

Modeling the transmission dynamics and vaccination strategies for human papillomavirus infection: An optimal control approach

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Abstract

Human papillomavirus (HPV) vaccines have been introduced in several countries and have shown positive results in reducing HPV infection and related diseases. Nevertheless, immunization programs remain suboptimal and more effort is needed to design efficient vaccination deployment. We formulate a two-sex deterministic mathematical model that incorporates the most important epidemiological features of HPV infection and associated cancers. To assess the population-level impact of HPV immunization programs, the model incorporates school-based vaccine delivery for juveniles and catch-up vaccination for adults. The dynamics of the model are rigorously analyzed using the next-generation operator, the center manifold theorem, and normal forms theory. We formulate an optimal control problem to determine the best deployment strategy for HPV vaccination for several plausible scenarios. We establish the existence of solutions of the optimal control problem, and use Pontryagin's Minimum Principle to characterize the necessary conditions for optimal control solutions. The findings suggest that if girls-only programs are complemented with catch-up vaccination for adult females, such program has the potential to achieve HPV-associated cancers eradication even if boys and males do not receive the vaccine. We also find that the optimal vaccine deployment, in term of minimizing HPV associated diseases and the cost of vaccination, is to allocate as much vaccines as possible at the initial phase of the epidemic and once a high vaccination coverage is reached then gradually decrease vaccination rates.

Keywords: Epidemic model, Optimal Control, Vaccination, HPV, Disease modeling

1. Introduction

Cervical cancer (CC) is currently estimated to be the fourth most common cancer in women worldwide and the second most frequent among women in low- and middle-income countries (LMICs). According to the Global Cancer Observatory (GLOBOCAN), in 2018, 570000 women were diagnosed with CC worldwide and more than 300 000 died from the disease [7]. Most cases of human papillomavirus (HPV) infections are asymptomatic and transient. However, persistent infection with oncogenic HPV types, also known as high-risk HPVs, is the main etiological factor for the development of cervical lesions [42]. Oropharyngeal, anal, cervical, vaginal, vulvar, and penile cancers have also been linked in varying degrees with high-risk HPV types. HPV genotypes are highly diverse and more than 200 have been identified to date of which approximately 40 infect the genital area [50]. However, only a small group of HPV genotypes are responsible for most of the burden, with 12 HPV types classified as carcinogenic to humans (HPVs 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59). In particular, approximately 70% of CC cases could be attributed to HPV-16 and 10% to HPV-18 [57]. HPV-CC has triggered the development of HPV vaccines. Currently, there are three vaccines available and approved by the U.S. Food and Drug Administration (FDA). The most recent, Gardasil 9 (9vHPV), is a 9-valent HPV vaccine approved for use in men and women aged 9 to 45 [22].

Widespread HPV vaccination has the potential to crucially reduce HPV-related cancers by preventing the infections that cause them. Nevertheless, HPV infection is still one of the most common sexually transmitted infections (STIs) worldwide and successful immunization has mainly occurred in high-income countries [58]. As a consequence, in 2018, approximately 85% of the 570000 CC cases occurred in LMICs [7]. In Latin America, the prevalence of HPV infection is almost twice as high in comparison with the worldwide average. Moreover, according to data of the Pan American Health Organization (PAHO), if current trends continue, by 2030, CC incidence in Latin America will increase to more than 110,000 cases annually [45]. In Mexico, current estimates indicate that every year approximately 10000 women are diagnosed with cervical cancer and almost 4500 die from the disease, making Mexico the country with the highest mortality from CC within OECD countries.

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In recognition that prevention with HPV vaccination and early treatment of CC are highly cost-effective strategies, the Director-General of the World Health Organization (WHO) made a global call in 2018 for action towards the elimination of CC [26]. Consequently, several key players have supported the WHO mission in multiple ways. As recently remarked by Brisson et al. [8], strategic mathematical modeling is needed to address fundamental questions in the global strategy. In particular, research is needed to evaluate and design the most efficient and cost-effective strategies to reach CC elimination.

In recent years, a number of mathematical modeling studies have been developed to investigate key epidemiological and clinical aspects of HPV infection, e.g. [1, 2, 5, 9, 20, 19, 24, 25, 35, 40, 39, 48, 47, 46, 50, 55, 54]. Although these and other relevant studies have greatly increased our knowledge about the natural history of HPV disease, ample opportunity remains for advancing our knowledge of HPV dynamics and guiding decision-makers in the implementation of immunization programs [31]. Since the introduction of HPV vaccines in 2006, they have been progressively introduced in a variety of national immunization schedules. By June 2020, 107 of the 194 WHO member states have introduced HPV vaccination nationwide. However, there have been large discrepancies in coverage and targeted groups among countries [10]. The vaccination program depends on country-specific factors, mainly on the economic and geographical constraints as well as the healthcare system organization. Early immunization programs targeted pre-adolescent girls 9-14 years old supported by some mathematical modeling studies that have found this intervention to be cost-effective (see [8] and the references therein). Some countries including Australia and the UK targeted a wider age range of females as part of catch-up programs with positive results reducing HPV associated burden [29, 33]. By 2019, more than 30% of the programs were gender-neutral (GN) in the sense that both females and males can receive the vaccine. Nevertheless, 79% of GN programs are from high-income countries and 21% from upper-middle-income countries [10]. The optimal vaccine distribution between genders is still a matter of debate. Further studies are needed to investigate under which conditions the inclusion of males and adult females into existing vaccination programs is cost-effective [59, 62].

The rest of this paper is organized as follows. In the next section, we formulate and calibrate a two-sex epidemic model to represent the transmission dynamics of HPV infection in a heterosexual population. The basic reproduction number and the stability properties of equilibrium points are obtained in section 3. Rigorous optimal control analysis is carry-out using Pontryagin's maximum principle in section 4. Extensive numerical simulations are presented in section 5 to support the analytical results. Finally, the

discussion of the results is given in section 6.

2. Model formulation

The main routes of transmission for HPV infection are skin-to-skin or skin-to-mucosa contacts. Mother-to-child transmission is also possible, but sexual intercourse is the primary route of HPV infection [4]. Consistent with this fact, we propose a Kermack-McKendrick-type model to investigate the transmission dynamics of the HPV in a heterosexual population of variable size $N(t)$ where acquisition of HPV infection is only possible by sexual intercourse. The model is structured by sex, hence, $N(t) = N_f(t) + N_m(t)$, where $N_f(t)$ is the total female population and $N_m(t)$ is the total male population (subscripts f, m will represent females and males, respectively). The epidemiological structure of our model is based on the natural history of infections with the HPV-types targeted by Gardasil-9 (HPVs 6, 11, 16, 18, 31, 33, 45, 52, and 58) given that these types are responsible for up to 90% of CC cases. As a simplification, we combined infection by any of these types into a single composite type.

In most cases, genital HPV infections do not develop clinical symptoms and clear within two years. In general, the average incubation period of HPV is between 1 month and two years [31]. Individuals with latent HPV infection can transmit the virus [2]. After the latent period, some individuals might develop a symptomatic infection that can persist for a long time (a persistent infection is commonly defined as detection of the same high-risk HPV types at 2 visits 4–6 months apart) [42]. Such persistent infections are the most important risk factor for cervical cancer precursor lesions. Females with a persistent HPV infection might develop cervical intraepithelial neoplasia (CIN), a precancerous condition in which abnormal cells grow on the surface of the cervix. CIN starts as a low-grade neoplasia (CIN 1) but may progress further to CIN 3 and cervical cancer if untreated [31]. Besides cervical, vaginal, and vulvar cancers, both oropharyngeal and anal cancers occur in both sexes. HPV-disease can cause precancerous conditions in men, in particular, penile intraepithelial neoplasia and invasive penile carcinomas [19]. In view of the above biological considerations, we subdivide the female (male) subpopulation of size $N_f(t)$ ($N_m(t)$) into six mutually exclusive compartments: susceptible females (males) $S_f(t)$ ($S_m(t)$), vaccinated females (males) $V_f(t)$ ($V_m(t)$), asymptomatic infectious females (males) $A_f(t)$ ($A_m(t)$), females (males) with a symptomatic and persistent infection $I_f(t)$ ($I_m(t)$), females (males) in a precancerous stage $P_f(t)$ ($P_m(t)$), and females (males) with HPV-related cancer $C_f(t)$ ($C_m(t)$). Therefore,

$$N_j(t) = S_j(t) + V_j(t) + A_j(t) + I_j(t) + P_j(t) + C_j(t), \quad j = f, m. \quad (1)$$

The model assumes that individuals enter the sexually active population at a constant rate Λ_k , and leave the population by ceasing sexual activity at a per capita rate μ_k ($k = f, m$). A fraction w_f (w_m) of adolescent females (males) are vaccinated before they enter the sexually active class and thus are recruited into their vaccinated compartment V_f (V_m). We also consider a vaccination program such that non-vaccinated susceptible sexually active females and males are vaccinated at per-capita rates u_f and u_m , respectively. Current HPV vaccines are prophylactic vaccines that do not treat pre-existing infections, hence, we do not consider their effect on people already infected [56]. HPV vaccines can efficiently prevent HPV infection and CC precursor lesions ($> 90\%$ efficacy [15]), but, for the sake of simplicity, we assume vaccines are 100% effective in preventing HPV infection. We assume that vaccine-induced immunity wanes at a rate θ_j ($j = f, m$); thus, for $\theta_j = 0$ the protection is lifelong. Susceptible females (males) might acquire HPV infection after sexual contacts with infectious males (females) with a force of infection λ_m (λ_f) that considers a frequency-dependent transmission,

$$\lambda_m = \frac{\beta_A^m A_m + \beta_I^m I_m}{N_m}, \quad \lambda_f = \frac{\beta_A^f A_f + \beta_I^f I_f}{N_f}. \quad (2)$$

Here β_A^m (β_A^f) is the transmission rate from asymptomatic infectious males (females) to susceptible females (males). Likewise, β_I^m (β_I^f) is the transmission rate from symptomatic infectious males with persistent HPV infection (females) to susceptible females (males). We assume that people who enter a precancerous stage do not contribute to the force of infection. Following infection, individuals enter to the corresponding asymptomatic infectious class A_j , ($j = f, m$), where a fraction q_A^j recovers from the disease and the rest develop a persistent HPV infection after a mean latent period of $1/k_A^j$ years ($j = f, m$). The population in the persistent infection class leave this class at a rate k_I^j with a fraction q_I^j recovered and a fraction $1 - q_I^j$ ($j = f, m$) that progress to the precancerous stage. k_P^j ($j = f, m$) denotes the rate at which individuals in the precancerous stage leave the class P_j ($j = f, m$) with a proportion q_P^j recovered and $1 - q_P^j$ developing HPV-associated cancer. The population in the classes C_j ($j = f, m$) decreases due to cancer-induced death at a rate δ_j ($j = f, m$). The existence and magnitude of the naturally acquired protection after HPV infection is still uncertain. Recent studies suggest that rather than inducing protective immunity, HPV infection increases the risk of future infection even by the same HPV-type [2, 52]. Accordingly, we assume no immunity after recovery in the classes A_j, I_j, P_j ($j = f, m$). Furthermore, since most individuals with HPV-associated cancers will require surgery that usually involves the removal of tissues around the cervix (for women), we

assume that in case of recovery, the population in the classes C_j ($j = f, m$) do not acquire reinfection and no longer contribute to the transmission of the infection [2, 40].

Under these considerations, the HPV epidemic model is given by the following system of 12 differential equations:

$$\begin{aligned}
\dot{S}_i &= (1 - w_i)\Lambda_i - (\lambda_j + u_i + \mu_i)S_i + q_A^i k_A^i A_i + q_I^i k_I^i I_i + q_P^i k_P^i P_i + \theta_i V_i, \\
\dot{V}_i &= w_i \Lambda_i + u_i S_i - (\mu_i + \theta_i) V_i, \\
\dot{A}_i &= \lambda_j S_i - (k_A^i + \mu_i) A_i, \\
\dot{I}_i &= (1 - q_A^i) k_A^i A_i - (k_I^i + \mu_i) I_i, \quad i, j \in \{f, m\}, \quad i \neq j, \\
\dot{P}_i &= (1 - q_I^i) k_I^i I_i - (k_P^i + \mu_i) P_i, \\
\dot{C}_i &= (1 - q_P^i) k_P^i P_i - (\delta_i + \mu_i) C_i,
\end{aligned} \tag{3}$$

where all the parameters are nonnegative. Fundamental state variables of the HPV model (3) are summarized in Table 1. The intervention measures, namely, the vaccination rates will be called controls and denoted by the vector $\mathbf{c} = (w_f, w_m, u_f, u_m)^T$.

Variable	Description
N_f (N_m)	Total female (male) population
S_f (S_m)	Susceptible females (males)
V_f (V_m)	Vaccinated females (males)
A_f (A_m)	Asymptomatic infectious females (males)
I_f (I_m)	Infectious females (males) with persistent HPV infection
P_f (P_m)	Females (males) in a precancerous stage
C_f (C_m)	Females (males) with HPV-related cancer

Table 1: Variables of the two-sex HPV epidemic model (3).

2.1. Model calibration

We consulted a wide range of HPV epidemiological studies to obtain appropriate model parameters for the system (3). When available, we used data sources relevant to the population in Mexico City. Table 2 provides a summary of parameter values and their reference.

2.1.1. Demographic parameters

2020 Census data from Mexico's National Institute of Statistics and Geography (INEGI) has shown that Mexico City's population was 9209494 (not including the larger metropolitan area that connects to other municipalities of other states). Approximately 70% of this population is aged 15-65 with approximately 52% females and 48% males. Therefore, for the purpose of our numerical simulations, we set $N_m(0) = 3094541$ and $N_f(0) = 3352419$ [44]. The estimated population annual growth rate in Mexico City during 2020 was 0.51% [44]. Hence, we can take a crude approximation of the recruitment rate of new sexually active males as $\Lambda_m = 0.0051 * N_m(0) = 15782$. Likewise, for females, we have $\Lambda_f = 0.0051 * N_f(0) = 17097$ per year. Using information gathered from more than 6000 women and men, it has been estimated that sexually active life expectancy was longer for men [37]. Accordingly, we assume $1/\mu_m = 50$ years, $1/\mu_f = 40$ years.

2.1.2. Parameters associated with disease progression and recovery

The average infectious period is a major element of the rate of spread of infectious diseases. Mechanistic epidemic models for HPV transmission usually separate the time spent with HPV infection before CIN apart from the time with CIN [2, 17, 21, 20, 19, 48]. Several studies have consistently shown that the majority of HPV infections are transient and no longer detectable within 2 years [3, 31, 41, 43]. In particular, approximately 70% of HPV infections clear within one year and 90% within two years. Therefore, we postulate an incubation period of $1/k_A^j = 1$ year in which 70% of the individuals recover from the disease $q_A^j \approx 0.7$ ($j = f, m$). Among women, the meta-analysis [53] found that the average duration of a clinical HPV infection was 9.8 months, so $1/k_I^f = 0.81$ years. Given that [3] and the references therein, reported a median time to clearance of 7.5 months for men, we take $1/k_I^m = 0.62$ years. We also assume up to 90% of infection clear before a detectable precancerous stage, hence, $q_I^j \approx 0.9$ ($j = f, m$). In women, progression from low-grade neoplasia CIN-1 to severe dysplasia CIN-3 may take several years [31]. In women with a normal immune system, it takes 15 to 20 years for an HPV infection to become an invasive cancerous growth. Nevertheless, in women with weakened immune systems, it can take only 5 to 10 years. We take an average time of $1/k_P^f = 15$ years. The development of cancers of the penis, anus, and oropharynx associated with HPV infections in men also takes several years. However, there is a knowledge gap concerning the natural history of HPV infection and progression to cancer in men [3]. For simplicity, we postulate $1/k_P^m = 15$ years. According to data from the Center for Disease Control (CDC), approximately 70% of HPV-associated cancers diagnosed annually occur in women and only 30% in men [14], there-

fore, $q_P^m > 2q_P^f$. For the purpose of the numerical experiments we assume $q_P^m = 0.9$, $q_P^f = 0.4$. Finally, the mortality rate induced by CC in women has been estimated to be between $\delta_f \in [0.0004, 0.0572]$ [35], we fix $\delta_f = 0.001$. The mortality rate induced by HPV-related cancers in men is assumed to be less in comparison with the females' rate, $\delta_m = 0.5\delta_f$.

2.1.3. Transmission rates and vaccine protection.

The high prevalence of HPV worldwide suggests that HPV is easily transmitted. Very few studies have examined HPV transmission dynamics in heterosexual couples [11, 27, 63]. Burchell et al. [11] estimated HPV transmission rates among 179 couples with documented sexual exposure to an infected partner. They found no difference between male-to-female transmission rates and female-to-male transmission rates. However, they argue that female-to-male transmission may occur more often, but may produce more transient infection in males that clear before the study follow-up time [11]. A more recent study [63] has found that female-to-male transmission appeared more common than male-to-female transmission. Moreover, their observed transmission rates were extremely high supporting a per-partnership transmission probability of close to 100% [63]. Assuming that both genders have between 0 and 6 sexual partners [6], we set $\beta_i^j \in [0.0, 6]$ $year^{-1}$ ($j = f, m$, $i = A, I$). In addition, considering that HPV infected individuals with clinical symptoms have on average higher viral load in comparison with asymptomatic carriers, we will assume that $\beta_A^j < \beta_I^j$ ($j = f, m$). In particular, we assume $\beta_I^f = 5.0$, $\beta_I^m = 3.0$, $\beta_A^f = 2.5$, $\beta_A^m = 1.5$. Recent evidence suggests that HPV vaccines can prevent the incidence of infection at least 10 years [15], we take $1/\theta_j = 20$ years ($j = f, m$).

3. Model analysis

3.1. Basic properties

It is straightforward to check that for both sexes, their population satisfies

$$\dot{N}_i = \Lambda_i - \mu_i N_i - \delta_i C_i \leq \Lambda_i - \mu_i N_i, \quad i \in \{f, m\}. \quad (4)$$

Hence, $\dot{N}_i < 0$ if $N_i > \Lambda_i/\mu_i = N_i^\dagger$ ($i = f, m$). Moreover, from standard comparison theorems for ODEs [34], we have

$$N_i(t) \leq N_i(0)e^{-\mu_i t} + \frac{\Lambda_i}{\mu_i}(1 - e^{-\mu_i t}), \quad i \in \{f, m\}. \quad (5)$$

As a consequence, $N_i \leq N_i^\dagger$ if $N_i(0) \leq N_i^\dagger$ ($i = f, m$). Therefore, the biologically feasible region for model (3) given by $\Omega = \Omega_f \cup \Omega_m$, where

Parameters	Range	Mean Value	units	References
Λ_f	[5000, 20000]	17097	<i>individuals year⁻¹</i>	[44]
Λ_m	[5000, 20000]	15782	<i>individuals years⁻¹</i>	[44]
$1/\mu_m$	[10, 60]	50	<i>years</i>	[37]
$1/\mu_f$	[10, 60]	40	<i>years</i>	[37]
$1/k_A^f, 1/k_A^m$	[0.1, 2]	1	<i>years</i>	[3, 31, 41, 43]
q_A^m	[0, 1]	0.8	<i>dimensionless</i>	[3, 31, 41]
q_A^f	[0, 1]	0.6	<i>dimensionless</i>	[3, 31, 41]
$1/k_I^f$	[0.1, 2]	0.81	<i>years</i>	[53]
$1/k_I^m$	[0.1, 2]	0.62	<i>years</i>	[3]
q_I^m	[0, 1]	0.9	<i>dimensionless</i>	[3, 31, 41]
q_I^f	[0, 1]	0.8	<i>dimensionless</i>	[3, 31, 41]
$1/k_P^f, 1/k_P^m$	[5, 30]	15	<i>years</i>	[31, 49]
q_P^f	[0, 1]	0.4	<i>dimensionless</i>	[14]
q_P^m	[0, 1]	0.9	<i>dimensionless</i>	[14]
δ_f	[0.0004, 0.0572]	0.001	<i>year⁻¹</i>	[35]
δ_m	[0.0004, 0.0572]	0.0005	<i>year⁻¹</i>	[3, 49]
β_I^f	[0.05, 6]	4.0	<i>year⁻¹</i>	[6]
β_I^m	[0.05, 6]	3.0	<i>year⁻¹</i>	[6]
β_A^f	[0.05, 6]	2.0	<i>year⁻¹</i>	[6, 55]
β_A^m	[0.05, 6]	1.5	<i>year⁻¹</i>	[6, 55]
$1/\theta_f, 1/\theta_m$	[5, 30]	20	<i>year</i>	[30]

Table 2: Parameters of the HPV epidemic model (3), sample units and source of estimation.

$$\begin{aligned}\Omega_f &= \left\{ S_f, V_f, A_f, I_f, P_f, C_f \geq 0 : N_f \leq N_f^\dagger \right\}, \\ \Omega_m &= \left\{ S_m, V_m, A_m, I_m, P_m, C_m \geq 0 : N_m \leq N_m^\dagger \right\},\end{aligned}$$

is positively-invariant. Furthermore, if $N_i(0) \geq N_i^\dagger$, then either the solution enters Ω in finite time, or $N_i(t) \rightarrow N_i^\dagger$ as $t \rightarrow \infty$ and the prevalence of the infection $A_i + I_i + P_i + C_i$ approaches zero ($i = f, m$). Thus, solutions trajectories satisfy the usual positiveness and continuity properties and the model is both epidemiologically and mathematically well-posed [28].

3.2. Disease-free equilibrium and the basic reproduction number

To compute the coordinates of the disease-free equilibrium (DFE), we set the rate of change of all state variables in model (3) equal to zero. Solving the system of algebraic equations we find a unique DFE

$$E_0 = (S_f^0, S_m^0, V_f^0, V_m^0, 0, 0, 0, 0, 0, 0, 0) \quad (6)$$

where

$$S_i^0 = \frac{((1-w_i)\mu_i + \theta_i)N_i^\dagger}{u_i + \mu_i + \theta_i}, \quad V_i^0 = \frac{(u_i + \mu_i w_i)N_i^\dagger}{u_i + \mu_i + \theta_i}, \quad i \in \{f, m\}. \quad (7)$$

To analyze the behavior of the epidemic at the early stage of the epidemic, we use the classical next generation operator $\mathbf{K} = \mathbf{F}\mathbf{V}^{-1}$; see [18]. Following the notation in [60], the vectors that describe the new infection terms and the transfer terms are given by,

$$\mathcal{F} = \begin{pmatrix} \lambda_m S_f \\ \lambda_f S_m \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad \text{and} \quad \mathcal{V} = \begin{pmatrix} (k_A^f + \mu_f)A_f \\ (k_A^m + \mu_m)A_m \\ -(1 - q_A^f)k_A^f A_f + (k_I^f + \mu_f)I_f \\ -(1 - q_A^m)k_A^m A_m + (k_I^m + \mu_m)I_m \\ -(1 - q_I^f)k_I^f I_f + (k_P^f + \mu_f)P_f \\ -(1 - q_I^m)k_I^m I_m + (k_P^m + \mu_m)P_m \\ -(1 - q_P^f)k_P^f P_f + (\delta_f + \mu_f)C_f \\ -(1 - q_P^m)k_P^m P_m + (\delta_m + \mu_m)C_m \end{pmatrix}.$$

Hence,

$$\mathbf{F} = \begin{bmatrix} \mathbf{F}_1 & \mathbf{0}_{4 \times 4} \\ \mathbf{0}_{4 \times 4} & \mathbf{0}_{4 \times 4} \end{bmatrix} \quad \text{and} \quad \mathbf{V} = \begin{bmatrix} \mathbf{V}_1 & \mathbf{0}_{4 \times 4} \\ \mathbf{V}_2 & \mathbf{V}_3 \end{bmatrix}. \quad (8)$$

where $\mathbf{F}_1, \mathbf{V}_j, j = 1, 2, 3$ are 4×4 matrices. In particular,

$$\mathbf{F}_1 = \begin{bmatrix} 0 & \frac{\beta_A^m S_f^0}{N_m^\dagger} & 0 & \frac{\beta_I^m S_f^0}{N_m^\dagger} \\ \frac{\beta_A^f S_m^0}{N_f^\dagger} & 0 & \frac{\beta_I^f S_m^0}{N_f^\dagger} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

$$\mathbf{V}_1 = \begin{bmatrix} k_A^f + \mu_f & 0 & 0 & 0 \\ 0 & k_A^m + \mu_m & 0 & 0 \\ -\left(1 - q_A^f\right) k_A^f & 0 & k_I^f + \mu_f & 0 \\ 0 & -(1 - q_A^m) k_A^m & 0 & k_I^m + \mu_m \end{bmatrix}.$$

Therefore, the basic reproduction number of the HPV epidemic model is given by

$$R_0 = \rho(\mathbf{K}) = \rho(\mathbf{F}\mathbf{V}^{-1}) = \rho(\mathbf{F}_1\mathbf{V}_1^{-1}) = \sqrt{R_m R_f} \quad (9)$$

where

$$R_i = \left(\frac{\beta_A^i}{(k_A^i + \mu_i)} + \frac{(1 - q_A^i)k_A^i\beta_I^i}{(k_A^i + \mu_i)(k_I^i + \mu_i)} \right) \frac{S_j^0}{N_i^\dagger}, \quad i, j \in \{f, m\}, i \neq j. \quad (10)$$

The biological interpretation of the reproduction number (10) is as follows. The term $\beta_A^i S_j^0 / (k_A^i + \mu_i) N_i^\dagger$ measures the contribution of asymptotically infected individuals, where $\beta_A^i S_j^0 / N_i^\dagger$ is the average number of effective contacts of asymptomatic individuals during their infectious period $(k_A^i + \mu_i)^{-1}$. In the second term in (10), a fraction $(1 - q_A^i)$ of the asymptomatic leaves the class at a rate k_A^i and enters the symptomatic infectious class. These individuals have on average $\beta_I^i S_j^0 / N_i^\dagger$ effective contacts during their infectious period $(k_I^i + \mu_i)^{-1}$.

As a consequence of Theorem 2 in [60], we can enunciate the following result.

Theorem 3.1. *The HPV epidemic model (3) has a unique disease-free equilibrium given by E_0 which is locally asymptotically stable if the basic reproduction number given by (9) satisfies $R_0 < 1$, and unstable otherwise.*

3.3. Existence and stability of the endemic equilibrium

In this section, we will show that there exists a unique positive equilibrium point for model (3) given by

$$E^* = (S_f^*, S_m^*, V_f^*, V_m^*, A_f^*, A_m^*, I_f^*, I_m^*, P_f^*, P_m^*, C_f^*, C_m^*). \quad (11)$$

We start by expressing the infectious classes I_j, P_j, C_j as functions of the asymptomatic infectious class A_j , ($j = f, m$), as follows,

$$\begin{aligned} I_f^* &= \alpha_0 A_f^*, & \alpha_0 &= \frac{(1 - q_A^f)k_A^f}{k_I^f + \mu_f}, \\ I_m^* &= \alpha_1 A_m^*, & \alpha_1 &= \frac{(1 - q_A^m)k_A^m}{k_I^m + \mu_m}, \\ P_f^* &= \alpha_2 A_f^*, & \alpha_2 &= \frac{(1 - q_I^f)k_I^f \alpha_0}{k_P^f + \mu_f}, \\ P_m^* &= \alpha_3 A_m^*, & \alpha_3 &= \frac{(1 - q_I^m)k_I^m \alpha_1}{k_P^m + \mu_m}, \\ C_f^* &= \alpha_4 A_f^*, & \alpha_4 &= \frac{(1 - q_P^f)k_P^f \alpha_2}{\delta_f + \mu_f}, \\ C_m^* &= \alpha_5 A_m^*, & \alpha_5 &= \frac{(1 - q_P^m)k_P^m \alpha_3}{\delta_m + \mu_m}. \end{aligned} \quad (12)$$

In an analogous way, solving the equations of model (3) for the variables V_f^* and V_m^* as function of S_f^* and S_m^* , respectively, we obtain

$$\begin{aligned}
V_f^* &= \alpha_6 + \alpha_7 S_f^*, & \alpha_6 &= \frac{w_f \Lambda_f}{\mu_f + \theta_f}, & \alpha_7 &= \frac{u_f}{\mu_f + \theta_f}, \\
V_m^* &= \alpha_8 + \alpha_9 S_m^*, & \alpha_8 &= \frac{w_m \Lambda_m}{\mu_m + \theta_m}, & \alpha_9 &= \frac{u_m}{\mu_m + \theta_m}.
\end{aligned} \tag{13}$$

If we substitute the equilibrium values (12) and (13) in the equations for the susceptible and asymptomatic individuals, after some algebraic manipulations we obtain

$$S_f^* = \frac{\alpha_{10} A_f^* + \alpha_{11}}{\alpha_{12}}, \quad S_m^* = \frac{\alpha_{13} A_m^* + \alpha_{14}}{\alpha_{15}},$$

and

$$\begin{aligned}
\frac{(\beta_A^m + \beta_I^m \alpha_1) A_m^* (\alpha_{10} A_f^* + \alpha_{11})}{(\alpha_{16} A_m^* + \alpha_{17}) \alpha_{12}} &= (k_A^f + \mu_f) A_f^*, \\
\frac{(\beta_A^f + \beta_I^f \alpha_0) A_f^* (\alpha_{13} A_m^* + \alpha_{14})}{(\alpha_{18} A_f^* + \alpha_{19}) \alpha_{15}} &= (k_A^m + \mu_m) A_m^*.
\end{aligned} \tag{14}$$

Solving for A_f^* as a function of A_m^* in the first equation in (14), gives

$$A_f^* = \frac{A_m^* \alpha_{15} \alpha_{11} (\beta_A^m + \beta_I^m \alpha_1)}{-\alpha_{10} (\beta_A^m + \beta_I^m \alpha_1) \alpha_{15} A_m^* + \alpha_{12} (\alpha_{13} A_m^* + \alpha_{14}) (1 + \alpha_9) (k_A^f + \mu_f) + \alpha_{21}} \equiv \phi_1(A_m^*).$$

Similarly, solving for A_m^* as a function of A_f^* in the second equation in (14), gives

$$A_m^* = \frac{A_f^* \alpha_{12} \alpha_{14} (\beta_A^f + \beta_I^f \alpha_0)}{-\alpha_{13} (\alpha_{12} \beta_A^f + \alpha_{12} \beta_I^f \alpha_0) A_f^* + \alpha_{15} (A_f^* \alpha_{10} + \alpha_{11}) (1 + \alpha_7) (k_A^m + \mu_m) + \alpha_{20}} \equiv \phi_2(A_f^*),$$

where the auxiliary coefficients are defined as follows,

$$\begin{aligned}
\alpha_{10} &= -k_A^f - \mu_f + q_P^f k_P^f \alpha_2 + q_A^f k_A^f + q_I^f k_I^f \alpha_0, & \alpha_{11} &= \Lambda_f (1 - w_f) + \theta_f \alpha_6, \\
\alpha_{12} &= \left(1 - \frac{\theta_f}{\mu_f + \theta_f}\right) u_f + \mu_f, & \alpha_{13} &= -k_A^m - \mu_m + q_A^m k_A^m + q_I^m k_I^m \alpha_1 + q_P^m k_P^m \alpha_3, \\
\alpha_{14} &= (1 - w_m) \Lambda_m + \theta_m \alpha_8, & \alpha_{15} &= \left(1 - \frac{\theta_m}{\mu_m + \theta_m}\right) u_m + \mu_m, \\
\alpha_{16} &= \frac{\alpha_{13} (1 + \alpha_9)}{\alpha_{15}} + 1 + \alpha_1 + \alpha_3 + \alpha_5, & \alpha_{17} &= \frac{\alpha_{14} (1 + \alpha_9)}{\alpha_{15}} + \alpha_8, \\
\alpha_{18} &= \frac{\alpha_{10} (1 + \alpha_7)}{\alpha_{12}} + 1 + \alpha_0 + \alpha_2 + \alpha_4, & \alpha_{19} &= \frac{\alpha_{11} (1 + \alpha_7)}{\alpha_{12}} + \alpha_6, \\
\alpha_{20} &= \alpha_{15} \alpha_{12} (\alpha_2 + \alpha_4 + \alpha_0 + 1) (k_A^m + \mu_m) A_f^* + \alpha_{15} \alpha_6 \alpha_{12} (k_A^m + \mu_m), \\
\alpha_{21} &= \alpha_{12} \alpha_{15} (\alpha_3 + \alpha_5 + \alpha_1 + 1) (k_A^f + \mu_f) A_m^* + \alpha_{12} \alpha_8 \alpha_{15} (k_A^f + \mu_f).
\end{aligned}$$

Observe that, if $\alpha_{10} < 0$, $\alpha_{13} A_m^* + \alpha_{14} > 0$, $\alpha_{13} < 0$, and $\alpha_{10} A_m^* + \alpha_{11} > 0$, then the denominators of the functions $\phi_1(A_m^*)$ and $\phi_2(A_f^*)$ are positive linear functions for all $A_f^* > 0$ and $A_m^* > 0$. Therefore, $\phi_1(A_m^*)$ is a concave monotonic increasing function of A_m^* while $\phi_2(A_f^*)$ is a concave monotonic increasing function of A_f^* (see Figure 1). The curves $\phi_1(A_m^*)$ and $\phi_2(A_f^*)$

intersect at $(0, 0)$ and at a point (A_{me}^*, A_{fe}^*) with positive coordinates defined as

$$A_{fe}^* = \frac{\alpha_{12}\alpha_{17}\alpha_{15}\alpha_{19}(k_A^m + \mu_m)(k_A^f + \mu_f)(R_0^2 - 1)}{\nu_1 - \alpha_{12}\alpha_{18}\alpha_{15}\alpha_{17}(k_A^m + \mu_m)(k_A^f + \mu_f)} \text{ where}$$

$$\nu_1 = \left(\alpha_{12}(-\alpha_{14}\alpha_{16} + \alpha_{17}\alpha_{13}) \left(k_A^f + \mu_f \right) + \alpha_{14}(\beta_A^m + \beta_I^m \alpha_1) \alpha_{10} \right) \left(\beta_A^f + \beta_I^f \alpha_0 \right).$$

Moreover,

$$A_{me}^* = \frac{A_f^* \alpha_{14} (\beta_A^f + \beta_I^f \alpha_0)}{-(\beta_A^f + \beta_I^f \alpha_0) \alpha_{13} + \alpha_{15} \alpha_{18} (k_A^m + \mu_m) A_f^* + \alpha_{15} \alpha_{19} (k_A^m + \mu_m)}.$$

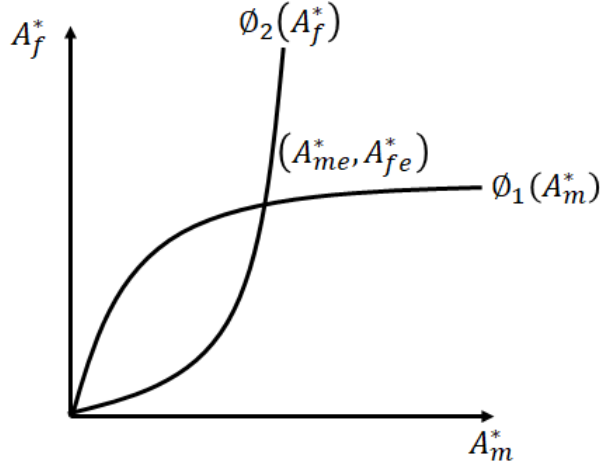


Figure 1: Curves $\phi_1(A_m^*)$ and $\phi_2(A_f^*)$.

Without loss of generality, we will denote the $A_{fe}^* = A_f^*$ and $A_{me}^* = A_m^*$. As a consequence, for the HPV epidemic model (3), there exists an endemic equilibrium point if and only if $R_0 > 1$. Next, we show that the HPV model (3) undergoes a forward bifurcation when $R_0 = 1$. For this, we use the center manifold theorem and normal forms, see [13, 61]. First, we relabel our variables:

$$\begin{aligned} A_f &= x_1, A_m = x_2, I_f = x_3, I_m = x_4, P_f = x_5, P_m = x_6, \\ C_f &= x_7, C_m = x_8, S_f = x_9, S_m = x_{10}, V_f = x_{11}, V_m = x_{12}. \end{aligned} \quad (15)$$

Let $(f_1, f_2, \dots, f_{12})$ be the vector field of system (3) in the notation (15), such that $\dot{x}_i = f_i$, $i = 1, \dots, 12$. Then,

$$\begin{aligned}
f_1 &= \lambda_m x_9 - (k_A^f + \mu_f) x_1, \\
f_2 &= \lambda_f x_{10} - (k_A^m + \mu_m) x_2, \\
f_3 &= (1 - q_A^f) k_A^f x_1 - (k_I^f + \mu_f) x_3, \\
f_4 &= (1 - q_A^m) k_A^m x_2 - (k_I^m + \mu_m) x_4, \\
f_5 &= (1 - q_I^f) k_I^f x_3 - (k_P^f + \mu_f) x_5, \\
f_6 &= (1 - q_I^m) k_I^m x_4 - (k_P^m + \mu_m) x_6, \\
f_7 &= (1 - q_P^f) k_P^f x_5 - (\delta_f + \mu_f) x_7, \\
f_8 &= (1 - q_P^m) k_P^m x_6 - (\delta_m + \mu_m) x_8, \\
f_9 &= (1 - w_f) \Lambda_f - (\lambda_m + u_f + \mu_f) x_9 + q_A^f k_A^f x_1 + q_I^f k_I^f x_3 + q_P^f k_P^f x_5 + \theta_f x_{11}, \\
f_{10} &= (1 - w_m) \Lambda_m - (\lambda_f + u_m + \mu_m) x_{10} + q_A^m k_A^m x_2 + q_I^m k_I^m x_4 + q_P^m k_P^m x_6 + \theta_m x_{12}, \\
f_{11} &= w_f \Lambda_f + u_f x_9 - (\mu_f + \theta_f) x_{11}, \\
f_{12} &= w_m \Lambda_m + u_m x_{10} - (\mu_m + \theta_m) x_{12}.
\end{aligned} \tag{16}$$

Let us first consider the case where $R_0 = 1$. Furthermore, we shall use β_A^f as the bifurcation parameter. Using (9), the value of β_A^f such that $R_0 = 1$ is given by

$$\beta_A^f = \beta^\dagger = \left(\frac{1}{R_f} - \frac{\beta_I^f k_A^f (1 - q_A^f) S_m^0}{(k_A^f + \mu_f)(k_I^f + \mu_f) N_f^\dagger} \right) \frac{S_m^0}{(k_A^f + \mu_f) N_f^\dagger}.$$

For the value β^\dagger , the Jacobian of the transformed system (16) evaluated at the disease-free equilibrium, denoted as $\mathbf{J}_\dagger(E_0)$, has a simple zero eigenvalue $\chi_1 = 0$, while the other eigenvalues are negative. The right eigenvector \mathbf{w} and the left eigenvector \mathbf{v} of $\mathbf{J}_\dagger(E_0)$ for $\chi_1 = 0$ such that $\mathbf{v} \cdot \mathbf{w} = 1$ are given by $\mathbf{w} = (w_1, \dots, w_{12})^T$ where

$$\begin{aligned}
w_1 &= \frac{(k_I^f + \mu_f) w_3}{(1 - q_A^f) k_A^f}, & w_2 &= \frac{k_I^m + \mu_m}{(1 - q_A^m) k_A^m}, & w_3 &= \frac{S_f^0 (\beta_A^m (k_I^m + \mu_m) + k_A^m \beta_I^m (1 - q_A^m)) (1 - q_A^f) k_A^f}{(1 - q_A^m) k_A^m (k_A^f + \mu_f) (k_I^f + \mu_f) N_m^\dagger}, \\
w_4 &= 1, & w_5 &= \frac{(1 - q_I^f) k_I^f w_3}{k_P^f + \mu_f}, & w_6 &= \frac{(1 - q_I^m) k_I^m}{k_P^m + \mu_m}, & w_7 &= \frac{(1 - q_P^f) k_P^f (1 - q_I^f) k_I^f w_3}{(k_P^f + \mu_f) (\delta_f + \mu_f)}, \\
w_8 &= \frac{(1 - q_P^m) k_P^m (1 - q_I^m) k_I^m}{(k_P^m + \mu_m) (\delta_m + \mu_m)}, & w_9 &= \frac{\eta_2 + \eta_3 + \eta_4 + \eta_5}{\eta_1}, & w_{10} &= \frac{\eta_7 + \eta_8 + \eta_9 + q_I^m k_I^m}{\eta_6}, \\
w_{11} &= \frac{u_f w_9}{\mu_f + \theta_f}, & w_{12} &= \frac{u_m w_{10}}{\mu_m + \theta_m},
\end{aligned}$$

and $\mathbf{v} = (v_1, v_2, v_3, v_4, 0, \dots, 0)^T$ where

$$\begin{aligned}
v_1 &= \frac{1}{w_1 + \eta_{10} + \eta_{11}}, & v_2 &= \frac{S_f^0 v_1 (\beta_A^m (k_I^m + \mu_m) + k_A^m \beta_I^m (1 - q_A^m))}{N_m^\dagger (k_I^m + \mu_m) (k_A^m + \mu_m)}, \\
v_3 &= \frac{\beta_I^f S_m^0 S_f^0 v_1 (\beta_A^m (k_I^m + \mu_m) + k_A^m \beta_I^m (1 - q_A^m))}{N_m^\dagger (k_I^m + \mu_m) (k_A^m + \mu_m) N_f^\dagger (k_I^f + \mu_f)}, & v_4 &= \frac{\beta_I^m S_f^0 v_1}{N_m^\dagger (k_I^m + \mu_m)}.
\end{aligned}$$

The coefficients η_j , ($j = 1, \dots, 11$) are constants that depend on the model parameters. To determine the direction of the bifurcation when $R_0 = 1$ we calculate the coefficients a and b described in Theorem 4.1 in [13],

$$\begin{aligned}
a &= 2w_1v_2 \left[w_1 \frac{\partial^2 f_2}{\partial x_1^2} + w_3 \frac{\partial^2 f_2}{\partial x_3 \partial x_1} + w_5 \frac{\partial^2 f_2}{\partial x_5 \partial x_1} + w_7 \frac{\partial^2 f_2}{\partial x_7 \partial x_1} + w_{10} \frac{\partial^2 f_2}{\partial x_{10} \partial x_1} + w_{11} \frac{\partial^2 f_2}{\partial x_{11} \partial x_1} \right] \\
&+ 2w_3v_2 \left[w_5 \frac{\partial^2 f_2}{\partial x_5 \partial x_3} + w_7 \frac{\partial^2 f_2}{\partial x_7 \partial x_3} + w_9 \frac{\partial^2 f_2}{\partial x_9 \partial x_3} + w_{10} \frac{\partial^2 f_2}{\partial x_{10} \partial x_3} + w_{11} \frac{\partial^2 f_2}{\partial x_{11} \partial x_3} \right] \\
&+ 2w_2v_1 \left[w_2 \frac{\partial^2 f_1}{\partial x_2^2} + w_4 \frac{\partial^2 f_1}{\partial x_4 \partial x_2} + w_6 \frac{\partial^2 f_1}{\partial x_6 \partial x_2} + w_8 \frac{\partial^2 f_1}{\partial x_8 \partial x_2} + w_9 \frac{\partial^2 f_1}{\partial x_9 \partial x_2} + w_{10} \frac{\partial^2 f_1}{\partial x_{10} \partial x_2} + w_{12} \frac{\partial^2 f_1}{\partial x_{12} \partial x_2} \right] \\
&+ 2w_4v_1 \left[w_4 \frac{\partial^2 f_1}{\partial x_4^2} + w_6 \frac{\partial^2 f_1}{\partial x_6 \partial x_4} + w_8 \frac{\partial^2 f_1}{\partial x_8 \partial x_4} + w_9 \frac{\partial^2 f_1}{\partial x_9 \partial x_4} + w_{10} \frac{\partial^2 f_1}{\partial x_{10} \partial x_4} + w_{12} \frac{\partial^2 f_1}{\partial x_{12} \partial x_4} \right].
\end{aligned}$$

and $b = v_2w_1 \left(\frac{S_m^0}{N_f^*} \right) > 0$. Since A_f^* is positive when $R_0 > 1$, it can be shown that the coefficient a is negative. Hence, the system (16) or equivalently the HPV model (3) shows a forward bifurcation when $R_0 = 1$. In other words, the endemic equilibrium is locally asymptotically stable for $R_0 > 1$. We summarize the results of this subsection below.

Theorem 3.2. *The HPV epidemic model (3), undergoes a transcritical forward bifurcation when the basic reproduction number given by (9) satisfies $R_0 = 1$. Furthermore, for $R_0 > 1$, model (3) has a unique endemic equilibrium E^* which is locally asymptotically stable.*

4. The optimal control problem

When health resources are limited there is a need to optimize time-varying controls for which optimal control theory is widely used [9, 39, 46, 55]. Due to economic costs associated with both control measures and disease, constant vaccination rates are rarely the best deployment strategy to successfully eradicate an epidemic. We introduce into the HPV model (3) time-dependent vaccination rates $\mathbf{c} = (w_f(t), w_m(t), u_f(t), u_m(t))^T$. Our aim is to find vaccination strategies that minimize the health burden associated with HPV while reducing total costs of vaccination. We propose the following objective functional to measure vaccination costs $(w_f(t), w_m(t), u_f(t), u_m(t))$, as well as health burden due to symptomatic infectious individuals (I_f, I_m) , individuals in precancerous stage (P_f, P_m) , and individuals in HPV-related cancerous

stage (C_f, C_m) :

$$J(\mathbf{c}) = \int_0^T \left(\left[\frac{A_1}{2} w_f^2(t) + \frac{A_2}{2} w_m^2(t) + \frac{A_3}{2} u_f^2(t) + \frac{A_4}{2} u_m^2(t) \right] + [B_1 I_f + B_2 I_m + B_3 P_f + B_4 P_m + B_5 C_f + B_6 C_m] \right) dt, \quad (17)$$

with a control set defined by

$$\mathcal{U} = \{\mathbf{c} | w_i(t), u_i(t) \text{ bounded and Lebesgue measurable on } [0, T], i = f, m\}, \quad (18)$$

and with bounds

$$0 \leq w_i(t) \leq w_i^{max}, \quad 0 \leq u_i(t) \leq u_i^{max}, \quad i = f, m, \quad (19)$$

for all $t \in [0, T]$, where T is the final time. The weight parameters A_i, B_j ($i = 1, \dots, 4; j = 1, \dots, 6$) describe the relative impact of the control or state variables on the value of the objective functional. We choose quadratic terms to measure control cost following the current trend of the literature [39, 46, 55].

The Optimal Control Problem (OCP) is stated as follows:

$$\min_{\mathbf{c} \in \mathcal{U}} J(\mathbf{c}) \text{ subject to model (3) and non-negative initial conditions.} \quad (20)$$

The Fillipov-Cesari theorem [23, Chapter III, Theorem 4.1] gives conditions to assert existence of solutions of the OCP.

Theorem 4.1. *There exists a solution $\mathbf{c}^* = (w_f^*(t), w_m^*(t), u_f^*(t), u_m^*(t))^T$ to the OCP (20).*

Proof. We need to check the hypotheses required by Theorem 4.1 in [23, Chapter III].

(H1) *The right-hand side of system (3) is bounded by a linear function in the state and control variables.* We have proven in Section 3 that solutions of system (3) are bounded. Let $\mathbf{f}(t, \mathbf{X}, \mathbf{c})$ be the right-hand side of system (3). Consider

$$\mathbf{f}(t, \mathbf{X}, \mathbf{c}) = \mathbf{g}(t, \mathbf{X}) + \mathbf{h}(t, \mathbf{X}) \cdot \mathbf{c}$$

where \mathbf{g} is the right-hand side of system (3) ignoring the terms that include control variables, and

$$\mathbf{h}(t, \mathbf{X}) \cdot \mathbf{c} = (-w_f \Lambda_f - u_f S_f, -w_m \Lambda_m - u_m S_m, w_f \Lambda_f + u_f S_f, w_m \Lambda_m + u_m S_m, 0, 0, 0, 0, 0, 0, 0, 0)^T.$$

Ignoring the negative terms of system (3), we obtain bounds for \mathbf{f} as

$$|\mathbf{f}| \leq |\mathbf{A}| \cdot |\mathbf{X}| + |\mathbf{u}| \leq \varphi \cdot (|\mathbf{X}| + |\mathbf{c}|)$$

where

$$\mathbf{A} = \begin{pmatrix} 0 & 0 & \theta_f & 0 & q_A^f k_A^f & 0 & q_I^f k_I^f & 0 & q_P^f k_P^f & 0 & 0 & 0 \\ 0 & 0 & 0 & \theta_m & 0 & q_A^m k_A^m & 0 & q_I^f k_I^f & 0 & q_P^f k_P^f & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \beta_A^m + \beta_I^m & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_A^f + \beta_I^f & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & k_A^f & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & k_A^m & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & k_I^f & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_I^m & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_P^f & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_P^m & 0 & 0 \end{pmatrix},$$

$$\mathbf{X} = (S_f^{sup}, S_m^{sup}, V_f^{sup}, V_m^{sup}, A_f^{sup}, A_m^{sup}, I_f^{sup}, I_m^{sup}, P_f^{sup}, P_m^{sup}, C_f^{sup}, C_m^{sup})^T,$$

and φ is a constant that depends on the parameters and bounds of solutions of system (3).

(H2) *The right-hand side of system (3) is a Lipschitz function on the state variables.* We need to prove that $|\mathbf{f}(t, \mathbf{X}_1, \mathbf{c}) - \mathbf{f}(t, \mathbf{X}_2, \mathbf{c})| \leq C \cdot |\mathbf{X}_1 - \mathbf{X}_2| \cdot (1 + |\mathbf{c}|)$. This follows from realizing that \mathbf{f} is a C^1 -class function, $\mathbf{f}(t, \mathbf{0}, \mathbf{0})$ is bounded, and $\frac{\partial}{\partial \mathbf{X}} \mathbf{f}(t, \mathbf{X}, \mathbf{c}) = \text{Jacobian}$ is bounded.

(H3) *The set of admissible state and control variables is not empty.* Observe that the admissible control variables are bounded, thus the right hand side of system (3) has bounded coefficients. By the Carathéodory theorem [38, Chapter IX, Theorem 9.2.1], the set of admissible state variables and control variables is not empty.

(H4) *The set \mathcal{U} is closed and convex.* Observe that U is closed and convex by definition.

(H5) *There is a compact set such that $\mathbf{X}(T)$ belongs to that set for every state variable X with non-negative initial conditions.* As proven in Section 3, there is an invariant, compact set that contains $\mathbf{X}(t)$ for every $t \geq 0$ with non-negative initial conditions.

(H6) *The right-hand side of system (3) is linear in the control variables, and the integrand of the objective function is convex in the control variables.*

From **H1**, we can see that the right-hand side of system (3) is linear in the control variables. Also, the integrand of the objective function is

$$L(t, \mathbf{X}, \mathbf{c}) = \left[\frac{A_1}{2} w_f^2 + \frac{A_2}{2} w_m^2 + \frac{A_3}{2} u_f^2 + \frac{A_4}{2} u_m^2 \right] + [B_1 I_f + B_2 I_m + B_3 P_f + B_4 P_m + B_5 C_f + B_6 C_m],$$

which is quadratic in the control variables and therefore is convex in the control variables.

(H7) *There exist constants $c_1 > 0$, $c_2 > 1$, $c_3 > 0$ such that $L(t, \mathbf{X}, \mathbf{c}) \geq c_1 \cdot |\mathbf{c}|^{c_2} - c_3$. Observe that*

$$L(t, \mathbf{X}, \mathbf{c}) \geq \frac{A_1}{2} w_f^2 + \frac{A_2}{2} w_m^2 + \frac{A_3}{2} u_f^2 + \frac{A_4}{2} u_m^2,$$

so we can take $c_1 = \min_{i=1,2,3,4} A_i/2$, $c_2 = 2$ and $c_3 = 0$. □

4.1. Necessary optimality conditions: Adjoint system

To obtain a characterization of optimal control solutions, we may define the Hamiltonian for OCP (20) as

$$H(t, \mathbf{X}, \mathbf{c}, \boldsymbol{\Lambda}) = \boldsymbol{\Lambda}^T(t) \cdot \mathbf{f}(t, \mathbf{X}, \mathbf{c}) + L(t, \mathbf{X}, \mathbf{c}) \quad (21)$$

where

$$\boldsymbol{\Lambda}(t) = (\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7, \lambda_8, \lambda_9, \lambda_{10}, \lambda_{11}, \lambda_{12})^T. \quad (22)$$

Explicitly,

$$\begin{aligned}
H = & \lambda_1 \cdot [(1 - w_f)\Lambda_f - (\lambda_m + u_f + \mu_f)S_f + q_A^f k_A^f A_f + q_I^f k_I^f I_f + q_P^f k_P^f P_f + \theta_f V_f] \\
& + \lambda_2 \cdot [(1 - w_m)\Lambda_m - (\lambda_f + u_m + \mu_m)S_m + q_A^m k_A^m A_m + q_I^m k_I^m I_m + q_P^m k_P^m P_m + \theta_m V_m] \\
& + \lambda_3 \cdot [w_f \Lambda_f + u_f S_f - (\mu_f + \theta_f) V_f] \\
& + \lambda_4 \cdot [w_m \Lambda_m + u_m S_m - (\mu_m + \theta_m) V_m] \\
& + \lambda_5 \cdot [\lambda_m S_f - (k_A^f + \mu_f) A_f] \\
& + \lambda_6 \cdot [\lambda_f S_m - (k_A^m + \mu_m) A_m] \\
& + \lambda_7 \cdot [(1 - q_A^f) k_A^f A_f - (k_I^f + \mu_f) I_f] \\
& + \lambda_8 \cdot [(1 - q_A^m) k_A^m A_m - (k_I^m + \mu_m) I_m] \\
& + \lambda_9 \cdot [(1 - q_I^f) k_I^f I_f - (k_P^f + \mu_f) P_f] \\
& + \lambda_{10} \cdot [(1 - q_I^m) k_I^m I_m - (k_P^m + \mu_m) P_m] \\
& + \lambda_{11} \cdot [(1 - q_P^f) k_P^f P_f - (\delta_f + \mu_f) C_f] \\
& + \lambda_{12} \cdot [(1 - q_P^m) k_P^m P_m - (\delta_m + \mu_m) C_m] \\
& + \left[\frac{A_1}{2} w_f^2 + \frac{A_2}{2} w_m^2 + \frac{A_3}{2} u_f^2 + \frac{A_4}{2} u_m^2 \right] \\
& + [B_1 I_f + B_2 I_m + B_3 P_f + B_4 P_m + B_5 C_f + B_6 C_m].
\end{aligned}$$

By the Pontryagin's Minimum Principle [51], we obtain the following result:

Theorem 4.2. *Let $(\mathbf{c}^*, \mathbf{X}^*)$ be an optimal pair for OCP (20). Then, there*

exist adjoint variables Λ that satisfy the following adjoint system:

$$\begin{aligned}
\dot{\lambda}_1 &= -\lambda_1 \left(-\mu_f - \frac{\beta_A^m A_m}{N_m} - \frac{\beta_I^m I_m}{N_m} - u_f \right) + \lambda_2 S_m \left(-\frac{\beta_A^f A_f}{(N_f)^2} - \frac{\beta_I^f I_f}{(N_f)^2} \right) \\
&\quad - \lambda_3 u_f - \lambda_5 \left(\frac{\beta_A^m A_m}{N_m} + \frac{\beta_I^m I_m}{N_m} \right) - \lambda_6 S_m \left(-\frac{\beta_A^f A_f}{(N_f)^2} - \frac{\beta_I^f I_f}{(N_f)^2} \right), \\
\dot{\lambda}_2 &= \lambda_1 S_f \left(-\frac{\beta_A^m A_m}{(N_m)^2} - \frac{\beta_I^m I_m}{(N_m)^2} \right) - \lambda_2 \left(-\mu_m - \frac{\beta_A^f A_f}{N_f} - \frac{\beta_I^f I_f}{N_f} - u_m \right) \\
&\quad - \lambda_4 u_m - \lambda_5 S_f \left(-\frac{\beta_A^m A_m}{(N_m)^2} - \frac{\beta_I^m I_m}{(N_m)^2} \right) - \lambda_6 \left(\frac{\beta_A^f A_f}{N_f} + \frac{\beta_I^f I_f}{N_f} \right), \\
\dot{\lambda}_3 &= -\lambda_1 \theta_f + \lambda_2 S_m \left(-\frac{\beta_A^f A_f}{(N_f)^2} - \frac{\beta_I^f I_f}{(N_f)^2} \right) - \lambda_3 (-\mu_f - \theta_f) \\
&\quad - \lambda_6 S_m \left(-\frac{\beta_A^f A_f}{(N_f)^2} - \frac{\beta_I^f I_f}{(N_f)^2} \right), \\
\dot{\lambda}_4 &= \lambda_1 S_f \left(-\frac{\beta_A^m A_m}{(N_m)^2} - \frac{\beta_I^m I_m}{(N_m)^2} \right) - \lambda_2 \theta_m - \lambda_4 (-\mu_m - \theta_m) \\
&\quad - \lambda_5 S_f \left(-\frac{\beta_A^m A_m}{(N_m)^2} - \frac{\beta_I^m I_m}{(N_m)^2} \right), \\
\dot{\lambda}_5 &= -\lambda_1 q_A^f k_A^f + \lambda_2 S_m \left(-\frac{\beta_A^f A_f}{(N_f)^2} + \frac{\beta_A^f}{N_f} - \frac{\beta_I^f I_f}{(N_f)^2} \right) - \lambda_5 (-\mu_f - k_A^f) \\
&\quad - \lambda_6 S_m \left(-\frac{\beta_A^f A_f}{(N_f)^2} + \frac{\beta_A^f}{N_f} - \frac{\beta_I^f I_f}{(N_f)^2} \right) - \lambda_7 k_A^f (1 - q_A^f), \\
\dot{\lambda}_6 &= \lambda_1 S_f \left(-\frac{\beta_A^m A_m}{(N_m)^2} + \frac{\beta_A^m}{N_m} - \frac{\beta_I^m I_m}{(N_m)^2} \right) - \lambda_2 q_A^m k_A^m \\
&\quad - \lambda_5 S_f \left(-\frac{\beta_A^m A_m}{(N_m)^2} + \frac{\beta_A^m}{N_m} - \frac{\beta_I^m I_m}{(N_m)^2} \right) - \lambda_6 (-\mu_m - k_A^m) \\
&\quad - \lambda_8 k_A^m (1 - q_A^m),
\end{aligned}$$

$$\begin{aligned}
\dot{\lambda}_7 &= -B_1 - \lambda_1 q_I^f k_I^f + \lambda_2 S_m \left(-\frac{\beta_A^f A_f}{(N_f)^2} - \frac{\beta_I^f I_f}{(N_f)^2} + \frac{\beta_I^f}{N_f} \right) \\
&\quad - \lambda_6 S_m \left(-\frac{\beta_A^f A_f}{(N_f)^2} - \frac{\beta_I^f I_f}{(N_f)^2} + \frac{\beta_I^f}{N_f} \right) - \lambda_7 (-\mu_f - k_I^f) - \lambda_9 k_I^f (1 - q_I^f), \\
\dot{\lambda}_8 &= -B_2 + \lambda_1 S_f \left(-\frac{\beta_A^m A_m}{(N_m)^2} - \frac{\beta_I^m I_m}{(N_m)^2} + \frac{\beta_I^m}{N_m} \right) - \lambda_2 q_I^m k_I^m \\
&\quad - \lambda_5 S_f \left(-\frac{\beta_A^m A_m}{(N_m)^2} - \frac{\beta_I^m I_m}{(N_m)^2} + \frac{\beta_I^m}{N_m} \right) - \lambda_8 (-\mu_m - k_I^m) - \lambda_{10} k_I^m (1 - q_I^m), \\
\dot{\lambda}_9 &= -B_3 - \lambda_1 q_P^f k_P^f + \lambda_2 S_m \left(-\frac{\beta_A^f A_f}{(N_f)^2} - \frac{\beta_I^f I_f}{(N_f)^2} \right) \\
&\quad - \lambda_6 S_m \left(-\frac{\beta_A^f A_f}{(N_f)^2} - \frac{\beta_I^f I_f}{(N_f)^2} \right) - \lambda_9 (-\mu_f - k_P^f) - \lambda_{11} k_P^f (1 - q_P^f), \\
\dot{\lambda}_{10} &= -B_4 + \lambda_1 S_f \left(-\frac{\beta_A^m A_m}{(N_m)^2} - \frac{\beta_I^m I_m}{(N_m)^2} \right) - \lambda_2 q_P^m k_P^m \\
&\quad - \lambda_5 S_f \left(-\frac{\beta_A^m A_m}{(N_m)^2} - \frac{\beta_I^m I_m}{(N_m)^2} \right) - \lambda_{10} (-\mu_m - k_P^m) - \lambda_{12} k_P^m (1 - q_P^m), \\
\dot{\lambda}_{11} &= -B_5 + \lambda_2 S_m \left(-\frac{\beta_A^f A_f}{(N_f)^2} - \frac{\beta_I^f I_f}{(N_f)^2} \right) \\
&\quad - \lambda_6 S_m \left(-\frac{\beta_A^f A_f}{(N_f)^2} - \frac{\beta_I^f I_f}{(N_f)^2} \right) - \lambda_{11} (-\mu_f - \delta_f), \\
\dot{\lambda}_{12} &= -B_6 + \lambda_1 S_f \left(-\frac{\beta_A^m A_m}{(N_m)^2} - \frac{\beta_I^m I_m}{(N_m)^2} \right) - \lambda_5 S_f \left(-\frac{\beta_A^m A_m}{(N_m)^2} - \frac{\beta_I^m I_m}{(N_m)^2} \right) \\
&\quad - \lambda_{12} (-\mu_m - \delta_m), \\
\lambda_i(T) &= 0 \quad \forall i = 1, 2, \dots, 12.
\end{aligned}$$

Furthermore, the optimal controls satisfy the following equations

$$\begin{aligned}
w_f^*(t) &= \max \left(\min \left(\frac{\Lambda_f(\lambda_1 - \lambda_3)}{A_1}, w_f^{max} \right), 0 \right), \\
w_m^*(t) &= \max \left(\min \left(\frac{\Lambda_m(\lambda_2 - \lambda_4)}{A_2}, w_m^{max} \right), 0 \right), \\
u_f^*(t) &= \max \left(\min \left(\frac{S_f(\lambda_1 - \lambda_3)}{A_3}, u_f^{max} \right), 0 \right), \\
u_m^*(t) &= \max \left(\min \left(\frac{S_m(\lambda_2 - \lambda_4)}{A_4}, u_m^{max} \right), 0 \right).
\end{aligned} \tag{23}$$

5. Numerical results

Here, we complement the analytical results in the previous sections with the numerical computation of the optimal control. To obtain the optimal control solutions we must solve the optimality system which is a two-point boundary value problem with an initial condition in the state equations (3) and a terminal condition on the adjoint system. We employ an iterative fourth-order Runge-Kutta integration scheme to solve the optimality system. First, we solve the HPV epidemic model forward in time using an initial guess for the time-dependent vaccination rates \mathbf{c} . The results obtained for the state variables are plugged into the adjoint system and we solve such a system with terminal conditions backward in time. The controls are updated using a convex combination of the previous controls and the new control obtained substituting the states and adjoints into its characterization. This process is repeated until the current state variables, adjoints, and controls converge within a pre-set tolerance value. This algorithm is usually known as the forward-backward sweep method [36].

Observe that by definition, the vaccination rates w_f and w_m are fractions, hence, $0 \leq w_f^{max}, w_m^{max} < 1$. We fix $w_f^{max} = w_m^{max} = 0.99$. To obtain an approximation for the adult vaccination rates u_f, u_m , let us consider a normalized total population $N(t)$ where no individuals has been vaccinated at the initial time. Assuming that the vaccination rate, denoted by u , is proportional to population size, we have $N'(t) = -uN(t)$, $N(0) = 1$. A direct computation allow us to obtain $N(t) = \exp(-ut)$, hence, the fraction of vaccinated individuals at time t , that is, the immunization coverage, C , is $C(t) = 1 - \exp(-ut)$. For a fixed time horizon τ , we have

$$C(\tau) = 1 - \exp(-u\tau) \quad \text{or} \quad u = -\ln(1 - C(\tau))/\tau. \quad (24)$$

Considering a very optimistic case in which health authorities achieve a vaccination coverage $C(\tau) = 80\%$ of the population in $\tau = 1$ year, we obtain that the constant vaccination rate $u \approx 1.60$ per year. Therefore, we fix the following bounds $0 \leq u_f^{max}, u_m^{max} \leq 1.60$.

We carry out extensive numerical simulations that aim to model some realistic scenarios associated with HPV vaccination policies. The clinical management and cost associated with HPV infection vary among countries. We choose the weight factors in the objective functional considering HPV cost in a Mexican setting. According to data in [32], the treatment cost of CIN in Mexico is approximately eight times more expensive than the cost of treating a typical HPV infection. Moreover, the treatment cost of CC is typically six times more expensive than the cost of treating the CIN stage. Therefore, we assume that $8B_1 = B_3$, and $6B_3 = B_5$. In addition, the monetary costs

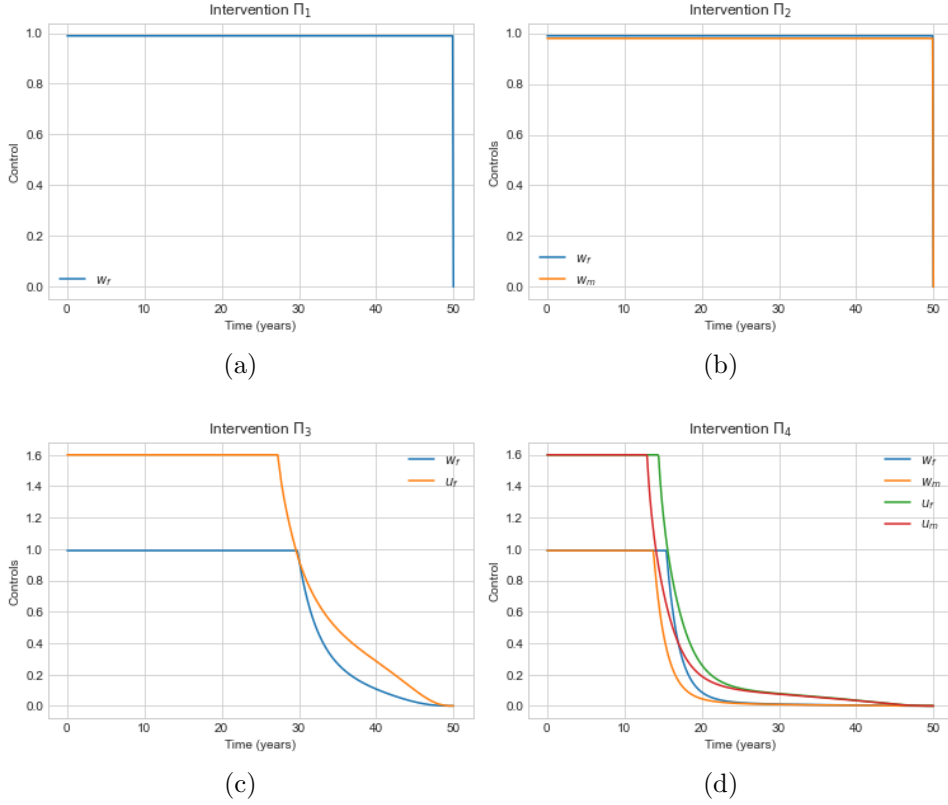


Figure 2: Optimal time-dependent vaccination rates derived from the OCP (20) for interventions Π_1 (a), Π_2 (b), Π_3 (c), Π_4 (d), respectively. For all scenarios the weigh parameters are taken as follows: $A_1 = A_2$, $A_3 = A_4 = B_1 = 1 \times 10^5$, $A_1 = A_3/5$, $8B_1 = B_3$, and $6B_3 = B_5$.

of vaccination programs are commonly small compared with the potential losses that an epidemic can inflict. Therefore, we assume $A_i \approx B_1$ ($i = 1, 2, 3, 4$). Nevertheless, one might argue that school-based vaccine delivery is logistically easier and therefore cheaper than vaccination for adults. We explore this hypothesis assuming $A_1, A_2 < A_3, A_4$. In particular, for the purpose of the numerical simulations, we fix $A_1 = A_2$, $A_3 = A_4 = B_1 = 1 \times 10^5$, $A_1 = A_3/5$. Regarding the values of the weight factors modeling the cost of HPV infection in men, we consider that the cost associated with HPV infection in men is approximately the same as the cost of HPV infection in women ($B_2 = B_1$, $B_4 = B_3$, $B_6 = B_5$).

As initial conditions we assume a 5% prevalence in the asymptomatic compartments A_i , a 3% prevalence of the infection in the persistent infectious classes I_i , and a 0.1% prevalence en the precancerous and cancerous classes

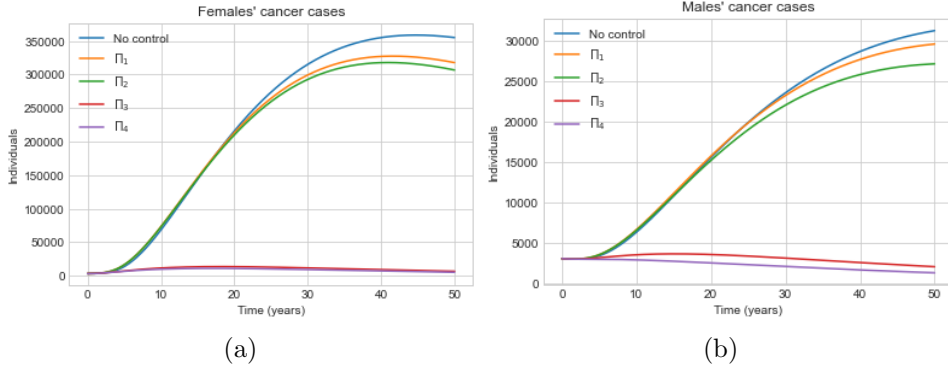


Figure 3: Simulation of the solutions of HPV epidemic model (3) as a function of time in the absence of control and using the optimal vaccination strategies Π_k ($k = 1, \dots, 4$) for cancer cases in females $C_f(t)$ (a) and in males $C_m(t)$ (b). Model parameters are taken from table 2. Initial conditions are described in the main text.

P_i, C_i , ($i = f, m$). Moreover, in Mexico, the HPV vaccination program has only targeted females, therefore $V_m(0) = 0$ and $V_f(0) > 0$. Currently, there is no official information on the actual number of females vaccinated against HPV. Hence, for the numerical simulations, we assume a 10% vaccination coverage in females. Under these conditions, we derive and compare the following time-dependent HPV vaccination strategies:

- Π_1 : Girls-only vaccination ($w_f^*(t)$).
- Π_2 : Girls and boys vaccination ($w_f^*(t), w_m^*(t)$).
- Π_3 : Girls and adult females vaccination ($w_f^*(t), u_f^*(t)$).
- Π_4 : Vaccination for all ($w_f^*(t), w_m^*(t), u_f^*(t), u_m^*(t)$).

Girls-only vaccination, intervention Π_1 , has been the standard intervention adopted in Mexico and several other countries [15]. Therefore, comparing Π_1 with the other proposed intervention Π_k ($k = 2, 3, 4$) will allow us to better understand the value of adding boys and adults into the existing girls-only standard strategy. The time-dependent optimal vaccination rates for interventions Π_k ($k = 1, \dots, 4$) are derived as particular cases of the OCP (20). Numerical approximations are presented in Figure 2 (a)-(d) where the horizontal axis represents time in years and the vertical axis the vaccination rates. The simulation presented in Figure 2 (a) shows the standard girls-only intervention. Observe that for intervention Π_1 the vaccination rate should be maintained at its maximum capacity for the whole time. This means that

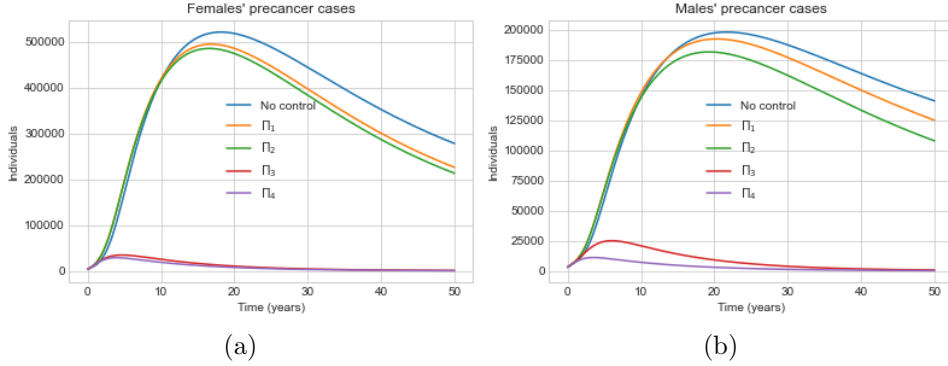


Figure 4: Simulation of the solutions of HPV epidemic model (3) as a function of time in the absence of control and using the optimal vaccination strategies Π_k ($k = 1, \dots, 4$) for precancer cases in females $P_f(t)$ (a) and in males $P_m(t)$ (b). Model parameters are taken from table 2. Initial conditions are described in the main text.

this control alone is not enough to successfully eradicate HPV infection. The simulation in Figure 2 (b) shows that the same is true for intervention Π_2 . Therefore, adding boys to existing girls-only vaccination programs is still not sufficient to control the epidemic. On the other hand, the optimal time-dependent vaccination profiles for intervention Π_3 (see Figure 2 (c)) show that if adult female vaccination is used in addition to girls vaccination, both controls should be executed at 100% for approximately 30 years and then decrease gradually to zero. Finally, if all controls are used together, in other words, if we use intervention Π_4 , all vaccination rates should be executed at 100% for approximately 15 years and then gradually decrease to zero to control the epidemic (see Figure 2 (d)). Observe that for all the interventions, the optimal vaccine deployment is to allocate as much vaccines as possible at the initial phase of the epidemic and once a high vaccination coverage is reached then gradually decrease vaccination rates to zero.

To compare and demonstrate the impact of the optimal vaccination interventions Π_k ($k = 1, \dots, 4$), we show the time series for the infected classes $I_j(t)$, $P_j(t)$, and $C_j(t)$ ($j = f, m$) for each of the interventions together with the model dynamics in the no control case (see Figures 3-5). The number of cancer cases for each strategy is graphically depicted in Figure 3, while Figure 4 depicts the number of cases in the precancerous stage. Figure 5 shows the number of people in the symptomatic infectious class. The simulations in Figures 3-5 show that for any of the interventions Π_k ($k = 1, \dots, 4$), the number of HPV-associated cancer, precancers and symptomatic cases in both females and males are reduced in comparison with the no control case. Nevertheless, such reduction is not significant for interventions Π_1 and Π_2 .

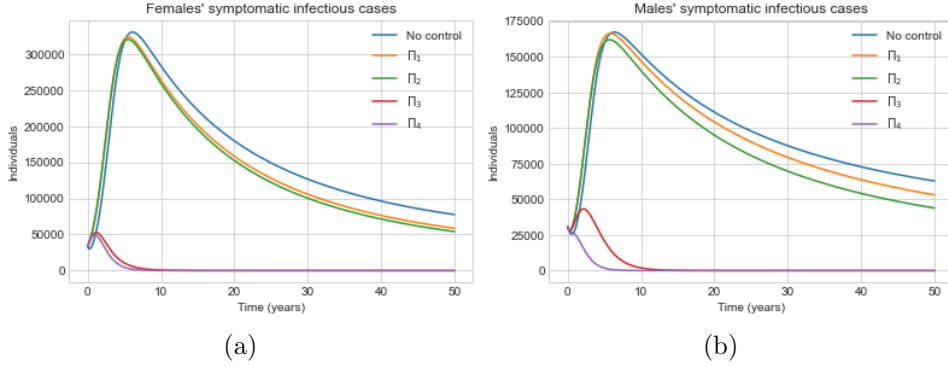


Figure 5: Simulation of the solutions of HPV epidemic model (3) as a function of time in the absence of control and using the optimal vaccination strategies Π_k ($k = 1, \dots, 4$) for symptomatic infected cases in females $I_f(t)$ (a) and in males $I_m(t)$ (b). Model parameters are taken from table 2. Initial conditions are described in the main text.

Hence, girls-only and girls plus boys vaccination will not be enough to eradicate HPV-associated cancers. Moreover, adding boys to existing girls-only vaccination programs does not change significantly epidemic dynamics. This suggests, under the conditions explored here, that girls-only vaccination is more cost-effective than girls and boys vaccination. Furthermore, from the simulations (see Figures 3-5) we can also observe that interventions Π_3 and Π_4 have the potential to eradicate HPV-associated diseases and cancer. At first glance, one might think that if HPV diseases can be successfully eradicated by vaccinating only females (both girls and adults), then there is no need to include boys and adult males in HPV vaccination programs. Nonetheless, as shown in Figure 2 (c)-(d), intervention Π_3 needs to be deployed at 100% for approximately twice the time in comparison with intervention Π_4 . In other words, HPV eradication can be achieved way faster with intervention Π_4 . Hence, if resources allow, consideration should be given to including the entire population at risk in vaccination programs. Yet, in a context of limited resources, such as the usual situation in low- and middle-income countries, the preferred strategy should be the vaccination of girls and adult females without including boys or adult males.

6. Discussion and concluding remarks

HPV infection, one of the most common sexually transmitted infections worldwide, poses a major health problem, especially in low- and middle-income countries. Although HPV vaccines were introduced more than a decade ago and have shown positive results reducing infection and associated

disease, immunization programs remain suboptimal [49]. Initially, the WHO recommended HPV vaccination focusing mainly on pre-adolescent girls aged 9-12, arguing that females are at risk of developing cervical cancer [15]. However, currently, the number of HPV-associated cancer cases of the oropharynx, oral cavity, and larynx in men were, respectively, 4, 2, and 7 times higher than in females [15]. In addition, in many countries, HPV vaccine coverage is less than 60%, making the protection against males difficult to achieve. Therefore, the recommended cohorts for immunization are both adolescent girls and boys 9-15 years of age [15, 62]. There are also important arguments to extend vaccination to older cohorts. First, since non-vaccinated sexually active individuals can acquire the infection and contribute to transmission, they constitute a reservoir of the infection. Another key argument is that the duration of vaccine-induced protection is unknown. If immunity wanes early vaccinated adolescents will need a booster later in life.

In this work, we used the optimal control theory to investigate the best deployment strategy for HPV vaccination programs. We develop a deterministic epidemic model based on the natural history of HPV infection and associated diseases. To investigate the population-level impact of HPV immunization programs, the model incorporates school-based vaccine delivery for juveniles and catch-up vaccination for adults. The dynamics of our 12-dimensional non-linear HPV epidemic model (3) are rigorously investigated. The next-generation matrix is used to get an analytical expression for the basic reproduction number R_0 and the local stability of the disease-free equilibria is demonstrated for $R_0 < 1$. We used the center manifold theorem and normal forms to show that if $R_0 > 1$, the HPV model has a unique endemic equilibrium that is locally asymptotically stable. Next, we incorporated time-dependent vaccination rates into the system (3) and applied Pontryagin's Maximum Principle to determine the optimal vaccination programs under several plausible scenarios. We prove the existence of solutions for the optimal control problem, characterize the optimal controls, and obtain numerical approximation using the forward-backward sweep method. The numerical simulations of the optimal control are implemented using a set of realistic parameter values mostly obtained from the international literature and demographic parameters calibrated from Mexico city data for illustration of theoretical HPV dynamics in a Mexican setting.

The findings of this study suggest that although girls-only vaccination can reduce HPV-associated burden, it cannot lead to complete eradication of the infection at least for a time horizon of 50 years in regions where HPV vaccination coverage is below 10%. Introducing boys into existing girls-only programs is still not enough to reach the eradication of HPV-associated cancers. However, our simulations suggest that if girls-only programs are com-

plemented with catch-up vaccination for adult females, such program has the potential to achieve HPV-associated cancers eradication as long as the coverage in females is maintained high for several years even if boys and males do not receive the vaccine. This finding is consistent with results in previous studies [5, 12, 16, 25] which suggest that the maximum reduction in the prevalence of infection is always achieved by single-sex vaccination. As a consequence, one might think that if HPV diseases can be successfully eradicated by vaccinating only females (both girls and adults), then there is no need at all to include boys and adult males in HPV vaccination programs. Nonetheless, our simulations also suggest that HPV eradication can be achieved way faster with a vaccination program in which both sexes are included (probably at a greater cost). This agrees with the conclusion in [32], where Insigna et al. found that the addition of a catch-up vaccination program for adults of both sexes provides considerably greater reductions in HPV disease over the short and medium term than the vaccination of 12-year-olds alone. Hence, if resources allow, consideration should be given to including the entire population at risk in vaccination programs. Yet, in a context of limited resources, such as the usual situation in low- and middle-income countries, the preferred strategy should be the vaccination of girls and adult females without including boys or adult males. Concisely, the results of this work suggest that the order of vaccination priority should be young girls, adult females, young boys, and finally adult males. However, we have to stress that these results are derived for a context where HPV vaccine is just being introduced and vaccine-induced protection wanes after approximately 20 years. Finally, the optimal profile for the time-dependent vaccination rates found in this work suggest that HPV vaccination programs should follow a hit-hard hit-early approach. In other words, the optimal vaccine deployment is to allocate as much vaccines as possible at the initial phase of the epidemic and once a high vaccination coverage is reached then gradually decrease vaccination rates to zero which agrees with the results in [25, 39].

While efforts were made to include the main epidemiological features of HPV infection, the proposed model can be extended. For instance, future studies might incorporate HPV-type-specific infection for a more detailed description of disease progression. However, complex HPV models might be difficult to calibrate given the potential limitation of existing studies to inform such models [2, 31]. Since screening is a key measure to prevent CC and other HPV-associated cancers, HPV models can also incorporate regular screening alongside vaccination programs [55]. Another possible extension is the inclusion of the homosexual and bisexual population [24]. Finally, we remark that the results for the OCP studied here are derived for a L_2 -type

objective functional. However, other formulations for the objective functional are also possible and deserve further study.

Declaration of competing interest

The authors declare they have no known competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

Code availability

All the code used in the simulations is available at https://github.com/arielcam27/Saldana-et-al_2022_HPV

Author contributions

FS: Conceptualization, Methodology, Analysis, Design of the simulations, Interpretation of results, Writing. **JACG:** Analysis, Code, Review, Editing. **GV:** Analysis, Methodology, Review, Editing. **JVH:** Interpretation of results, Review, Editing, Supervision.

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