

Within-host HPV-immune dynamics with epithelial turnover and downstream cervical disease burden: invasion, Hopf bifurcation, and intervention modelling

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Research Article

Keywords: Human papillomavirus, within-host dynamics, epithelial turnover, cervical precancer, Hopf bifurcation, immune response, optimal control

Posted Date: October 20th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11414350/v1>

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Additional Declarations: No competing interests reported.

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Abstract

We formulate a deterministic within-host model for high-risk human papillomavirus (HPV) infection, epithelial renewal, cellular immunity, precancerous epithelial burden, and downstream cervical-cancer burden. Susceptible, infected, and precancerous epithelial states share a normalised tissue-capacity constraint, while cancer is represented as a downstream progression/removal compartment rather than an autonomous tumour-growth subsystem. This keeps the long-term disease module deliberately simple and avoids introducing an unsupported malignant-establishment threshold. We prove positivity and boundedness, identify the infection-free, epithelial-depleted infected-boundary, and positive coexistence equilibria, and derive an HPV invasion threshold that includes both infected-cell division and viral-load-mediated infection. Because cancer does not feed back into the epithelial–viral–lesion–immune subsystem, local oscillatory stability is governed by a five-dimensional core, while the cancer direction is automatically stable for positive removal. For an explicitly illustrative, non-calibrated benchmark, numerical continuation gives a simple Hopf point at $\mu_V \approx \mathbf{0.08722}$, with nonzero transversality and negative first Lyapunov coefficient under the stated convention. Long integrations confirm a stable periodic attractor on the unstable side of the crossing, although convergence is exceptionally slow. We also derive Pontryagin necessary conditions for therapeutic immune stimulation, screen-linked lesion treatment, and cancer therapy. The benchmark is intended for mathematical demonstration only; quantitative biological calibration, particularly of epithelial proliferation and immune/viral parameters, remains necessary before clinical interpretation.

Keywords: Human papillomavirus; within-host dynamics; epithelial turnover; cervical precancer; Hopf bifurcation; immune response; optimal control.

1 Introduction

Human papillomavirus (HPV) infection is one of the most common viral infections of the anogenital tract and is the necessary causal factor for the great majority of cervical cancers [1, 2]. Although most HPV infections are transient and are cleared by the host immune system, a subset persists within the cervical epithelium and may progressively give rise to precancerous abnormalities and, in a smaller proportion of cases, invasive cervical cancer [3]. This natural history encompasses processes operating on markedly different time scales. Viral replication, epithelial turnover, and local immune responses may evolve over days to months, whereas the establishment of persistent lesions and their progression towards invasive disease generally occur over years [4].

The various stages of HPV-related disease create separate possibilities for prevention and treatment [5]. Vaccination against HPV prevents new infection but does not remove an existing one [6].

In case of an infection, the process of virus replication, infection of epithelial cells, and the reaction of the host immune system will decide whether the infection will be cleared or persisted [7, 8]. Persistent infection can result in pre-cancerous lesion that can be detected and treated through screening before the emergence of cancer [9–11]. Following the emergence of cancer, additional treatment is necessary [11]. This is the reason why a mathematical model considering HPV infection, pre-cancerous lesion, and cervical cancer along with their biological properties and methods of intervention should be developed. Moreover, the rapid processes of viral infection and slowly-developing cervical disease need to be distinguished.

Mathematical models of HPV infection have incorporated various combinations of susceptible and infected epithelial cells, viral load, immune responses, precancerous lesions, cancer progression, vaccination, and treatment [12, 13]. Such models have provided important insights into viral persistence, disease progression, and potential intervention strategies [14–16]. Other formulations have considered additional biological mechanisms, including stochastic maintenance of HPV episomes, cellular dormancy, and immune-mediated effects [17, 18]. These studies demonstrate the usefulness of mathematical modelling for investigating HPV pathogenesis while also illustrating a fundamental modelling challenge: increasing biological detail does not necessarily lead to a more transparent or analytically tractable dynamical system. In particular, representing cancer as an autonomous tumour-growth subsystem may require additional assumptions concerning malignant-cell proliferation, carrying capacity, or tumour-establishment thresholds. When such mechanisms are not the primary focus of the within-host analysis, their inclusion may obscure the infection and lesion dynamics that determine the onset and persistence of HPV-associated disease.

An additional motivation for the time scales represented in the model comes from recent longitudinal observations of HPV viral load. The PAPCLEAR study of Tessandier et al. [19] followed young women using frequent sampling and reconstructed population-level viral-load trajectories characterized by an approximately two-month increase followed by a plateau lasting about 14 months (95% credibility interval: 11–18 months), with a median infection duration of approximately 16 months (95% credibility interval: 13–20 months). The associated data and analysis scripts have also been made publicly available [20]. These observations provide useful biological context for the time scales that a within-host model should be capable of representing. They are not, however, used for statistical parameter fitting in the present study. Accordingly, the parameter set used in the numerical experiments should be interpreted as an illustrative dynamical regime rather than as a quantitatively calibrated representation of HPV infection in humans.

Motivated by this consideration, we formulate a deterministic within-host model that describes the interaction between epithelial turnover, HPV infection, viral load, local immunity, precancerous disease, and downstream cancer burden. Epithelial turnover is incorporated directly into the tissue dynamics rather than being treated solely as an external demographic process. The available tissue capacity $H = 1 - E_S - E_I - P$ regulates epithelial proliferation, thereby coupling cellular turnover to the infection and lesion dynamics. HPV infection is represented through an effective viral-load variable V , while local cellular immunity is described by the immune-activity variable Z . Susceptible epithelial cells can consequently become infected through a viral-load-dependent process, infected cells can proliferate within the available epithelial space, and infected cells can be removed through immune-mediated and other loss mechanisms.

The infection dynamics are subsequently coupled to the development of precancerous disease. Infected epithelial cells can transition into a precancerous population, which may regress or be removed through a screening-associated treatment mechanism. A fraction of the precancerous burden may progress to a downstream cancer-burden variable C . Rather than introducing an independent

tumour-growth subsystem, we represent C as a progression compartment. Consequently, cancer burden does not feed back into the epithelial–viral–immune subsystem. This modelling choice separates the downstream accumulation and treatment of cancer burden from the mechanisms responsible for HPV establishment and persistence. It also avoids introducing an additional malignant-establishment threshold or autonomous tumour-growth assumptions that are not required for the questions addressed here. This structure has an important mathematical consequence. The epithelial, infection, viral, immune, and precancerous variables constitute the dynamical core of the system, whereas the cancer variable is downstream from this core. The local stability properties governing infection establishment and oscillatory behaviour can therefore be investigated through the lower-dimensional infection–lesion–immune subsystem. In particular, when the cancer removal rate is positive, the cancer direction contributes a stable eigenvalue and does not alter the local stability conditions of the upstream subsystem. This separation makes it possible to study invasion and oscillatory instability without conflating these phenomena with assumptions concerning autonomous long-term tumour growth.

Within this framework, the first mathematical question concerns HPV invasion. We determine the conditions under which HPV can successfully establish itself in an otherwise uninfected epithelial environment. The resulting invasion threshold incorporates two complementary mechanisms: the production of infected epithelial cells through viral-load-mediated infection and the contribution of infected-cell proliferation. Thus, the threshold is derived from the structure of the epithelial–viral system rather than being based solely on free-virus production. We subsequently characterize the infection-free, infected-boundary, and positive coexistence equilibria and investigate their local stability. The second question concerns the possibility of sustained temporal variability generated by the interaction between epithelial turnover, viral replication, immune activity, and lesion formation. To address this, we derive the characteristic polynomial associated with the infection–lesion–immune subsystem and apply the Routh–Hurwitz criteria to identify the relevant stability boundaries. Numerical continuation is then used to demonstrate a Hopf bifurcation with the viral-clearance parameter μ_V as the bifurcation parameter. Simulations beyond the stability boundary illustrate the emergence of a stable periodic solution. Because convergence to the asymptotic periodic orbit can be particularly slow near the bifurcation, sufficiently long numerical integrations are required to distinguish the resulting oscillations from long-lived transients.

The model also provides a framework for examining interventions acting at different stages of HPV-associated disease. Three control mechanisms are considered: therapeutic stimulation of the immune response, treatment of precancerous lesions associated with screening, and treatment of downstream cancer burden. These controls act on distinct biological compartments and therefore allow their effects to be separated within the model. Screening-associated treatment removes precancerous tissue, whereas cancer therapy acts directly on the downstream cancer-burden variable. The resulting optimal-control problem is formulated using Pontryagin’s Maximum Principle, from which the corresponding adjoint system and characterizations of the optimal controls are obtained. Finally, the invasion threshold provides a compact measure through which the mathematical influence of model parameters can be assessed. Normalised sensitivity indices [21] are therefore calculated to examine the effects of viral transmission, viral production and clearance, infected-cell proliferation, immune-mediated removal, and epithelial turnover on the invasion threshold. These calculations identify parameters that are influential within the mathematical formulation and may consequently be useful candidates for future parameter calibration. They are not interpreted as direct evidence that modifying a particular parameter would necessarily produce an equivalent effect in vivo.

The remainder of the paper is organised as follows. Section 2 introduces the within-host HPV model, defines the state variables and parameters, and specifies the intervention controls. Section 3 establishes positivity and control-uniform boundedness. Section 4 derives the infection-free and infected equilibria and obtains the HPV invasion threshold. Section 5 examines local stability, derives the characteristic polynomial and Routh–Hurwitz conditions, and investigates the illustrative Hopf bifurcation numerically. Section 6 formulates the optimal-control problem and derives the associated adjoint equations and optimality conditions. Section 7 examines the sensitivity of the HPV invasion threshold to the principal model parameters. The final section discusses the biological interpretation of the results, the limitations of the present formulation, reproducibility, and the empirical data required for future calibration and model extension.

2 Model formulation

In this section, we present a detailed formulation of the mathematical model describing within-host HPV–immune dynamics, incorporating epithelial turnover and the downstream progression of cervical disease burden, as discussed in the previous section.

Let $E_S(t)$, $E_I(t)$, and $P(t)$ denote susceptible, HPV-infected, and precancerous epithelial fractions of a normalised local tissue capacity. Define the unoccupied epithelial fraction

$$H(t) = 1 - E_S(t) - E_I(t) - P(t). \quad (1)$$

Let $V(t)$ denote an effective HPV-load variable, $C(t)$ a downstream cervical-cancer burden, and $Z(t)$ local cellular-immune activity. The following assumptions are made:

- (A1) Susceptible epithelial cells divide at rate r subject to the shared capacity factor H and are lost at rate μ_S .
- (A2) Infected cells divide at rate b under the same crowding constraint. Infection occurs at rate $\beta E_S V$. Infected cells are lost at rate μ_I , enter the precancer compartment at rate σ , and are killed by immune effectors at a rate a , modeled via the term $a(1 + \eta_1 u_1) E_I Z$ where u_1 represents therapeutic immune stimulation.
- (A3) Viral load is produced at rate $\pi_V E_I$ and cleared at rate $\mu_V V$.
- (A4) Precancer regresses or is removed at rate μ_P , is additionally removed by screen-linked treatment at rate τu_2 , and progresses to cancer at rate ρ .
- (A5) Cancer is treated as a downstream burden, produced by precancer progression and removed at rate $\mu_C + du_3$.
- (A6) The local cellular immune response is stimulated at a constant basal rate λ , enhanced by infected cells at rate α , and removed at rate μ_Z .
- (A7) The controls satisfy $0 \leq u_i(t) \leq 1$: u_1 is therapeutic immune stimulation, u_2 is averaged screen-linked treatment of detected precancer, and u_3 is oncologic therapy.

The model is finally give as below:

$$\begin{aligned} \frac{dE_S}{dt} &= rE_S H - \mu_S E_S - \beta E_S V, \\ \frac{dE_I}{dt} &= \beta E_S V + bE_I H - (\mu_I + \sigma)E_I - a(1 + \eta_1 u_1)E_I Z, \\ \frac{dV}{dt} &= \pi_V E_I - \mu_V V, \end{aligned} \quad (2)$$

$$\begin{aligned}
\frac{dP}{dt} &= \sigma E_I - (\mu_P + \tau u_2 + \rho)P, \\
\frac{dC}{dt} &= \rho P - (\mu_C + du_3)C, \\
\frac{dZ}{dt} &= \lambda + \alpha E_I - \mu_Z Z.
\end{aligned}$$

All initial data are nonnegative i.e.

$$E_S(0) > 0, E_I(0) > 0, V(0) > 0, P(0) > 0, C(0) > 0, Z(0) > 0. \quad (3)$$

Remark 1 (Interpretation of the cancer compartment). *Equation of C of the system (2) is intentionally a disease-burden equation rather than a mechanistic tumour-population model. It records the accumulation of invasive disease downstream of precancer and its removal under treatment. Autonomous malignant growth, metastatic spread, and density-dependent tumour ecology would require additional data and should be introduced only in a dedicated oncology extension.*

Table 1 Parameters in the corrected working formulation. Numerical values listed for the Hopf core are illustrative search-selected values, not estimates from PAPCLEAR or clinical data.

Parameter	Biological interpretation	Benchmark/value	Units
r	susceptible epithelial proliferation	0.0521694	day ⁻¹
μ_S	susceptible epithelial loss	0.00481370	day ⁻¹
b	infected epithelial proliferation	0.756024	day ⁻¹
β	effective infection coefficient	0.0246697	load ⁻¹ day ⁻¹
μ_I	infected epithelial loss	0.0299651	day ⁻¹
σ	infected-to-precancer transition	4.05286×10^{-4}	day ⁻¹
a	immune killing coefficient	0.0732445	immune ⁻¹ day ⁻¹
π_V	effective viral-load production	0.438929	load day ⁻¹
μ_V	effective viral-load clearance	bifurcation parameter	day ⁻¹
μ_P	precancer regression/removal	0.00144698	day ⁻¹
ρ	precancer-to-cancer progression	9.59441×10^{-5}	day ⁻¹
λ	basal immune influx	0.00884473	immune day ⁻¹
α	immune recruitment by infected epithelium	0.318469	immune day ⁻¹
μ_Z	immune loss	0.00587975	day ⁻¹
η_1, τ, d	intervention efficacy coefficients	not calibrated	model-specific
μ_C	cancer-burden removal	not calibrated	day ⁻¹

Remark 2 (Biological status of the benchmark). *The values of r and especially b in the illustrative Hopf benchmark should not be interpreted as validated in-vivo cervical epithelial proliferation rates. The benchmark was selected to demonstrate a mathematically admissible Hopf regime with substantial tissue occupancy. A publication-grade biological analysis should replace search-selected values with experimentally constrained ranges or fitted values and should report whether the Hopf regime survives those constraints.*

3 Positivity and uniform boundedness

Theorem 1 (Positive invariance). *For every nonnegative initial condition (3) and every measurable admissible control, the nonnegative orthant is positively invariant for the system (2).*

Proof. Consider the vector field of system (2) on the boundary of the nonnegative orthant. When each state variable is zero, while all other state variables remain nonnegative, the corresponding derivatives satisfy

$$\dot{E}_S|_{E_S=0} = 0, \quad \dot{E}_I|_{E_I=0} = \beta E_S V \geq 0, \quad \dot{V}|_{V=0} = \pi_V E_I \geq 0,$$

$$\dot{P}|_{P=0} = \sigma E_I \geq 0, \quad \dot{C}|_{C=0} = \rho P \geq 0, \quad \dot{Z}|_{Z=0} = \lambda + \alpha E_I > 0.$$

Hence, the vector field points into or is tangent to the nonnegative orthant on its boundary. By the standard positive-invariance result for ordinary differential equations, the nonnegative orthant is positively invariant. Consequently, $E_S(t) \geq 0, E_I(t) \geq 0, V(t) \geq 0, P(t) \geq 0, C(t) \geq 0, Z(t) \geq 0$, for $t \geq 0$. Therefore, all state variables remain nonnegative, and the theorem is proved. $\square$ $\square$

Theorem 2 (Control-uniform boundedness). *All nonnegative solutions are global and uniformly bounded, with bounds independent of admissible controls.*

Proof. Let $X = E_S + E_I + P$. Then

$$\dot{X} = (rE_S + bE_I)(1 - X) - \mu_S E_S - \mu_I E_I - a(1 + \eta_1 u_1)E_I Z - (\mu_P + \tau u_2 + \rho)P. \quad (4)$$

For $X \geq 1$, the first term is nonpositive and every remaining term is nonpositive. Hence

$$0 \leq X(t) \leq M_X := \max\{X(0), 1\}. \quad (5)$$

Therefore E_S, E_I, P are bounded. Comparison gives

$$V(t) \leq \max\left\{V(0), \frac{\pi_V M_X}{\mu_V}\right\}, \quad Z(t) \leq \max\left\{Z(0), \frac{\lambda + \alpha M_X}{\mu_Z}\right\}.$$

Finally,

$$\frac{dC}{dt} \leq \rho M_X - \mu_C C,$$

because $u_3 \geq 0$. Hence

$$C(t) \leq \max\left\{C(0), \frac{\rho M_X}{\mu_C}\right\}$$

whenever $\mu_C > 0$. Thus all state variables are uniformly bounded and finite-time blow-up is impossible. $\square$

4 Equilibria and the HPV invasion threshold

For equilibrium and bifurcation calculations the controls are held constant. Define

$$A = a(1 + \eta_1 u_1), \quad D_0 = \mu_I + \sigma + A \frac{\lambda}{\mu_Z}, \quad k = \frac{\beta \pi_V}{\mu_V}, \quad m_P = \mu_P + \tau u_2 + \rho, \quad \delta_C = \mu_C + d u_3, \quad (6)$$

and assume $r > \mu_S$ and $\delta_C > 0$. The infection-free epithelial level and basal immune activity are

$$S_0 = 1 - \frac{\mu_S}{r}, \quad Z_0 = \frac{\lambda}{\mu_Z}. \quad (7)$$

4.1 Tissue-free and normal HPV-free equilibria

The tissue-free HPV-free state

$$\mathcal{E}_{\emptyset,0} = (0, 0, 0, 0, 0, Z_0)$$

always exists. It is unstable in the susceptible-epithelial direction whenever $r > \mu_S$, since the corresponding eigenvalue is $r - \mu_S > 0$.

The normal HPV-free state is

$$\mathcal{E}_0 = (S_0, 0, 0, 0, 0, Z_0). \quad (8)$$

Because cancer receives input only from P , there are no autonomous HPV-free positive-cancer equilibria in this simplified formulation.

4.2 HPV invasion threshold

Near $\mathcal{E}_0$, the infected-cell/viral-load block is

$$\begin{pmatrix} \dot{E}_I \\ \dot{V} \end{pmatrix} = \begin{pmatrix} b\frac{\mu_S}{r} - D_0 & \beta S_0 \\ \pi_V & -\mu_V \end{pmatrix} \begin{pmatrix} E_I \\ V \end{pmatrix} + O(\|(E_I, V)\|^2).$$

A next-generation decomposition that counts infected-cell division and viral-load-mediated infection as production of infected units gives the basic reproduction number, $\mathcal{R}_{\text{HPV}}$, as

$$\mathcal{R}_{\text{HPV}} = \frac{\frac{b\mu_S}{r} + \frac{\beta S_0 \pi_V}{\mu_V}}{D_0}, \quad (9)$$

where $D_0 = \mu_I + \sigma + A\frac{\lambda}{\mu_Z}$. The determinant of the invasion block is $\mu_V D_0(1 - \mathcal{R}_{\text{HPV}})$, and $\mathcal{R}_{\text{HPV}} < 1$ also implies negative trace. Hence the infection directions of $\mathcal{E}_0$ are locally stable exactly when $\mathcal{R}_{\text{HPV}} < 1$.

Remark 3. *The invasion threshold, $\mathcal{R}_{\text{HPV}}$, contains two distinct contributions to HPV establishment. The first arises from proliferation of infected epithelial cells, while the second arises from viral-load-mediated infection of susceptible epithelium. Thus, infected-cell division and extracellular or effective viral transmission enter the invasion mechanism through separate pathways. The threshold also makes explicit the effects of viral clearance, infected-cell loss, immune killing, and therapeutic immune stimulation. This structure provides a biologically interpretable criterion for local HPV invasion while retaining the tissue-capacity constraint of the full model.*

4.3 Epithelial-depleted infected boundary equilibrium

Set $E_S = 0$ and seek $E_I > 0$. With

$$P = q_P E_I, \quad q_P = \frac{\sigma}{m_P}, \quad Z = \frac{\lambda + \alpha E_I}{\mu_Z},$$

the infected-cell balance gives

$$E_I^B = \frac{b - D_0}{b(1 + q_P) + A\alpha/\mu_Z}, \quad (10)$$

provided $b > D_0$. Then

$$V^B = \frac{\pi_V}{\mu_V} E_I^B, \quad P^B = q_P E_I^B, \quad Z^B = \frac{\lambda + \alpha E_I^B}{\mu_Z}, \quad C^B = \frac{\rho P^B}{\delta_C}. \quad (11)$$

The susceptible-invasion eigenvalue at this boundary state is

$$\lambda_S^B = r(1 - E_I^B - P^B) - \mu_S - \beta V^B. \quad (12)$$

Thus $\lambda_S^B > 0$ makes the boundary state unstable to restoration of susceptible epithelium. The condition $\lambda_S^B = 0$ is the natural boundary at which a coexistence branch can meet $E_S = 0$.

4.4 Positive coexistence equilibrium, $\mathcal{E}^*(E_S^*, E_I^*, V^*, P^*, Z^*, C^*)$

Let $\gamma = A\alpha/\mu_Z$. For $E_S^*, E_I^* > 0$, we obtain

$$V^* = \frac{\pi_V}{\mu_V} E_I^*, \quad P^* = q_P E_I^*, \quad Z^* = \frac{\lambda + \alpha E_I^*}{\mu_Z}, \quad C^* = \frac{\rho P^*}{\delta_C}.$$

The susceptible balance gives

$$E_S^* = S_0 - \left(1 + q_P + \frac{k}{r}\right) E_I^*, \quad (13)$$

where $S_0 = 1 - \frac{\mu_S}{r}$. Substitution into the infected-cell equation yields

$$E_I^* = \frac{D_0(\mathcal{R}_{\text{HPV}} - 1)}{L}, \quad L = k \left(1 + q_P + \frac{k}{r} - \frac{b}{r}\right) + \gamma. \quad (14)$$

A biologically admissible coexistence equilibrium therefore requires $\mathcal{R}_{\text{HPV}} > 1$, $L > 0$, and $E_S^* > 0$.

5 Local stability and Hopf bifurcation

Because C does not feed back into (E_S, E_I, V, P, Z) , the Jacobian at a coexistence equilibrium has block form

$$J_* = \begin{pmatrix} B_5 & 0 \\ * & -\delta_C \end{pmatrix}, \quad (15)$$

where the five-dimensional epithelial-viral-lesion-immune Jacobian, ordered as (E_S, E_I, V, P, Z) , is

$$B_5 = \begin{pmatrix} j_{11} & -rE_S^* - \beta E_S^* - rE_S^* & 0 \\ \beta V^* - bE_I^* & j_{22} & \beta E_S^* - bE_I^* - AE_I^* \\ 0 & \pi_V & -\mu_V & 0 & 0 \\ 0 & \sigma & 0 & -m_P & 0 \\ 0 & \alpha & 0 & 0 & -\mu_Z \end{pmatrix}, \quad (16)$$

with

$$j_{11} = r(1 - 2E_S^* - E_I^* - P^*) - \mu_S - \beta V^*, \quad j_{22} = b(1 - E_S^* - 2E_I^* - P^*) - (\mu_I + \sigma) - AZ^*.$$

At a positive equilibrium, $j_{11} = -rE_S^*$. Hence,

$$\det(\xi I - J_*) = (\xi + \delta_C) \det(\xi I - B_5). \quad (17)$$

The cancer direction is therefore strictly stable whenever $\delta_C > 0$, and any Hopf bifurcation is determined entirely by B_5 . For Hopf bifurcation, let μ be a scalar parameter and suppose a biologically admissible coexistence equilibrium exists smoothly near μ_c . If $B_5(\mu_c)$ has one simple pair $\lambda_{1,2} = \pm i\omega_c$, $\omega_c > 0$, its three remaining eigenvalues have negative real parts, and

$$\left. \frac{d}{d\mu} \Re \lambda_1(\mu) \right|_{\mu=\mu_c} \neq 0,$$

then the full six-dimensional system undergoes a Hopf bifurcation at μ_c .

5.1 Stability of $\mathcal{E}^*$ and Hopf bifurcation

The characteristic equation associated with the matrix B_5 is given by

$$\det(\lambda I - B_5) = \lambda^5 + a_1\lambda^4 + a_2\lambda^3 + a_3\lambda^2 + a_4\lambda + a_5 = 0, \quad (18)$$

where

$$\begin{aligned} a_1 &= \mu_V + m_P + \mu_Z - j_{11} - j_{22}, \\ a_2 &= \mu_V m_P + \mu_V \mu_Z + m_P \mu_Z - j_{22}(\mu_V + m_P + \mu_Z) - \beta E_S^* \pi_V + b E_I^* \sigma + A E_I^* \alpha \\ &\quad - j_{11}(\mu_V + m_P + \mu_Z - j_{22}) - r E_S^*(b E_I^* - \beta V^*), \\ a_3 &= \mu_V m_P \mu_Z - j_{22}(\mu_V m_P + \mu_V \mu_Z + m_P \mu_Z) - \beta E_S^* \pi_V (m_P + \mu_Z) \\ &\quad + b E_I^* \sigma (\mu_V + \mu_Z) + A E_I^* \alpha (\mu_V + m_P) \\ &\quad - j_{11} \left[\mu_V m_P + \mu_V \mu_Z + m_P \mu_Z - j_{22}(\mu_V + m_P + \mu_Z) - \beta E_S^* \pi_V + b E_I^* \sigma + A E_I^* \alpha \right] \\ &\quad - (b E_I^* - \beta V^*) \left[r E_S^* (\mu_V + m_P + \mu_Z) + r E_S^* \pi_V + \beta E_S^* \sigma + r E_S^* \alpha \right], \\ a_4 &= -j_{22} \mu_V m_P \mu_Z - \beta E_S^* \pi_V m_P \mu_Z + b E_I^* \sigma \mu_V \mu_Z + A E_I^* \alpha \mu_V m_P \\ &\quad - j_{11} \left[\mu_V m_P \mu_Z - j_{22}(\mu_V m_P + \mu_V \mu_Z + m_P \mu_Z) - \beta E_S^* \pi_V (m_P + \mu_Z) \right. \\ &\quad \left. + b E_I^* \sigma (\mu_V + \mu_Z) + A E_I^* \alpha (\mu_V + m_P) \right] \\ &\quad - (b E_I^* - \beta V^*) \left[r E_S^* (\mu_V m_P + \mu_V \mu_Z + m_P \mu_Z) + r E_S^* \pi_V (m_P + \mu_Z) \right. \\ &\quad \left. + \beta E_S^* \sigma (\mu_V + \mu_Z) + r E_S^* \alpha (\mu_V + m_P) \right], \\ a_5 &= j_{11} j_{22} \mu_V m_P \mu_Z + j_{11} \beta E_S^* \pi_V m_P \mu_Z - j_{11} b E_I^* \sigma \mu_V \mu_Z - j_{11} A E_I^* \alpha \mu_V m_P \\ &\quad - (b E_I^* - \beta V^*) \left[r E_S^* \mu_V m_P \mu_Z + r E_S^* \pi_V m_P \mu_Z + \beta E_S^* \sigma \mu_V \mu_Z + r E_S^* \alpha \mu_V m_P \right]. \end{aligned}$$

If the following inequalities

$$\left\{ \begin{array}{l} a_i > 0, \quad i = 1, 2, 3, 4, 5, \\ a_1 a_2 - a_3 > 0, \\ a_1 a_2 a_3 - a_1^2 a_4 - a_3^2 > 0, \\ (a_1 a_4 - a_5)(a_1 a_2 a_3 - a_1^2 a_4 - a_3^2) - a_5(a_1 a_2 - a_3)^2 - a_1 a_5^2 > 0. \end{array} \right. \quad (19)$$

are satisfied, all eigenvalues of J_* lie strictly in the left half-plane, and therefore the equilibrium $\mathcal{E}^*$ is locally asymptotically stable.

Hopf bifurcation analysis:

We investigate the occurrence of a Hopf bifurcation at the coexistence equilibrium $\mathcal{E}^*$ as the parameter μ varies. Let $J^*(\mu)$ denote the Jacobian matrix evaluated at $\mathcal{E}^*(\mu)$, and suppose that its characteristic polynomial is given by

$$p(\lambda, \mu) = \lambda^5 + a_1(\mu)\lambda^4 + a_2(\mu)\lambda^3 + a_3(\mu)\lambda^2 + a_4(\mu)\lambda + a_5(\mu). \quad (20)$$

Assume that the coefficients $a_i(\mu)$ are continuously differentiable in a neighbourhood of μ^* and that $\mathcal{E}^*(\mu)$ is feasible in this neighbourhood.

Theorem 3. *Suppose that the dynamical system is of class C^3 and that the coexistence equilibrium $\mathcal{E}^*(\mu)$ exists in a neighbourhood of $\mu = \mu^*$. Let*

$$\Phi(\mu) = (a_3 - a_1a_2)(a_2a_5 - a_3a_4) - (a_5 - a_1a_4)^2. \quad (21)$$

Assume that the following conditions hold at $\mu = \mu^*$:

(i) *The characteristic coefficients satisfy*

$$\Phi(\mu^*) = 0, \quad a_3 - a_1a_2 \neq 0, \quad (22)$$

and

$$\omega_*^2 = \frac{a_5 - a_1a_4}{a_3 - a_1a_2} > 0. \quad (23)$$

(ii) *The characteristic polynomial has a simple pair of purely imaginary roots*

$$\lambda_{1,2}(\mu^*) = \pm i\omega_*, \quad \omega_* > 0, \quad (24)$$

and its remaining three roots have strictly negative real parts.

(iii) *The imaginary eigenvalue pair crosses the imaginary axis transversally, that is,*

$$(a'_1\omega_*^4 - a'_3\omega_*^2 + a'_5)(a_4 - 3a_2\omega_*^2 + 5\omega_*^4) + (a'_4\omega_* - a'_2\omega_*^3)(2a_3\omega_* - 4a_1\omega_*^3) \neq 0.$$

Then the system undergoes a Hopf bifurcation at the coexistence equilibrium $\mathcal{E}^*$ when $\mu = \mu^*$. In particular, a family of small-amplitude periodic solutions bifurcates from $\mathcal{E}^*$ as μ passes through μ^* .

Proof. Suppose that $\lambda = i\omega$, where $\omega > 0$, is a root of the characteristic equation $p(\lambda, \mu^*) = 0$. Substitution of $\lambda = i\omega$ into (20) and separation into real and imaginary parts yield

$$\begin{cases} a_1\omega^4 - a_3\omega^2 + a_5 = 0, \\ \omega^5 - a_2\omega^3 + a_4\omega = 0. \end{cases} \quad (25)$$

Since $\omega > 0$, the second equation in (25) can be divided by ω . Setting $x = \omega^2 > 0$, we obtain

$$\begin{cases} a_1x^2 - a_3x + a_5 = 0, \\ x^2 - a_2x + a_4 = 0. \end{cases} \quad (26)$$

Multiplying the second equation of (26) by a_1 and subtracting it from the first equation gives

$$(a_3 - a_1 a_2)x = a_5 - a_1 a_4. \quad (27)$$

Because $a_3 - a_1 a_2 \neq 0$, it follows that

$$x = \frac{a_5 - a_1 a_4}{a_3 - a_1 a_2}. \quad (28)$$

Condition (23) therefore ensures that $x = \omega_*^2 > 0$. Substituting (28) into the second equation of (26) gives

$$(a_5 - a_1 a_4)^2 - (a_3 - a_1 a_2)(a_2 a_5 - a_3 a_4) = 0. \quad (29)$$

Equivalently, $\Phi(\mu^*) = 0$. Conversely, under (22) and (23), the equality $\Phi(\mu^*) = 0$ guarantees that $x = \omega_*^2$ satisfies both equations in (26). Hence

$$p(i\omega_*, \mu^*) = 0.$$

Since the coefficients of the characteristic polynomial are real, $p(-i\omega_*, \mu^*) = 0$ as well. Thus, the algebraic conditions establish the existence of the purely imaginary pair $\lambda = \pm i\omega_*$.

By assumption (ii), the roots $\pm i\omega_*$ are simple and the remaining three eigenvalues have strictly negative real parts. Consequently, the imaginary pair is isolated from the remaining spectrum. The implicit function theorem therefore guarantees the existence of a differentiable eigenvalue branch $\lambda(\mu)$ near μ^* such that

$$p(\lambda(\mu), \mu) = 0, \quad \lambda(\mu^*) = i\omega_*.$$

Differentiating the characteristic equation with respect to μ yields

$$p_\lambda(\lambda(\mu), \mu)\lambda'(\mu) + p_\mu(\lambda(\mu), \mu) = 0.$$

Since the eigenvalue is simple, $p_\lambda(i\omega_*, \mu^*) \neq 0$, and hence

$$\lambda'(\mu^*) = -\frac{p_\mu(i\omega_*, \mu^*)}{p_\lambda(i\omega_*, \mu^*)}. \quad (30)$$

In terms of the characteristic coefficients, this expression becomes

$$\lambda'(\mu^*) = -\frac{a'_1(i\omega_*)^4 + a'_2(i\omega_*)^3 + a'_3(i\omega_*)^2 + a'_4 i\omega_* + a'_5}{5(i\omega_*)^4 + 4a_1(i\omega_*)^3 + 3a_2(i\omega_*)^2 + 2a_3 i\omega_* + a_4}. \quad (31)$$

For convenience, define

$$\begin{aligned} A &= a'_1 \omega_*^4 - a'_3 \omega_*^2 + a'_5, \\ B &= a'_4 \omega_* - a'_2 \omega_*^3, \\ C &= a_4 - 3a_2 \omega_*^2 + 5\omega_*^4, \\ D &= 2a_3 \omega_* - 4a_1 \omega_*^3. \end{aligned}$$

Then

$$\lambda'(\mu^*) = -\frac{A + iB}{C + iD}.$$

Multiplying the numerator and denominator by $C - iD$ yields

$$\lambda'(\mu^*) = -\frac{(AC + BD) + i(BC - AD)}{C^2 + D^2}.$$

Consequently,

$$\operatorname{Re} \lambda'(\mu^*) = -\frac{AC + BD}{C^2 + D^2}.$$

Since $i\omega_*$ is a simple root of the characteristic equation, $p_\lambda(i\omega_*, \mu^*) \neq 0$, and hence $C^2 + D^2 > 0$. Therefore, the transversality condition is equivalent to

$$AC + BD \neq 0.$$

Equivalently, in terms of the characteristic coefficients,

$$(a'_1\omega_*^4 - a'_3\omega_*^2 + a'_5)(a_4 - 3a_2\omega_*^2 + 5\omega_*^4) + (a'_4\omega_* - a'_2\omega_*^3)(2a_3\omega_* - 4a_1\omega_*^3) \neq 0.$$

Under this condition, the real part of the critical eigenvalue satisfies

$$\operatorname{Re} \lambda(\mu) = \operatorname{Re} \lambda'(\mu^*)(\mu - \mu^*) + o(|\mu - \mu^*|).$$

Thus, the conjugate eigenvalue pair crosses the imaginary axis with nonzero speed as μ passes through μ^* , establishing the transversality condition required for the Hopf bifurcation. $\square$

6 Optimal control problem

To determine an optimal intervention strategy that minimizes the burden of HPV infection, here we derive an optimal control problem. The aim is to minimize precancerous lesions, and cervical cancer while accounting for the costs associated with therapeutic immune stimulation, screening and early intervention, and oncologic treatment.

Let $T > 0$ denote the final time of the intervention period. The control variables are $u_1(t), u_2(t), u_3(t)$, where u_1 , u_2 , and u_3 represent therapeutic immune stimulation, screening and early intervention, and oncologic treatment, respectively.

The admissible control set is defined by

$$\mathcal{U} = \{(u_1, u_2, u_3) : u_i \in L^\infty(0, T), 0 \leq u_i \leq 1 \text{ a.e.}\}.$$

To formulate the optimal control problem, we consider the objective functional

$$J = \int_0^T \left[A_I E_I + A_P P + A_C C + \frac{B_1}{2} u_1^2 + \frac{B_2}{2} u_2^2 + \frac{B_3}{2} u_3^2 \right] dt \quad (32)$$

The quadratic terms in the controls account for the increasing marginal cost of intervention intensity. Thus, the optimal control problem is to determine an admissible control $u^* = (u_1^*, u_2^*, u_3^*) \in \mathcal{U}$ such that

$$J(u_1^*, u_2^*, u_3^*) = \min_{(u_1, u_2, u_3) \in \mathcal{U}} J(u_1, u_2, u_3). \quad (33)$$

subject to the state system

$$\begin{aligned}
\frac{dE_S}{dt} &= rE_S H - \mu_S E_S - \beta E_S V, \\
\frac{dE_I}{dt} &= \beta E_S V + bE_I H - (\mu_I + \sigma)E_I - a(1 + \eta_1 u_1)E_I Z, \\
\frac{dV}{dt} &= \pi_V E_I - \mu_V V, \\
\frac{dP}{dt} &= \sigma E_I - (\mu_P + \tau u_2 + \rho)P, \\
\frac{dC}{dt} &= \rho P - (\mu_C + du_3)C, \\
\frac{dZ}{dt} &= \lambda + \alpha E_I - \mu_Z Z.
\end{aligned} \tag{34}$$

Theorem 4 (Existence of an optimal control). *For every finite T and nonnegative initial condition, at least one optimal control exists.*

Proof. The admissible set is nonempty, closed, convex, and bounded in L^∞ . Section 3 gives state bounds uniform in the controls. On these bounded sets the vector field is continuous in the states, measurable and affine in the controls, and locally Lipschitz in the state variables. The running cost is convex and coercive in the controls because $B_i > 0$. Standard deterministic optimal-control existence results apply [22]. $\square$

To derive the necessary conditions for optimality, we introduce the adjoint variables $\lambda_i(t)$, $i = 1, 2, \dots, 6$ corresponding to the state variables E_S, E_I, V, P, C, Z , respectively. The Hamiltonian associated with the optimal control problem is given by

$$\begin{aligned}
\mathcal{H} &= A_I E_I + A_P P + A_C C + \frac{B_1}{2} u_1^2 + \frac{B_2}{2} u_2^2 + \frac{B_3}{2} u_3^2 + \lambda_1 \left[rE_S \left(1 - \frac{E_S + E_I}{N} \right) - \beta E_S V \right] \\
&\quad + \lambda_2 [\beta E_S V + bE_I - \mu_I E_I - \sigma E_I - a(1 + \eta_1 u_1)E_I Z] + \lambda_3 [\kappa \mu_I E_I - \mu_V V] \\
&\quad + \lambda_4 \left[\sigma E_I - \mu_P P - (1 - \eta_2 u_2) \frac{\omega P}{c + P} \right] + \lambda_5 \left[(1 - \eta_2 u_2) \frac{\omega P}{c + P} - \mu_C C - u_3 dC \right] \\
&\quad + \lambda_6 [\lambda + \alpha E_I - \mu_Z Z].
\end{aligned} \tag{35}$$

According to Pontryagin's Maximum Principle, the adjoint variables satisfy

$$\frac{d\psi_i}{dt} = -\frac{\partial \mathcal{H}}{\partial x_i}, \quad i = 1, \dots, 6, \tag{36}$$

where $x = (E_S, E_I, V, P, C, Z)$. Since there is no terminal cost and the terminal states are free, the transversality conditions are

$$\lambda_i(T) = 0, \quad i = 1, \dots, 6. \tag{37}$$

Using (36), the adjoint system is determined as

$$\begin{aligned}
\frac{d\psi_1}{dt} &= -\psi_1 [r(1 - 2E_S - E_I - P) - \mu_S - \beta V] - \psi_2 (\beta V - bE_I), \\
\frac{d\psi_2}{dt} &= -A_I + rE_S \psi_1 + \psi_2 [(\mu_I + \sigma) + a(1 + \eta_1 u_1)Z - b(1 - E_S - 2E_I - P)]
\end{aligned}$$

$$\begin{aligned}
& -\pi_V\psi_3 - \sigma\psi_4 - \alpha\psi_6, \\
\frac{d\psi_3}{dt} &= \beta E_S(\psi_1 - \psi_2) + \mu_V\psi_3, \\
\frac{d\psi_4}{dt} &= -A_P + rE_S\psi_1 + bE_I\psi_2 + (\mu_P + \tau u_2 + \rho)\psi_4 - \rho\psi_5, \\
\frac{d\psi_5}{dt} &= -A_C + (\mu_C + du_3)\psi_5, \\
\frac{d\psi_6}{dt} &= a(1 + \eta_1 u_1)E_I\psi_2 + \mu_Z\psi_6.
\end{aligned} \tag{38}$$

The optimal controls are obtained by minimizing the Hamiltonian with respect to u_1 , u_2 , and u_3 . Therefore,

$$\frac{\partial \mathcal{H}}{\partial u_1} = B_1 u_1 - a\eta_1 E_I Z \psi_2, \quad \frac{\partial \mathcal{H}}{\partial u_2} = B_2 u_2 - \tau P \psi_4, \quad \frac{\partial \mathcal{H}}{\partial u_3} = B_3 u_3 - dC \psi_5. \tag{39}$$

For an interior optimal control, setting the above derivatives equal to zero gives the corresponding unconstrained controls

$$u_1 = \frac{a\eta_1 E_I Z \psi_2}{B_1}, \quad u_2 = \frac{\tau P \psi_4}{B_2}, \quad u_3 = \frac{dC \psi_5}{B_3}. \tag{40}$$

Taking into account the bounds $0 \leq u_i \leq 1$, the optimal controls are therefore given by the projection formulas

$$\begin{aligned}
u_1^*(t) &= \min \left\{ 1, \max \left\{ 0, \left(\frac{a\eta_1 E_I Z \psi_2}{B_1} \right) \right\} \right\}, \\
u_2^*(t) &= \min \left\{ 1, \max \left\{ 0, \left(\frac{\tau P \psi_4}{B_2} \right) \right\} \right\}, \\
u_3^*(t) &= \min \left\{ 1, \max \left\{ 0, \left(\frac{dC \psi_5}{B_3} \right) \right\} \right\}.
\end{aligned} \tag{41}$$

The optimal control problem is actually the state system (34), adjoint system (38) and the optimal controls (41). Thus it is a two point boundary value problem.

Remark 4. *These are mathematical necessary conditions, not calibrated clinical recommendations. Immune stimulation, screening-linked lesion treatment, and oncologic therapy act on different biological and clinical time scales. Numerical forward-backward sweeps should therefore be deferred until state, intervention, and cost parameters are calibrated on compatible horizons. Scheduled or impulsive screening may ultimately be more realistic than a continuous u_2 .*

7 Sensitivity analysis using HPV invasion threshold $\mathcal{R}_{\text{HPV}}$

We analyze the relative influence of parameters on the HPV invasion threshold $\mathcal{R}_{\text{HPV}}$. From (9), we rewrite the expression for $\mathcal{R}_{\text{HPV}}$ as

$$\mathcal{R}_{\text{HPV}} = \frac{Q}{D_0}, \quad Q = b \frac{\mu_S}{r} + \frac{\beta S_0 \pi_V}{\mu_V}, \quad S_0 = 1 - \frac{\mu_S}{r}, \quad D_0 = \mu_I + \sigma + A \frac{\lambda}{\mu_Z}, \tag{42}$$

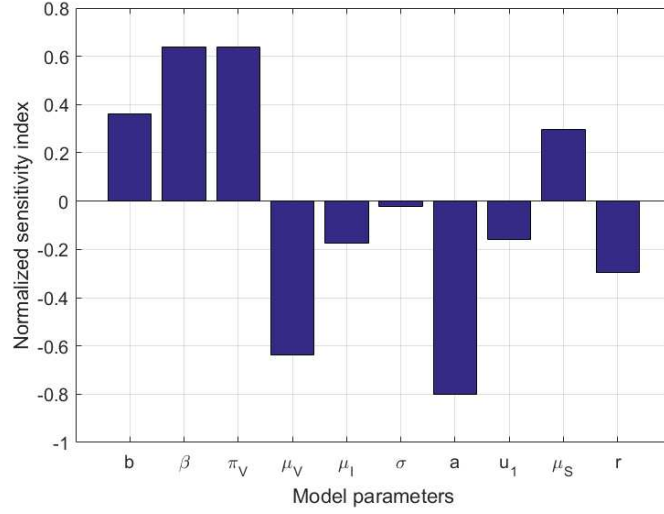


Fig. 1 Sensitivity indices are plotted using parameters as in Table 1.

with $A = a(1 + \eta_1 u_1)$. For any parameter p , the normalized sensitivity index is defined by

$$\Upsilon_p^{\mathcal{R}_{\text{HPV}}} = \frac{\partial \mathcal{R}_{\text{HPV}}}{\partial p} \frac{p}{\mathcal{R}_{\text{HPV}}}. \quad (43)$$

using this, we derive the sensitivity indices as follows:

$$\begin{aligned} \Upsilon_b^{\mathcal{R}_{\text{HPV}}} &= \frac{b\mu_S/r}{Q}, & \Upsilon_\beta^{\mathcal{R}_{\text{HPV}}} &= \frac{\beta S_0 \pi_V / \mu_V}{Q}, & \Upsilon_{\pi_V}^{\mathcal{R}_{\text{HPV}}} &= \frac{\beta S_0 \pi_V / \mu_V}{Q}, \\ \Upsilon_{\mu_V}^{\mathcal{R}_{\text{HPV}}} &= -\frac{\beta S_0 \pi_V / \mu_V}{Q}, & \Upsilon_{\mu_I}^{\mathcal{R}_{\text{HPV}}} &= -\frac{\mu_I}{D_0}, & \Upsilon_\sigma^{\mathcal{R}_{\text{HPV}}} &= -\frac{\sigma}{D_0}, \\ \Upsilon_A^{\mathcal{R}_{\text{HPV}}} &= -\frac{A(\lambda/\mu_Z)}{D_0}, & \Upsilon_a^{\mathcal{R}_{\text{HPV}}} &= -\frac{a(1 + \eta_1 u_1)(\lambda/\mu_Z)}{D_0}, & \Upsilon_{u_1}^{\mathcal{R}_{\text{HPV}}} &= -\frac{a\eta_1 u_1(\lambda/\mu_Z)}{D_0}, \\ \Upsilon_{\mu_S}^{\mathcal{R}_{\text{HPV}}} &= \frac{\mu_S}{Q} \left(\frac{b}{r} - \frac{\beta \pi_V}{\mu_V r} \right), & \Upsilon_r^{\mathcal{R}_{\text{HPV}}} &= \frac{r}{Q} \left(-\frac{b\mu_S}{r^2} + \frac{\beta \pi_V \mu_S}{\mu_V r^2} \right). \end{aligned} \quad (44)$$

Positive indices indicate parameters that increase $\mathcal{R}_{\text{HPV}}$ (β, π_V), while negative indices correspond to parameters that reduce it (μ_V, μ_I, σ, A). Ranking $|\Upsilon_p^{\mathcal{R}_{\text{HPV}}}|$ quantifies parameter importance in HPV invasion. Figure 1 displays the normalized forward sensitivity indices of $\mathcal{R}_{\text{HPV}}$ with respect to the principal parameters. A positive index indicates that increasing the parameter raises $\mathcal{R}_{\text{HPV}}$, while a negative index indicates a decrease. The transmission rate β and viral production rate π_V exhibit the largest positive sensitivities (≈ 0.64), implying that increases in these parameters substantially elevate the invasion threshold. The proliferation parameter b (≈ 0.36) and μ_S (≈ 0.30) also contribute positively.

In contrast, the viral clearance rate μ_V shows a strong negative sensitivity (≈ -0.64), while the treatment-modified parameter a has the largest negative effect (≈ -0.80). Moderate negative sensitivities are observed for u_1 (≈ -0.16) and μ_I (≈ -0.17). The sensitivity of σ is negligible, and the epithelial growth rate r has a negative sensitivity of ≈ -0.30 .

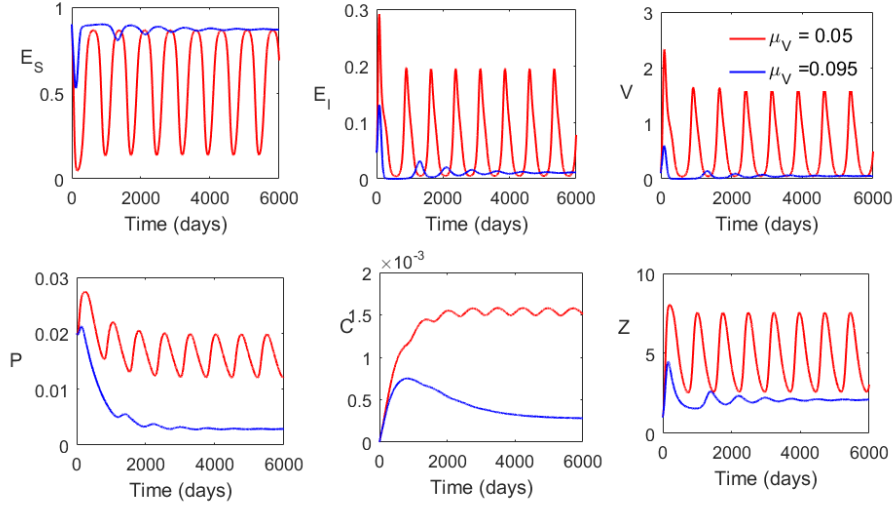


Fig. 2 Numerical solutions for two values of μ_V plotted using parameter values in Table ?? . Here, $\mu_V = 0.095$ (blue lines), $\mu_V = 0.05$ (red lines).

Overall, β , π_V , a , and μ_V emerge as the most influential parameters. Transmission and production enhance invasion potential, whereas clearance and treatment mechanisms reduce it.

8 Numerical stability and simulations

In this section, we verified the analytical predictions using numerical calculations and simulations. First we simulate the system with fixed control, then the system with optimal control.

Time series solutions are plotted in Figure 2 for two values of the rate μ_V . For lower value of this parameter, system shows periodic solutions whereas for a higher value, the solution converges to the endemic equilibrium value.

The benchmark in this section is a mathematical demonstration rather than a biological calibration. It was selected to avoid the extreme low-occupancy regime of earlier exploratory parameter sets while retaining a moderate invasion number and a months-to-years oscillatory timescale. The values are given in Table 1. Controls are set to zero and μ_V is varied.

Numerical continuation gives a simple Hopf point at $\mu_V^H \approx 0.0872174 \text{ day}^{-1}$. At the crossing, $(E_S^*, E_I^*, V^*, P^*, Z^*) \approx (0.849475, 0.0159931, 0.0804865, 0.00420097, 2.37051)$, so epithelial occupancy is $E_S^* + E_I^* + P^* \approx 0.869669$, and $\mathcal{R}_{\text{HPV}} \approx 1.29815$. The critical pair is approximately $\lambda_{1,2} = \pm 0.00909191i$, corresponding to a linearised period $T_H = \frac{2\pi}{0.00909191} \approx 691$ days. A centred finite-difference calculation gives

$$\left. \frac{d}{d\mu_V} \Re \lambda \right|_H \approx -0.06650 \neq 0, \quad (45)$$

and the Kuznetsov first-Lyapunov calculation for the quadratic five-dimensional core gives $l_1(H) \approx -0.30524$, under the convention used in the accompanying code, indicating a supercritical Hopf bifurcation.

At $\mu_V = 0.08 \text{ day}^{-1}$ the equilibrium is only weakly unstable. Consequently, integrations over only 10^4 – 1.2×10^4 days can still show a visibly growing envelope and should not be described as

a settled limit cycle. Extending the integration to 10^5 days gives converged infected-cell extrema approximately

$$E_{I,\min} \approx 0.00172057, \quad E_{I,\max} \approx 0.0703568, \quad (46)$$

with a peak-to-peak period of approximately 759 days. These long numerical transients are a mathematical property of the illustrative benchmark, not a claim about the duration of a real HPV infection.

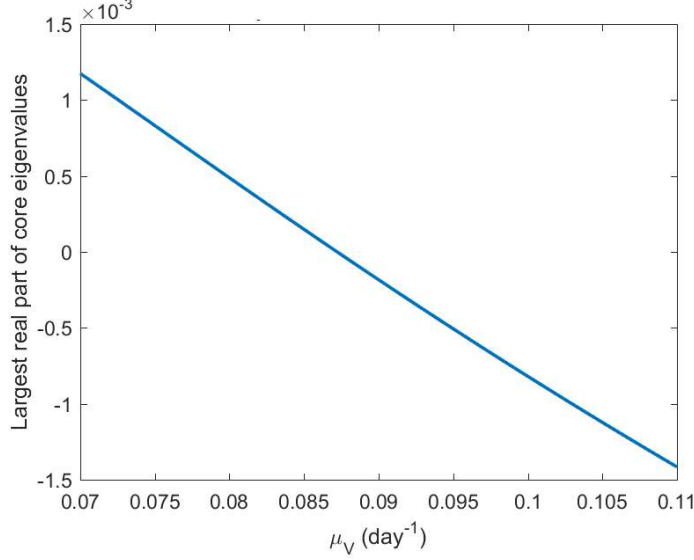


Fig. 3 Continuation diagnostic for the illustrative benchmark. The largest real part of the five-dimensional core spectrum crosses zero at $\mu_V \approx 0.0872174 \text{ day}^{-1}$.

We evaluate the coexistence equilibrium and invasion number, locates the Hopf point in μ_V , computes the crossing speed and first Lyapunov coefficient, performs the long-time integration at $\mu_V = 0.08 \text{ day}^{-1}$, and regenerates Figures 3–5.

Figure 6 illustrates how variations in the parameters a , b , β , and r influence the stability of the endemic equilibrium $\mathcal{E}^*$. In Figure 6(a) and Figure 6(b), the effects of immune-mediated killing strength a , infected epithelial cell proliferation rate b , and susceptible epithelial cell proliferation rate r are investigated. An increase in a enhances the stability regions indicating that elimination of HPV-infected epithelial cells by immune effectors increase stability in the system because it potentially reduced viral production and increase the persistence of infection. In contrast, an increase in b promotes the proliferation of infected epithelial cells, which may sustain viral replication and alter the stability of the endemic equilibrium. An increase in r promotes the regeneration of susceptible epithelial cells, potentially increasing the availability of target cells for HPV infection.

Figure 6(c) and Figure 6(d) demonstrate the combined effects of immune-mediated killing strength a , HPV transmission rate β , and susceptible epithelial cell proliferation rate r on the stability of coexisting equilibrium $\mathcal{E}^*$. The interaction between β and a is particularly important because enhanced transmission may counteract immune-mediated clearance. Similarly, variations in r modify the availability of susceptible cells and thereby influence the persistence and dynamics of infection. The figure shows that β can destabilize the system though the killing rate a is higher.

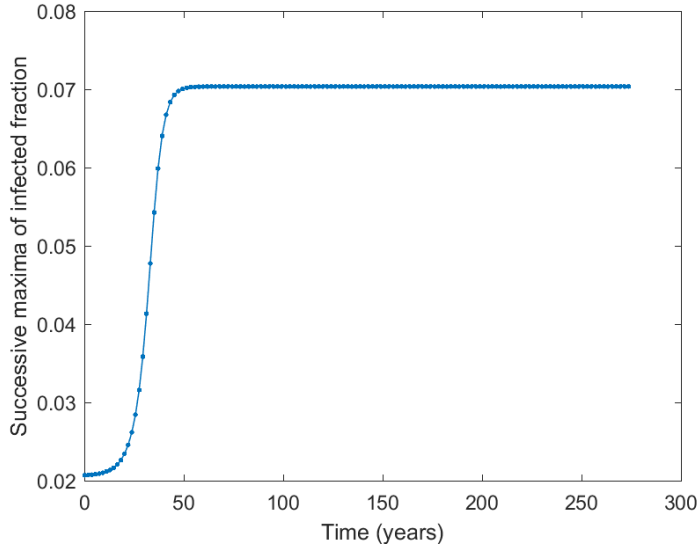


Fig. 4 Successive maxima of the infected-epithelial fraction at $\mu_V = 0.08 \text{ day}^{-1}$. The envelope converges only after a very long transient because the instability is weak.

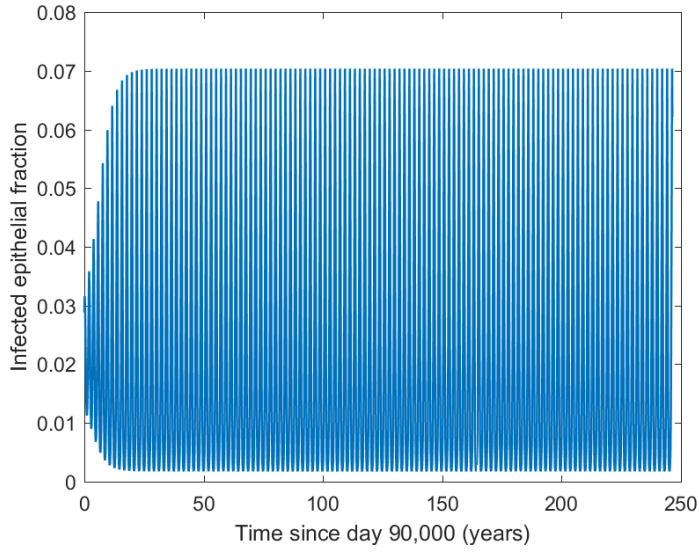


Fig. 5 Long-time infected-epithelial dynamics at $\mu_V = 0.08 \text{ day}^{-1}$, plotted after day 90,000. The settled oscillation has extrema approximately 0.00172 and 0.07036 with period approximately 759 days.

The transition between these regions indicates a change in the qualitative dynamics of the system. Where this transition is confirmed to occur through a Hopf bifurcation, periodic oscillations may emerge in the populations of infected epithelial cells, viral load, immune effectors, and precancerous lesion cells.

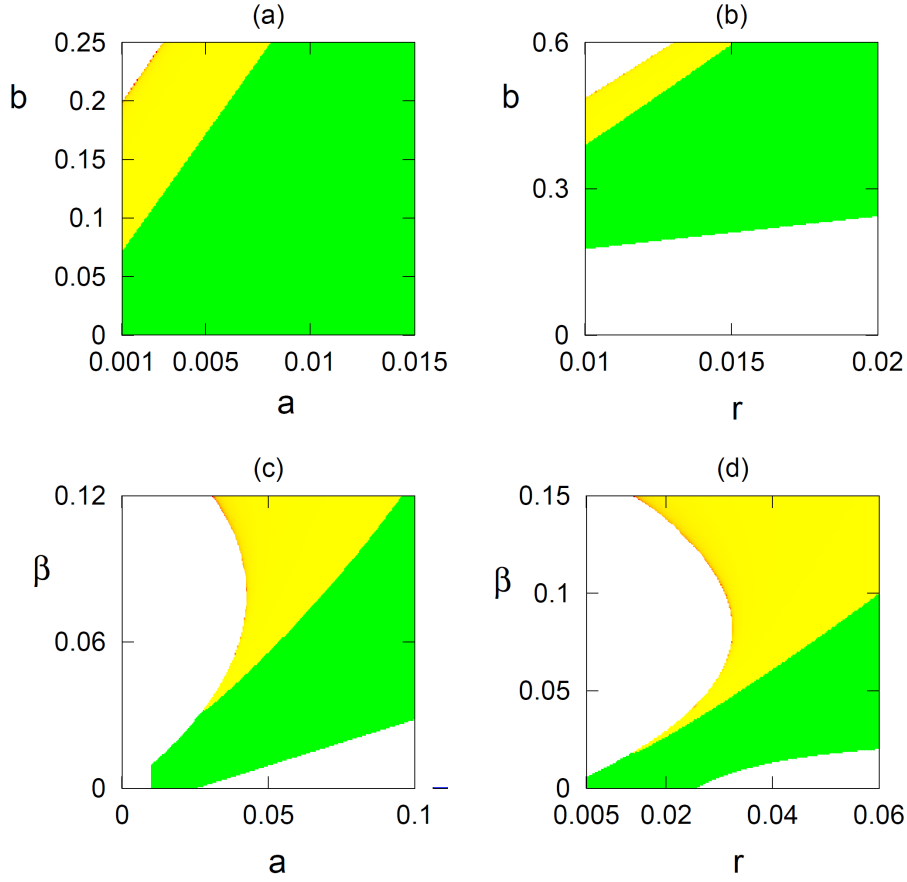


Fig. 6 Region of stability of the endemic equilibria $\mathcal{E}^*$: (a) in $b - a$ plane, (b) in $b - r$ plane, (c) $a - \beta$ plane and (d) in $\beta - r$ plane. In green region $\mathcal{E}^*$ is stable and it is unstable in yellow region. In the white region, $\mathcal{E}^*$ is not feasible.

8.1 Dynamics with optimal control

The optimal control problem is solved by means of a forward-backward sweep technique. Given an initial estimate of the controls, the state differential equations are solved forward in time from the initial conditions (3). Then, the adjoint differential equations are solved backward in time, based on the terminal conditions $\psi_i(T) = 0$, $i = 1, \dots, 6$. The control variables given by (41) are then updated, taking into account the optimality condition that is obtained using Pontryagin Maximum Principle, and mapped onto the feasible interval $[0, 1]$.

The numerical iteration is terminated when

$$\max_{i=1,2,3} \|u_i^{(k+1)} - u_i^{(k)}\|_{\infty} < 10^{-6}.$$

The objective functional is evaluated using the trapezoidal rule. The numerical solution therefore consists of the state trajectories, adjoint trajectories, and corresponding optimal control functions satisfying the necessary optimality system to the prescribed numerical tolerance. For the simulations, the intervention period was taken as $T = 10$ days, with a time step of $\Delta t = 0.01$ days.

The control variables are constrained by $0 \leq u_i(t) \leq 1$, $i = 1, 2, 3$. The initial conditions were chosen as $(E_S(0), E_I(0), V(0), P(0), C(0), Z(0)) = (0.80, 0.05, 0.02, 0.02, 0.005, 0.01)$. The resulting

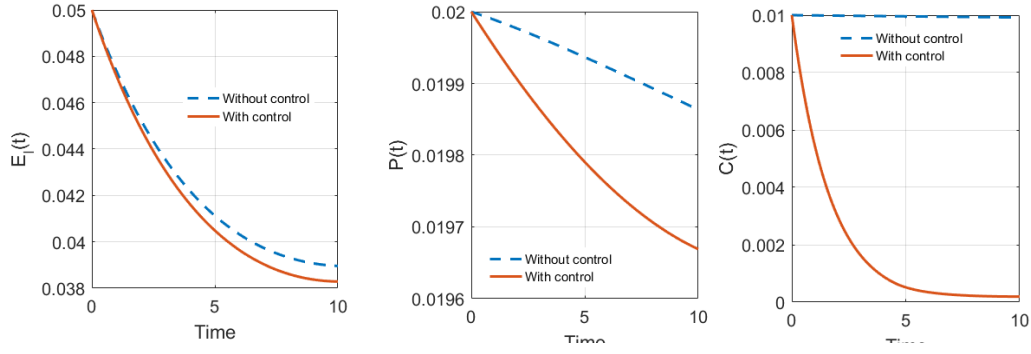


Fig. 7 Optimal system solutions are plotted using parameter values as in Table 1 except $\beta = 0.0124, \mu_V = 0.05$.

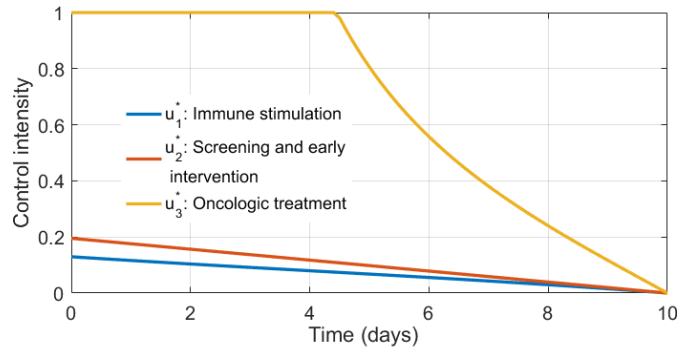


Fig. 8 Control functions are plotted as function of time. Parameter values are same as in Figure 7.

trajectories are used to examine the temporal evolution of infected epithelial cells, viral load, precancerous lesions, cervical cancer, and the immune response under optimal intervention. To assess the effect of intervention, the controlled trajectories are compared with the corresponding uncontrolled model obtained by setting $u_1(t) = u_2(t) = u_3(t) = 0$ throughout the simulation period.

Figure 7 illustrates the temporal dynamics of the infected epithelial cell population $E_I(t)$, precancerous lesion population $P(t)$, and cervical cancer population $C(t)$, with and without optimal control. The infected epithelial cell population decreases in both scenarios, with a slightly faster reduction under optimal control. This suggests that the combined interventions improve the suppression of HPV infection. Similarly, the precancerous lesion population decreases more noticeably under optimal control, indicating the potential benefit of screening-linked treatment and early intervention in limiting precancerous disease. The most pronounced difference is observed in the cervical cancer population, which declines rapidly under optimal control but remains nearly constant without control. This result highlights the potential importance of oncologic treatment in reducing the cancer burden.

Figure 8 shows the plots for the optimal control of immune stimulation $u_1^*(t)$, screening and early intervention $u_2^*(t)$, and oncologic treatment $u_3^*(t)$. Optimal control for immune stimulation and screening are utilized at low intensity initially and then decreases to zero progressively with the advancement of the time horizon. On the other hand, the optimal oncologic treatment is utilized initially at its maximum intensity and then progressively decreases to zero near the terminal time.

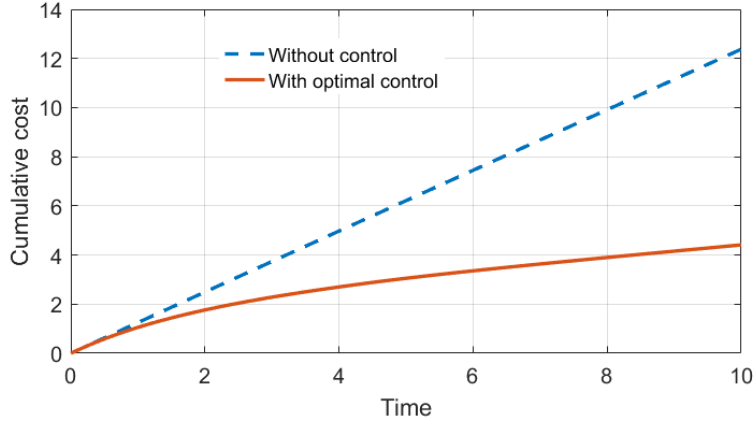


Fig. 9 Cost function is plotted for two cases: with and without control. Parameter values are same as in Figure 7.

Such a behavior indicates that an intensive oncologic treatment is given priority in the initial time period when the reduction in cancer burden becomes significant.

Figure 9 shows the comparison between the accumulated objective functional with and without optimal control. Cost accumulates over time regardless of the presence of the optimal control strategy. In spite of such accumulation, the cost accumulated under the optimal control remains significantly lower than the case without optimal control. At the final time $T = 10$, the accumulated cost under optimal control is around 4.4 while without optimal control the value of the objective function is around 12.4.

In summary, the results from the optimal control problem show that the best strategy of control can reduce the impact of HPV infection along with the effects that it causes on people which include the development of precancerous and cancers cases. It was also found through the simulation that timing and the strength of the intervention measures are crucial to managing the disease effectively. The above findings are predictions based on the assumed model parameters and should not be viewed as a clinical treatment plan.

9 Discussion and Conclusion

In our work, we constructed a deterministic within-host model accounting for the interaction between HPV infection, epithelial turnover, viral load, cell-mediated immunity, premalignant lesion, and resulting cervical cancer burden. In this model, there is a common epithelial capacity restriction that captures the process of tissue renewal and crowding, while the cancer component is a downstream progression-removal compartment. This model takes account of the main features of the infection and lesion process without any unnecessary assumption regarding the autonomous tumor growth process.

The mathematical analysis proves the positivity and boundedness of the solution and describes the infection-free equilibrium, infected boundary equilibrium, and positive coexistence equilibrium. The HPV invasion condition in this model reflects the process of infection and infected cell multiplication due to both viral infection and viral load. Moreover, since the cancer component does not affect the upstream submodel, its eigenvalue is negative whenever the removal rate is positive. Therefore, the stability and Hopf bifurcation conditions are governed by the five-dimensional epithelial-viral-immune-lesion submodel.

Numerical simulations show that changes in viral clearance, epithelial proliferation, transmission, and immune system-induced clearance affect the stability and feasibility of the coexistence equilibrium. Numerically, there is an interesting Hopf bifurcation at $\mu_V^H \approx 0.0872174 \text{ day}^{-1}$. Transversality of the bifurcation together with the negative value of the first Lyapunov coefficient confirm the supercritical character of the bifurcation based on the convention used here. For $\mu_V = 0.08 \text{ day}^{-1}$, the simulation of long-term dynamics confirms sustained oscillations with the period of 759 days. Exceptionally large transient time demonstrates the necessity to integrate for sufficiently long times in case of investigation of weak instabilities. Nevertheless, this is an illustrative mathematical example and not a calibrated description of HPV dynamics in humans.

Three different intervention methods within the optimal control approach are: immune stimulation therapy, screening-based treatment of precancerous lesions and oncologic treatment of cancer burden. In this study, Pontryagin's Maximum Principle is used to find the corresponding adjoint equations and optimal control characterizations. The numerical solution of the problem with the forward-backward sweep algorithm shows how the intervention intensity can vary through the period of treatment depending on the disease burden and intervention costs. From the comparison of controlled and uncontrolled dynamics, it can be concluded that the interventions can help to lower the levels of infection, precancerous lesion and cancer burden in the model. However, the results obtained depend on the parameter values, initial conditions, objective function and period of intervention chosen.

The sensitivity analysis of the invasion threshold provides further insight into the relative influence of model parameters on HPV establishment. Such analysis can help identify influential parameters for future calibration, although sensitivity of the invasion threshold does not necessarily imply equivalent sensitivity of long-term disease burden or optimal intervention outcomes. Careful interpretation is therefore required when translating mathematical sensitivity results into biological or therapeutic conclusions.

A significant drawback of this study is the lack of parameter calibration and independent validation for quantitative model analysis. Longitudinal data and public data from the PAPCLEAR study offer the opportunity to perform such a calibration procedure for the infection-immune subsystem [19, 20]. One may wish to determine whether the model captures observed rises and falls in viral load with consideration of parameter uncertainty and identifiability. Special attention must be paid to epithelial proliferation and turnover, viral production and elimination, and immune-mediated elimination. Additional natural history and clinical data will be needed to obtain accurate estimates of precancer progression and cancer elimination parameters. It would be possible to consider genotype-specific infection, additional immune mechanisms, and realistic screening and treatment protocols in future extensions of the model.

In summary, the developed mathematical model offers a unified framework to study HPV invasion, epithelial-immune interactions, dynamical systems with oscillations, development of precancerous lesions, subsequent cancer burden, and optimization of interventions. The main contributions of this study include an invasion threshold that takes into account infected cell proliferation and virus spread, the demonstration of Hopf bifurcations in the illustrative case, and optimal interventions at various stages of the disease progression process.

Acknowledgments

The authors extend their appreciation to the Deanship of Research and Graduate Studies at King Khalid University for funding this work through the Large Group Project under grant number (RGP.2/58/46).

Conflict of interest

The authors declare there is no conflict of interest.

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