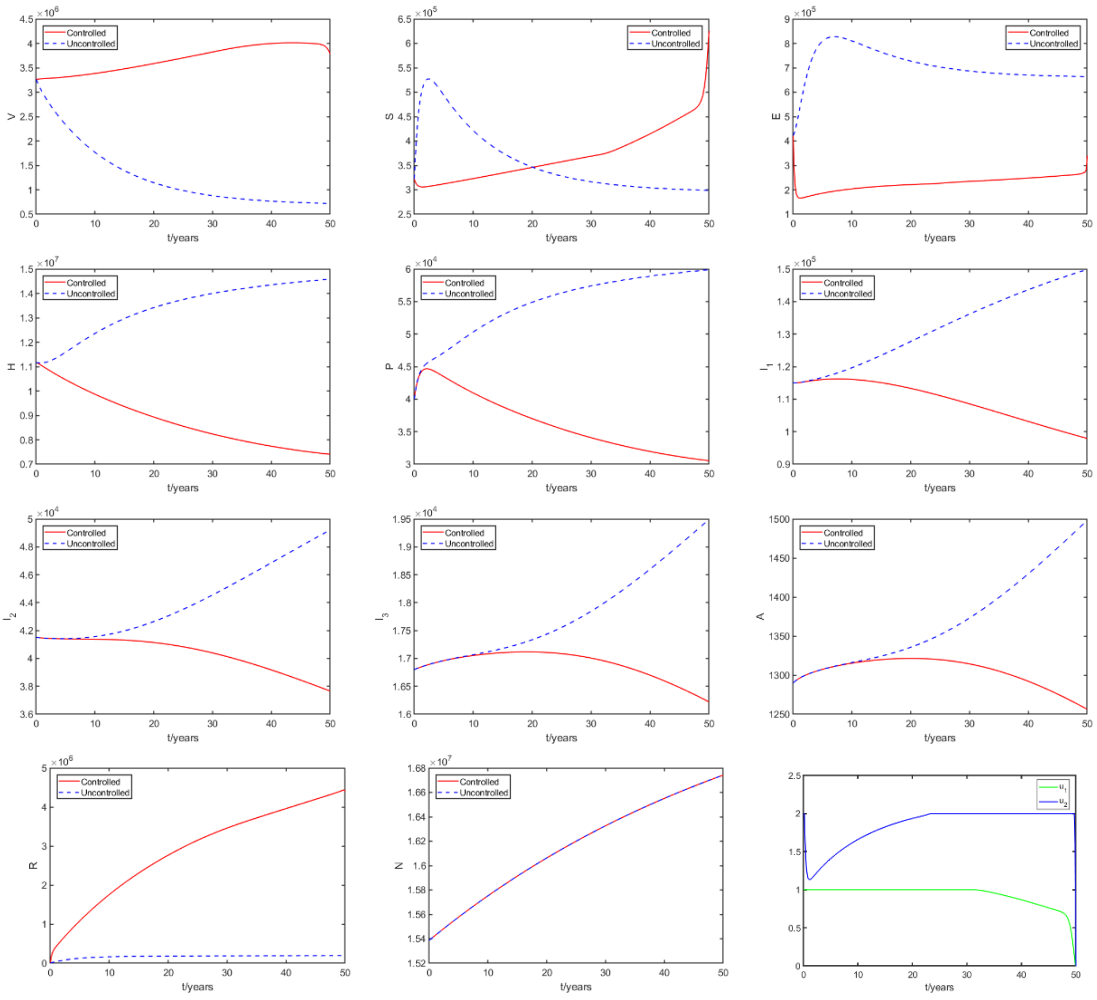

Figure 7. Simulations of model (2). Dashed lines: Populations with optimal control. Solid lines: Populations without control. Parameter values are $B_1 = 8.3e8$ and $B_2 = 4e8$.

The controlled solutions together with the solutions for the uncontrolled case are presented in Figure 7. It can be seen that the control strategy is effective. Vaccinated individuals increase steadily and reach almost 400% at the terminal end. Susceptible individuals keep increasing and then stabilize during the whole period. The number of infected individuals decreases significantly when optimal control strategies are used compared to the number in the absence of control strategies.

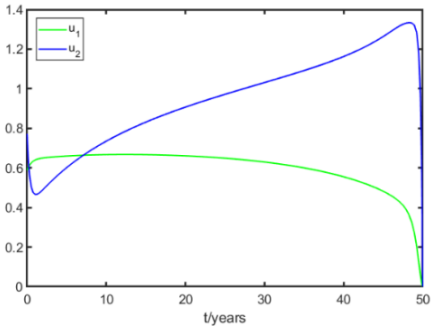

Figure 8. The different strategies of $u_1(t)$ and $u_2(t)$ are plotted for $B_1 = 4e9$ and $B_2 = 3e9$. Other parameter values are the same as those in Figure 7.

We considered another set of weights, the simulation results are shown in Figure 8. A higher focus on the control strategies leads to a drop in the importance of the vaccination and screening strategies. As the number of asymptomatic individuals depends on the immunity of the susceptible individuals and the protection of the susceptible population, we should consider strengthening their immunity or implement regular cost-effective screening to control HPV transmission.

6. Conclusions

The human papillomavirus is among the most common sexually transmitted infections. Following infection, cervical carcinogenesis is a complex stepwise process characterized by slow progression. According to the known pathology, we represented the CIN stages with three corresponding components in the model. Our model accounted for the fact that preventive vaccines become ineffective over time. We derived three types of equilibria and their conditions of existence, analyzed the stability of the equilibria, and characterized the threshold condition as backward bifurcation for the stable fixed points. We also obtained the conditions for the elimination of the disease. We found that the possibility of HPV transmission to lead to endemic disease can be reduced by strengthening the protection after cure. We then simulated and compared practical mitigation strategies and performed sensitivity analysis to illustrate the key factors for the threshold condition. The results show that increasing the vaccination rate is the most effective way to reduce the basic reproduction number. The effect of optimal control was illustrated numerically, and a comparison of HPV infection was presented under different control strategies.

Acknowledgements

This work was supported by the Fundamental Research Funds for the Central Universities (31920200037; 31920200070), the Research Fund for Humanities and Social Sciences of the

Ministry of Education(20XJAZH006), the Program for Young Talent of State Ethnic Affairs Commission of China (No. [2014]121), the Innovation Team of Intelligent Computing and Dynamical System Analysis and Application.

Conflict of interest

The authors declare that no conflict of interest.

References

1. M. Arbyn, X. Castellsagué, S. de Sanjosé, L. Bruni, M. Saraiya, F. Bray, et al, Worldwide burden of cervical cancer in 2008, *Ann. Oncol. Circuits*, **22** (2011), 2675–2686.
2. G. Bogani, U. L. R. Maggiore, M. Signorelli, F. Martinelli, A. Ditto, I. Sabatucci, et al, The role of human papillomavirus vaccines in cervical cancer: Prevention and treatment, *Crit. Rev. Oncol. Hemat.*, **122** (2018), 92–97.
3. J. K. Oh, E. Weiderpass, Infection and cancer: Global distribution and burden of diseases, *Ann. Glob. Health*, **80** (2014), 384–392.
4. D. M. Parkin, F. Bray, J. Ferlay, P. Pisani, Estimating the world cancer burden: Globocan 2000, *Int. J. Cancer*, **94** (2001), 153–156.
5. D. M. Parkin, F. Bray, J. Ferlay, P. Pisani, Global cancer statistics, 2002, *Ca-Cancer J. Clin.*, **55** (2005), 74–108.
6. D. M. Parkin, F. Bray, The burden of HPV-related cancers, *Vaccine*, **24** (2005), S11–S25.
7. G. Hancock, K. Hellner, L. Dorrell, Therapeutic HPV vaccines, *Best Prcat. Res .Cl. Ob.*, **47** (2018), 59–72.
8. K. Miura, H. Mishima, A. Kinoshita, C. Hayashida, S. Abe, K. Tokunaga, et al, Genome-wide association study of HPV−associated cervical cancer in Japanese women, *J. Med. Virol.*, **86** (2014), 1153–1158.
9. E. L. Franco, E. Duarte-Franco, A. Ferenczy, Cervical cancer: epidemiology, prevention and the role of human papillomavirus infection, *Cmaj*, **164** (2001), 1017–1025.
10. International Agency for Research on Cancer Working Group, Human papillomaviruses, *IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans*, Lyon, 1995.
11. T. Malik, J. Reimer, A. Gumel, E. Elbasha, S. Mahmud, The impact of an imperfect vaccine and pap cytology screening on the transmission of human papillomavirus and occurrence of associated cervical dysplasia and cancer, *Math. Biosci. Eng.*, **10** (2013), 1173–1205.
12. L. A. Denny, Jr. T. C. Wright, Human papillomavirus testing and screening, *Best Prcat. Res. Cl. Ob.*, **19** (2005), 501–515.
13. T. G. Harris, R. D. Burk, J. M. Palefsky, L. S. Massad, J. Bang, K. Anastos, et al, Incidence of cervical squamous intraepithelial lesions associated with HIV serostatus, CD4 cell counts, and human papillomavirus test results, *Jama*, **293** (2005), 1471–1476.
14. M. Schiffman, P. Castle, J. Jeronimo, A. C. Rodriguez, S. Wacholder, Human papillomavirus and cervical cancer, *Lancet*, **370** (2000), 890–907.
15. R. L. Winer, J. P. Hughes, Q. Feng, S. O'Reilly, N. B. Kiviat, K. K. Holmes, et al, Condom use and the risk of genital human papillomavirus infection in young women, *New Engl. J. Med.*, **354** (2006), 2645–2654.

16. International Collaboration of Epidemiological Studies of Cervical Cancer, Carcinoma of the cervix and tobacco smoking: Collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies, *Int. J. Cancer*, **118** (2006), 1481–1495.
17. International Collaboration of Epidemiological Studies of Cervical Cancer, Cervical carcinoma and reproductive factors: Collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies, *Int. J. Cancer*, **119** (2006), 1108–1124.
18. J. S. Smith, J. Green, A. B. de. Gonzalez, P. Appleby, P. J. Peto, M. Plummer, et al, Cervical cancer and use of hormonal contraceptives: a systematic review, *Lancet*, **361** (2003), 1159–1167.
19. D. Saslow, D. Solomon, H. W. Lawson, M. Killackey, S. L. Kulasingam, J. Cain, 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, *Ca-Cancer J. Clin.*, **62** (2012), 147–172.
20. M. Al-arydah, R. Smith, An age-structured model of human papillomavirus vaccination, *Math. Comput. Simulat.*, **82** (2011), 629–652.
21. O. Sharomi, T. Malik, A model to assess the effect of vaccine compliance on Human Papillomavirus infection and cervical cancer, *Appl. Math. Model*, **47** (2017), 528–550.
22. A. Omame, R. A. Umana, D. Okuonghae, S. C. Inyama, Mathematical analysis of a two-sex Human Papillomavirus (HPV) model, *Int. J. Biomath.*, **11** (2018), 1850092.
23. E. H. Elbasha, Global stability of equilibria in a two-sex HPV vaccination model, *B Math. Biol.*, **70** (2008), 894.
24. E. H. Elbasha, Impact of prophylactic vaccination against human papillomavirus infection, *Contemp. Math.*, **410** (2006), 113–128.
25. Z. Qu, L. Xue, J. M. Hyman, Modeling the transmission of Wolbachia in mosquitoes for controlling mosquito-borne diseases, *SIAM J. Appl. Math.*, **78** (2018), 826–852.
26. O. Sharomi, C. N. Podder, A. B. Gumel, S. M. Mahmud, E. Rubinstein, Modelling the transmission dynamics and control of the novel 2009 swine influenza (H1N1) pandemic, *B Math. Biol.*, **73** (2011), 515–548.
27. H. W. Hethcote, The mathematics of infectious diseases, *SIAM Review*, **42** (2000), 599–653.
28. P. Van den Driessche, J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, *Math. Biosci.*, **180** (2002), 29–48.
29. L. Perko, *Differential Equations and Dynamical Systems*, Springer, New York, 1996.
30. S. M. Blower, H. Dowlatabadi, Sensitivity and uncertainty analysis of complex models of disease transmission: an HIV model, as an example, *Int. Stat. Rev.*, **62** (1994), 229–243.
31. M. H. A. Biswas, L. T. Paiva, M. D. R. De Pinho, A SEIR model for control of infectious diseases with constraints, *Math. Biosci. Eng.*, **11** (2014), 761–784.
32. X. Wang, H. Peng, B. Shi, D. Jiang, S. Zhang, B. Chen, Optimal vaccination strategy of a constrained time-varying SEIR epidemic model, *Commun. Nonlinear SCI*, **67** (2019), 37–48.
33. W. H. Fleming, R. W. Rishel, *Deterministic and stochastic optimal control*, Springer Verlag, New York, 1975.
34. R. Bellman, L. S. Pontryagin, V. G. Boltyanskii, R. V. Gamkrelidze, E. F. Mischenko, The mathematical theory of optimal processes, *Math. Comput.*, **19** (1965), 159.

35. H. Peng, Q. Gao, Z. Wu, W. Zhong, Symplectic approaches for solving two-point boundary-value problems, *J. Guid. Control. Dynam.*, **35** (2012), 653–658.
36. M. Li, H. Peng, W. Zhong, A symplectic sequence iteration approach for nonlinear optimal control problems with state-control constraints, *J. Franklin I*, **352** (2015), 2381–2406.
37. H. Peng, Q. Gao, Z. Wu, W. Zhong, Efficient sparse approach for solving receding-horizon control problems, *J. Guid. Control. Dynam.*, **36** (2013), 1864–1872.
38. H. Peng, Q. Gao, Z. Wu, W. Zhong, Symplectic adaptive algorithm for solving nonlinear two-point boundary value problems in astrodynamics, *Celest Mech. Dyn. Astr.*, **110** (2011), 319–342.
39. X. Wang, H. Peng, S. Zhang, B. Chen, W. Zhong, A symplectic pseudospectral method for nonlinear optimal control problems with inequality constraints, *ISA T*, **68** (2017), 335–352.
40. H. Peng, X. Wang, M. Li, B. Chen, An hp symplectic pseudospectral method for nonlinear optimal control, *Commun. Nonlinear. Sci.*, **42** (2017), 623–644.
41. X. Wang, H. Peng, S. Zhang, B. Chen, W. Zhong, A symplectic local pseudospectral method for solving nonlinear state-delayed optimal control problems with inequality constraints, *Int. J. Robust Nonlinear Control*, **28** (2018), 2097–2120.
42. X. Wang, J. Liu, X. Dong, C. Li, Y. Zhang, A symplectic pseudospectral method for constrained time-delayed optimal control problems and its application to biological control problems, *Optimization*, 2020.
43. J. Liu, W. Han, X. Wang, J. Li, Research on cooperative trajectory planning and tracking problem for multiple carrier aircraft on the deck, *IEEE Syst.*, **14** (2020), 3027–3038.
44. X. Wang, J. Liu, Y. Zhang, B. Shi, D. Jiang, H. Peng, A unified symplectic pseudospectral method for motion planning and tracking control of 3D underactuated overhead cranes, *Int. J. Robust Nonlinear Control*, **29** (2019), 2236–2253.
45. H. Peng, X. Wang, B. Shi, S. Zhang, B. Chen, Stabilizing constrained chaotic system using a symplectic psuedospectral method, *Commun. Nonlinear SCI*, **56** (2018), 77–92.
46. J. Carr, *Applications of Centre Manifold Theory*, Springer Science & Business Media, 2012.
47. C. Castillo-Chavez, B. Song, Dynamical models of tuberculosis and their applications, *Math. Biosci. Eng.*, **1** (2004), 361–404.

Appendix A

Table A1. A detailed explanation of Theorem 3.2.

a	c	b	Results
$a>0$	$c>0$	$b>0$	Two negative points
		$b=0$	No equilibrium points
		$b<0$	Two endemic equilibria if $b^2-4ac>0$
	$c=0$	$b>0$	A negative point and a DFE
		$b=0$	Two DFE
		$b<0$	A DFE and an EEP (or $b^2-4ac=0$)
	$c<0$	$b>0$	A negative point and an EEP
		$b=0$	A negative point and an EEP
		$b<0$	A negative point and an EEP

Appendix B

Here, we explore the existence of backward bifurcation using the center manifold theory [46−47]. To apply this theory, it is necessary to carry out the following change of variables.

Let $E = x_1$, $H = x_2$, $P = x_3$, $I_3 = x_4$, $I_2 = x_5$, $I_1 = x_6$, $A = x_7$, $R = x_8$, $S = x_9$, $V = x_{10}$, so that

$$N = \sum_{i=1}^{10} x_i .$$

Further, using the vector notation

$$X_1 = \left(x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9, x_{10}\right)^T .$$

Model (2) can be rewritten in the form

$$\frac{dX_1}{dt} = F = \left(f_1,\ f_2,\ f_3,\ f_4,\ f_5,\ f_6, f_7, f_8, f_9, f_{10}\right)^T ,$$

as follows:

$$\begin{cases}
\frac{dx_1}{dt} = \alpha_1(t)x_9(t) + \delta_3\alpha_1(t)x_7(t) + \sigma_2 x_3(t) - \left(\alpha_2 + c_p c_q \gamma_1 \sigma_1 + d\right)x_1(t), \\
\frac{dx_2}{dt} = \alpha_2 x_1(t) + \sigma_3 x_3(t) - \left(\sigma_2 + \gamma_2\sigma_2 + \alpha_3 + d\right)x_2(t), \\
\frac{dx_3}{dt} = \alpha_3 x_2(t) + \sigma_4 x_6(t) - \left(\alpha_4 + \gamma_3\sigma_3 + \sigma_3 + d\right)x_3(t), \\
\frac{dx_4}{dt} = \alpha_6 x_5(t) - \left(\sigma_6 + \gamma_6\sigma_6 + \alpha_7 + d\right)x_4(t), \\
\frac{dx_5}{dt} = \alpha_5 x_6 + \sigma_6 x_4(t) - \left(\sigma_5 + \gamma_5\sigma_5 + \alpha_6 + d\right)x_5(t), \\
\frac{dx_6}{dt} = \alpha_4 x_3(t) + \sigma_5 x_5(t) - \left(\alpha_5 + \gamma_4\sigma_4 + \sigma_4 + d\right)x_6(t), \\
\frac{dx_7}{dt} = \alpha_7 x_4(t) - \left(\gamma_7 + d + d_1\right)x_7(t), \\
\frac{dx_8}{dt} = c_p c_q \gamma_1 \sigma_1 x_1(t) + \gamma_2\sigma_2 x_2(t) + \gamma_3\sigma_3 x_3(t) + \gamma_4\sigma_4 x_5(t) + \gamma_5\sigma_5 x_5(t) + \gamma_6\sigma_6 x_4(t) + \gamma_7 x_7(t) \\
\qquad - \left(\delta_3\alpha_1(t) + d\right)x_8(t), \\
\frac{dx_9}{dt} = \Lambda + \delta_1 x_{10}(t) - \left(\delta_2 + \delta_4 + \alpha_1(t) + d\right)x_9(t), \\
\frac{dx_{10}}{dt} = \delta_2 x_9(t) + \delta_4 x_9(t) - \left(d + \delta_1\right)x_{10}(t),
\end{cases} \tag{B.1}$$

with

$$\alpha_1(t) = \frac{\beta\alpha c_n c_k \left(1 - c_c c_a\right)\left(x_1 + \theta_1 x_2 + \theta_2 x_3 + \theta_3 x_6 + \theta_4 x_5 + \theta_5 x_4\right)}{N} .$$

Consider the case when R_0=1. Suppose, further, that δ_2 is chosen as a bifurcation parameter.

Solving for $\delta_2 = \delta_{2^*}$ from R_0 gives

$$\delta_{2^*} = \frac{a_1 MM_1}{\left(a_3 D_6 - \sigma_2 D_5\right)} - a_1 - \delta_4 .$$

The Jacobian of model (B.1) evaluated at the DFE is given as

$$J\left(\varepsilon_0\right) = \begin{bmatrix} J_{11} & J_{12} \\ J_{21} & J_{22} \end{bmatrix},$$

where

$$J_{11} = \begin{bmatrix} a_{10} - a_3 & a_{10}\theta_1 + \sigma_2 & a_{10}\theta_2 & a_{10}\theta_5 & a_{10}\theta_4 & a_{10}\theta_3 \\ \alpha_2 & -a_4 & \sigma_3 & 0 & 0 & 0 \\ 0 & \alpha_3 & -a_5 & 0 & 0 & \sigma_4 \\ 0 & 0 & 0 & -a_8 & \alpha_6 & 0 \\ 0 & 0 & 0 & \sigma_6 & -a_7 & \alpha_5 \\ 0 & 0 & \alpha_4 & 0 & \sigma_5 & -a_6 \end{bmatrix}, \quad J_{12} = \left[0\right]_{6\times 4},$$

$$J_{21} = \begin{bmatrix} 0 & 0 & 0 & \alpha_7 & 0 & 0 \\ c_p c_q \gamma_1 \sigma_1 & \gamma_2 \sigma_2 & \gamma_3 \sigma_3 & \gamma_6 \sigma_6 & \gamma_5 \sigma_5 & \gamma_4 \sigma_4 \\ -a_{10} & 0 & -a_{10}\theta_1 & -a_{10}\theta_4 & -a_{10}\theta_3 & -a_{10}\theta_2 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$J_{22} = \begin{bmatrix} -a_9 & 0 & 0 & 0 \\ \gamma_7 & -d & 0 & 0 \\ 0 & 0 & -a_2 & \delta_1 \\ 0 & 0 & \delta_2 + \delta_4 & -a_1 \end{bmatrix}.$$

It is easy to verify that the transformed model (B.1), with $\delta_2 = \delta_{2^*}$, has a hyperbolic equilibrium point (i.e., the linearized system has a simple eigenvalue with zero real part, and all other eigenvalues have negative real parts). Hence, the center manifold theory can be used to analyse the dynamics of model (B.1) near $\delta_2 = \delta_{2^*}$.

It can be shown that the Jacobian of model (B.1) at $\delta_2 = \delta_{2^*}$ has a right eigenvector (associated with the zero eigenvalue) given by $w = \left(w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9, w_{10}\right)^T$, where

$$w_1 = \frac{a_4 D_5 - \sigma_3 D_4}{\alpha_2} w_4 = D_6 w_4 > 0, \quad w_2 = \frac{a_5 D_4 - \sigma_4 D_3}{\alpha_3} w_4 = D_5 w_4 > 0,$$

$$w_3 = \frac{a_6 D_3 - \sigma_5 D_2}{\alpha_4} w_4 = D_4 w_4 > 0, \quad w_4 = w_4 > 0, \quad w_5 = \frac{a_8}{\alpha_6} w_4 = D_2 w_4 > 0,$$

$$w_6=\frac{a_7D_2-\sigma_6}{\alpha_5}w_4=D_3w_4>0,\ \ w_7=\frac{\alpha_7}{a_9}w_4=D_1w_4>0,$$

$$w_8=\frac{c_pc_q\gamma_1\sigma_1D_6+\gamma_2\sigma_2D_5+\gamma_3\sigma_3D_4+\gamma_6\sigma_6+\gamma_5\sigma_5D_2+\gamma_4\sigma_4D_3+\gamma_7D_1}{d}w_4>0,$$

$$w_9=\frac{a_1}{\delta_2+\delta_4}w_{10}=G_1G_2w_4=G_3w_4,\ \ w_{10}=\frac{\sigma_2D_5-a_3D_6}{a_2G_1-\delta_1}w_4=G_2w_4.$$

The components of the left eigenvector of $J_{\varepsilon_0}\big|_{\delta_2=\delta_{2^*}}$, $v=(v_1,v_2,v_3,v_4,v_5,v_6,v_7,v_8,v_9,v_{10})$, satisfying $v\cdot w=1$ are

$$v_1>0,\ \ v_2=\frac{a_3}{\alpha_2}v_1,\ \ v_3=\frac{a_3a_4-\alpha_2\sigma_2}{\alpha_2\alpha_3}v_1>0,\ \ v_4=\frac{\sigma_6}{a_8}v_5,$$

$$v_5=\frac{a_3a_4a_5a_6-a_5a_6\sigma_2\alpha_2-a_3a_6\sigma_3\alpha_3-a_3a_4\sigma_4\alpha_4+\sigma_4\alpha_4\sigma_2\alpha_2}{\alpha_2\alpha_3\alpha_4\alpha_5}>0,$$

$$v_6=\frac{a_3a_4a_5-a_5\sigma_2\alpha_2-a_3\sigma_3\alpha_3}{\alpha_2\alpha_3\alpha_4}>0,\ \ v_7=v_8=0,\ \ v_9=v_1,\ \ v_{10}=\frac{\delta_1}{a_1}v_1.$$

It follows from [26]:

$$a=\sum_{k,i,j=1}^{10}v_k\omega_i\omega_j\frac{\partial^2f_k}{\partial x_i\partial x_j}(0,0),\ \ b=\sum_{k,i=1}^{10}v_k\omega_i\frac{\partial^2f_k}{\partial x_i\partial\delta_{2^*}}(0,0),$$

are computed to be

$$\begin{aligned}a&=\sum_{k,i,j=1}^{10}v_kw_iw_j\frac{\partial^2f_k}{\partial x_i\partial x_j}(0,0)\\&=\frac{2v_1w_8M\delta_3}{S^0+V^0}\left(w_1+\theta_1w_2+\theta_2w_3+\theta_5w_4+\theta_3w_6\right)\\&>0,\end{aligned}\tag{B.2}$$

$$\begin{aligned}b&=\sum_{k,i=1}^{10}v_kw_i\frac{\partial^2f_k}{\partial x_i\partial\delta_{2^*}}(0,0)\\&=v_9w_9\frac{\partial^2f_9}{\partial x_9\partial\delta_{2^*}}(0,0)+v_{10}w_9\frac{\partial^2f_{10}}{\partial x_9\partial\delta_{2^*}}(0,0)\\&=-v_1\frac{\sigma_2D_5-a_3D_6}{a_2G_1-\delta_1}\times\frac{a_1}{\delta_2+\delta_4}w_4+\frac{\delta_1}{a_1}v_1\frac{\sigma_2D_5-a_3D_6}{a_2G_1-\delta_1}\times\frac{a_1}{\delta_2+\delta_4}w_4\\&=\left(\frac{\delta_1}{a_1}-1\right)v_1\frac{\sigma_2D_5-a_3D_6}{a_2\left(\dfrac{a_1}{\delta_2+\delta_4}\right)-\delta_1}\times\frac{a_1}{\delta_2+\delta_4}w_4\\&>0.\end{aligned}\tag{B.3}$$

Thus, we have made the following conclusions

Theorem A.1 Model (B.1) (or, equivalently, model (2)) undergoes a backward bifurcation at $R_0 = 1$ if all parameters are positive.

Appendix C

Table C1. PRCC values of R_0 with corresponding values of p (significant for $p \leq 0.01$).

Parameter	PRCC	p values
θ_1	0.1079	1.3332e-06
θ_2	0.0619	0.0056
θ_3	0.0375	0.0939
θ_4	0.0363	0.1050
θ_5	0.0130	0.5625
δ_1	0.2219	1.0079e-23
δ_2	−0.0972	1.3420e-05
δ_3	0.0139	0.5334
δ_4	−0.0503	0.0246
σ_1	−0.0474	0.0342
σ_2	−0.0907	4.8958e-05
σ_3	−0.1749	3.3636e-15
σ_4	−0.0631	0.0047
σ_5	−0.0038	0.8662
σ_6	0.0162	0.4703
γ_1	−0.0491	0.0280
γ_2	−0.1101	7.9369e-07
γ_3	−0.1100	8.1799e-07
γ_4	−0.0857	0.0001
γ_5	−0.0117	0.6015
γ_6	−0.0179	0.4227
γ_7	−0.0254	0.2562
α_2	0.1070	1.6317e-06
α_3	0.0391	0.0806
α_4	0.0389	0.0823
α_5	0.0347	0.1209
α_6	−0.0100	0.6578

Continued on next page

Parameter	PRCC	p values
α_7	−0.0331	0.1389
Λ	0.0106	0.6363
d_1	0.0018	0.9352
d	−0.2728	1.7789e-35
c_p	−0.1683	3.5473e-14
c_q	−0.1044	2.9039e-06
c_c	−0.0685	0.0022
c_a	−0.0648	0.0037
c_n	0.3778	7.0664e-69
c_k	0.2383	3.1497e-27
α	0.2481	1.9591e-29
β	0.6344	1.0688e-225

AIMS Press