

When optimal is not the best: Cost-effectiveness analysis for HPV epidemic models

Cuando lo óptimo no es lo mejor: análisis de costo-efectividad para modelos epidemiológicos del VPH

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Abstract—This paper aims to evaluate the potential cost-effectiveness of healthcare interventions against human papillomavirus (HPV). For this, we consider a two-sex epidemic model for the transmission dynamics of HPV which includes screening, vaccination of adolescent boys and girls, and vaccination of sexually active adults. We first propose public health policies using constant control parameters and develop a cost-effectiveness analysis (CEA) to identify which intervention delivers the best effectiveness for the money invested. Secondly, we consider time-dependent control parameters and formulate an optimal control problem to obtain time-dependent versions of the interventions. As in the case of constant control parameters, we perform a CEA to investigate the cost-effectiveness of the time-dependent control interventions. Our findings suggest that females' vaccination, including adolescent girls and adult women, is the most cost-effective strategy. We also compare constant against the time-dependent healthcare interventions which are optimal in the sense that they minimize the objective functional of the optimal control problem. The results indicate that time-dependent controls are not always more cost-effective than constant controls.

Keywords—Epidemic model, Optimal control, Cost-effectiveness analysis, HPV, Disease modeling

Resumen— Este artículo tiene como objetivo evaluar el potencial costo y efectividad de las intervenciones sanitarias contra el virus del papiloma humano (VPH). Para ello consideramos un modelo epidemiológico estructurado por sexo para la dinámica de transmisión del VPH en una población heterosexual. Este modelo incluye como controles exámenes de tamizaje, vacunación de niños y niñas antes de su iniciación sexual y vacunación de adultos sexualmente activos. Primero proponemos políticas de salud pública utilizando parámetros de control constante y desarrollamos un análisis de costo-efectividad para identificar qué intervención ofrece la mejor efectividad por el dinero invertido. En segundo lugar, consideramos los parámetros de control dependientes del tiempo y formulamos un problema de control óptimo para obtener versiones dependientes del tiempo de las estrategias de control. Como en el caso de los parámetros de control constante, realizamos un CEA para investigar la rentabilidad de las intervenciones de control dependientes del tiempo. Los resultados sugieren que la vacunación de las mujeres, incluidas las adolescentes y las mujeres adultas, es la estrategia más costo-efectiva. También comparamos las intervenciones sanitarias constantes con las dependientes del tiempo que son óptimas en el sentido de que minimizan el funcional objetivo del problema de control óptimo. Los resultados indican que los controles dependientes del tiempo no siempre son más rentables que los controles constantes.

Palabras clave— Modelos epidemiológicos, control óptimo, análisis de costo-efectividad, VPH, epidemiología matemática

INTRODUCTION

Persistent human papillomavirus (HPV) infection is seen as the most important factor contributing to the development of cervical cancer (Herrera et al., 2020). In 2018, about 311 thousand women died of cervical cancer, 85% of these deaths occurred in low- and middle-income countries (Bray et al., 2018). In Mexico, there were more than 7,800 new cases of cervical cancer and more than 4,100 deaths from this cause (Bray et al., 2018). Vaccination against the human papillomavirus is the basic strategy for primary prevention of cervical cancer. The U.S. Food and Drug Administration (FDA) has approved three vaccines for the prevention of HPV infection: 9-valent HPV vaccine (Gardasil 9, 9vHPV), quadrivalent HPV vaccine (Gardasil, 4vHPV), and bivalent HPV vaccine (Cervarix, 2vHPV). The three vaccines protect against infection by HPV types 16 and 18, two of the high-risk human papillomaviruses that cause most cervical cancers (about 70%). Gardasil-9 was originally approved for use in males and females aged 9 through 26 years. Nevertheless, in 2018, The U.S. Food and Drug Administration approved a supplemental application for Gardasil 9 expanding the approved use of the vaccine to include women and men aged 27 through 45 years (Levy and Downs, 2019).

Since the introduction of HPV vaccines in 2006, HPV vaccination programs have been implemented in several countries. However, there are large discrepancies in coverage and targeted groups of vaccination strategies among countries (Soe et al., 2018). The vaccination program depends on country-specific factors, such as the economic and geographical constraints as well as the healthcare system organization. In several countries, prophylactic vaccination of pre-adolescent females has been introduced supported by modeled evaluations that have found this intervention to be cost-effective (Bogaards et al., 2015). Vaccination of pre-adolescent males may also be cost-effective if females' coverage is below 50% (Canfell et al., 2012). Therefore, it is important to investigate under which conditions the inclusion of males and adult females into existing vaccination programs is cost-effective.

Identifying interventions which have the potential to reduce substantially the disease burden at the best cost is of paramount importance for decision-makers faced with the choice of resource allocation. A number of mathematical models have been proposed to study the epidemiology of HPV and the development of vaccination strategies, for example, (Allali, 2021; Alsaleh and Gumel, 2014; Bogaards et al., 2011; Elbasha and Dasbach, 2010; Malik et al., 2013; Saldaña and Barradas, 2020; Smith et al., 2011). In this context, the optimal control theory has proven to be a very useful tool to identify optimal and potentially practical disease management strategies (Sharomi and Malik, 2017). In spite of this, to the best of authors' knowledge, only a very few studies have used the optimal control framework to investigate the cost-effectiveness of HPV vaccination programs (Brown and Jane White, 2011; Malik et al., 2016).

Here, we consider a two-sex epidemic model consisting of ordinary differential equations based on the susceptible-infected-vaccinated-susceptible (SIVS) compartmental structure. This model was considered in a previous work (Saldaña et al., 2019), and the optimal, in the sense of

minimizing the number of cervical cancer cases and related diseases in females was found there. In this study, we focus on the use of cost-effectiveness analysis to estimate the costs and health gains of alternative healthcare policies. Our ultimate goal is to prioritize the allocation of resources by identifying policies that have the potential to successfully control HPV infection in an efficient manner for the least resources.

HPV MODEL

To study the transmission dynamics of the HPV in a heterosexual population, we consider a two-sex, compartmental model under the SIVS framework introduced in (Saldaña et al., 2019). Only those HPV strains targeted by the nonavalent HPV vaccine are considered in this study. We classify the sexually active population of variable size $N(t)$ by the gender and the infection status; the subscripts f and m denote the female and male subpopulations, respectively.

Since the majority of HPV cases are asymptomatic, we subdivide the female subpopulation of size $N_f(t)$ into four mutually exclusive compartments: the susceptibles, $S_f(t)$, the vaccinated, $V_f(t)$, and the infectious females unaware, $U_f(t)$, and aware, $I_f(t)$, of their infection, respectively. For the male subpopulation of size $N_m(t)$, we only consider three compartments: the susceptibles, $S_m(t)$, the vaccinated, $V_m(t)$, and the infectious males $I_m(t)$.

The basic assumptions of the model are as follows:

- (i) 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 ($k = f, m$).
- (ii) A fraction w_1 of females and a fraction w_2 of males (where $0 \leq w_1, w_2 \leq 1$) are vaccinated before they enter the sexually active class and thus are recruited into their vaccinated compartment. Moreover, the susceptible sexually active females and males are vaccinated at per capita rates u_1 and u_2 , respectively.
- (iii) The vaccine reduces the force of infection by a factor ε with $0 \leq \varepsilon \leq 1$. Thus, the vaccine is absolutely effective when $\varepsilon = 0$ and absolutely ineffective when $\varepsilon = 1$. Therefore, $1 - \varepsilon$ is the vaccine efficacy.
- (iv) The exact duration of vaccine protection is unknown, but clinical trials (Huh et al., 2017) have shown sustained efficacy for at least 5 years. We assume that vaccine-induced immunity wanes at a rate θ ; thus, for $\theta = 0$ the protection is lifelong.
- (v) Females have on average c_f sexual contacts per unit of time. Thus, if h is a transmission probability per contact, then the susceptible females are infected at a rate $c_f h I_m / N_m = \beta_m I_m / N_m$. Analogously, the susceptible males are infected by the unaware infected females at a rate $\beta_f U_f / N_f$ and by the aware infected females at a rate $\tilde{\beta}_f I_f / N_f$. We assume that $0 < \tilde{\beta}_f < \beta_f$, since a female conscious of her infection may take precautions to reduce the probability of transmission.
- (vi) After infection, a fraction p of the infected females may develop symptoms and become aware of their infection, entering the $I_f(t)$ class. The remaining infected females

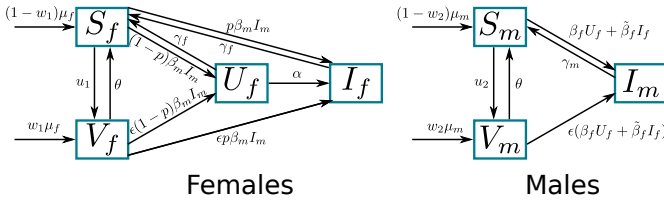


Figure 1: Flow chart of model (1).

move to the unaware class $U_f(t)$. However, the screening allows the unaware infected females to detect their infection and change their status at a rate α .

- (vii) The infected individuals clear the infection naturally at a rate γ_k ($k = f, m$). The existence and magnitude of the naturally acquired protection after HPV infection is still uncertain (Ranjeva et al., 2017). Therefore, we assume no permanent immunity after recovery.

Moreover, since we are interested in the evaluation of several control interventions in a finite time interval $[0, T]$, the host population could be considered as constant. In mathematical terms, we assume $\Lambda_k = r_k N_k$ ($k = f, m$), where the per capita recruitment rate, r_k , is equal to the per capita rate of ceasing sexual activity, μ_k . Please observe that $r_k N_k$ is the total number of individuals recruited into the sexually active population per unit of time. In addition, without loss of generality, we consider a rescaling of our model assuming that $N_f = 1$ and $N_m = 1$. Then, the state variables are expressed as fractions of the populations of each gender and we get the following system of differential equations:

$$\begin{aligned}
 \dot{S}_f &= (1 - w_1)\mu_f - (\beta_m I_m + u_1 + \mu_f)S_f + \gamma_f(U_f + I_f) + \theta V_f, \\
 \dot{U}_f &= (S_f + \varepsilon V_f)(1 - p)\beta_m I_m - (\gamma_f + \alpha + \mu_f)U_f, \\
 \dot{I}_f &= (S_f + \varepsilon V_f)p\beta_m I_m + \alpha U_f - (\gamma_f + \mu_f)I_f, \\
 \dot{V}_f &= w_1\mu_f + u_1 S_f - \varepsilon\beta_m V_f I_m - (\mu_f + \theta)V_f, \\
 \dot{S}_m &= (1 - w_2)\mu_m - (\beta_f U_f + \tilde{\beta}_f I_f + u_2 + \mu_m)S_m + \gamma_m I_m + \theta V_m, \\
 \dot{I}_m &= (\beta_f U_f + \tilde{\beta}_f I_f)(S_m + \varepsilon V_m) - (\gamma_m + \mu_m)I_m, \\
 \dot{V}_m &= w_2\mu_m - (\beta_f U_f + \tilde{\beta}_f I_f)\varepsilon V_m + u_2 S_m - (\mu_m + \theta)V_m.
 \end{aligned} \tag{1}$$

A flow chart depicting the model (1) is shown in Fig. 1. Here all the parameters are assumed to be nonnegative. The intervention measures, namely, the screening and vaccination rates will be called controls and denoted by vector $c = (w_1, w_2, u_1, u_2, \alpha)$. The biologically feasible region for system (1) is

$$\Omega = \{x \in \mathbb{R}_+^7 : S_f + U_f + I_f + V_f = 1, S_m + I_m + V_m = 1\}.$$

Model (1) has a unique disease-free equilibrium state $E_o(c)$ which depends directly on the vector of controls c . The stability properties of $E_o(c)$ are determined by the effective reproduction number $\mathcal{R}_e(c)$.

We remark that the definition of the basic reproduction number, \mathcal{R}_0 , assumes a fully susceptible population and, hence, control measures such as mass vaccination that reduce the number of susceptible individuals in the population should, technically not reduce the value of \mathcal{R}_0 . Therefore, alongside to \mathcal{R}_0 we introduce the effective reproduction number, denoted here as \mathcal{R}_e , which is defined as the actual average number of secondary cases per a primary case. \mathcal{R}_e does not assume

the complete susceptibility of the population; and, therefore, vaccination and other control measures could potentially reduce the value of \mathcal{R}_e . Consequently, in the presence of vaccination, the effective reproduction number can be a better metric for understanding the transmissibility of infectious diseases (Delamater et al., 2019).

Mathematically, both reproduction numbers can be computed via the next-generation operator introduced by Diekmann et al. (Diekmann et al., 1990). Under this approach (see (Saldaña et al., 2019)), we obtain that the effective reproduction number is the geometric mean of the infection transfer from males to females $T_m^f(c)$ and the infection transfer from females to males $T_f^m(c)$, that is,

$$\mathcal{R}_e(c) = \sqrt{T_m^f(c) \cdot T_f^m(c)}. \tag{2}$$

As a consequence of the van den Driessche theorem (Van den Driessche and Watmough, 2002), $\mathcal{R}_e(c)$ is a threshold value and we establish the following result regarding the local stability of the disease-free equilibrium.

Corollary 1 *The disease-free equilibrium $E_o(c)$ of system (1) is locally asymptotically stable for $\mathcal{R}_e(c) < 1$ and unstable for $\mathcal{R}_e(c) > 1$.*

Corollary 1 implies that, if initial infection levels are sufficiently low, reducing and maintaining $\mathcal{R}_e(c) < 1$ ensures disease's elimination. On the contrary, if the value of $\mathcal{R}_e(c)$ is higher than unity, the disease can persist in the population. Fig. 2 illustrates these two possibilities. In Fig. 2(a), we choose screening and vaccination rates that guarantee $\mathcal{R}_e(c) < 1$, so that the infection eventually decreases to zero. On the contrary, in Fig. 2 (b), the screening and vaccination rates are taken equal to zero, thus giving $\mathcal{R}_e(0) > 1$, so the system converges to an endemic equilibrium. Other parameters are fixed with their baseline values in Table 1.

COST-EFFECTIVENESS ANALYSIS FOR CONSTANT CONTROLS

In the following, we carry out a cost-effectiveness analysis to investigate the most cost-effective control strategy against HPV transmission. We propose realistic strategies based on the combination of the five controls incorporated into our model. These strategies are summarized below.

- Strategy S_1 : all controls.
- Strategy S_2 : teenagers' vaccination.
- Strategy S_3 : adults' vaccination.
- Strategy S_4 : females' vaccination.
- Strategy S_5 : males' vaccination.
- Strategy S_6 : teenagers' vaccination and screening.
- Strategy S_7 : adults' vaccination and screening.
- Strategy S_8 : females' vaccination and screening.

Parameter	Range	Mean Value	Units	Source
Vaccine efficacy ($1 - \epsilon$)	[0,9, 1]	0,95	<i>adimensional</i>	(Brisson et al., 2016)
Average duration of vaccine protection ($1/\theta$)	[5, 50]	20	<i>year</i>	(Huh et al., 2017)
Male's transmission rate (β_m)	[0,05, 5]	2,0	year^{-1}	(Brisson et al., 2016)
Unaware females transmission rate (β_f)	[0,05, 5]	2,0	year^{-1}	(Brisson et al., 2016)
Aware females transmission rate ($\tilde{\beta}_f$)	[0,025, 2,5]	0,5	year^{-1}	Assumed
Female's infectious period ($1/\gamma_f$)	[0,83, 2]	1,3	<i>year</i>	(Muñoz et al., 2004)
Male's infectious period ($1/\gamma_m$)	[0,33, 1,2]	0,6	<i>year</i>	(Anic and Giuliano, 2011)
Female fraction that develop symptoms (p)	[0, 1]	0,4	<i>adimensional</i>	Assumed
Female's ceasing sexual activity rate (μ_f)	[0,02, 1]	1/20	year^{-1}	(Malik et al., 2013)
Male's ceasing sexual activity rate (μ_m)	[0,02, 1]	1/25	year^{-1}	(Malik et al., 2013)

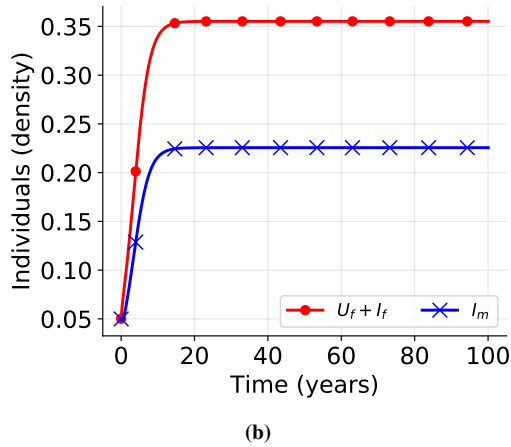
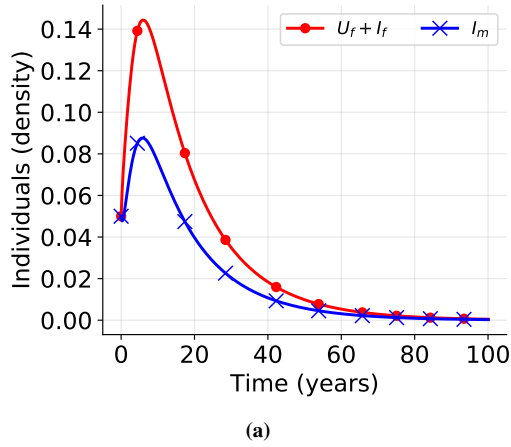
TABLE 1: PARAMETERS OF SYSTEM (1), SAMPLE UNITS AND SOURCE OF ESTIMATION


Figure 2: Prevalence levels for model (1) with $\mathcal{R}_e(c) = 0,9479 < 1$ (a) and $\mathcal{R}_e(c) = 1,4151 > 1$ (b). In case (a) the values of the screening and vaccination rates are $w_1 = 0,1$, $w_2 = 0,07$, $u_1 = 0,05$, $u_2 = 0,03$, and $\alpha = 0,1$. In case (b), the screening and vaccination rates are taken equal to zero. The rest of the parameters are as described in Table 1. The initial conditions are: $S_f(0) = 0,95$, $U_f(0) = 0,03$, $I_f(0) = 0,02$, $V_f(0) = 0$, $S_m(0) = 0,95$, $I_m(0) = 0,05$, $V_m(0) = 0$.

The main objective is to compare the health outcomes of the proposed interventions with respect to their application costs. To this end, we introduce the incremental cost-effectiveness ratio (ICER), which is usually defined as the additional cost, divided by its additional benefit compared with the next most expensive strategy. Mathematically speaking, for two strategies S_1 and S_2 , the ICER is defined as

$$ICER(S_1, S_2) = \frac{C(S_2) - C(S_1)}{E(S_2) - E(S_1)}, \quad (3)$$

provided that $E(S_1) \neq E(S_2)$. Function $C(\cdot)$ measures the total costs (e.g. intervention cost, cost associated with illness, cost of treatment and monitoring, etc), while function $E(\cdot)$ measures the effectiveness of the intervention using some appropriate health outcome (such as lives saved, total number of infections averted, years of life gained, etc) (Camacho et al., 2019).

We also define the average cost-effectiveness ratio (ACER) for a strategy S as

$$ACER(S) = \frac{C(S)}{E(S)}. \quad (4)$$

The ICER could be interpreted as the additional cost incurred per additional health outcome, and the ACER as the net cost incurred per a unit of health outcome (Bang and Zhao, 2014).

In this study, we measure the effectiveness of the intervention S computing its cumulative level of infection averted using the following functional:

$$E(S) = \int_0^T (U_f(t) - \tilde{U}_f(t)) + (I_f(t) - \tilde{I}_f(t)) dt, \quad (5)$$

where $U_f(t)$ are the infected unaware females for no control scenario at time t and $\tilde{U}_f(t)$ are the infected unaware females under intervention S (analogously for the infected aware females I_f). The functional (5) focuses on the females because they are at a considerable higher risk of developing severe disease (e.g. cervical cancer) after an HPV infection.

To compute the costs, we propose the following functional

$$C(S) = \int_0^T L(S) + B_1 \tilde{U}_f(t) + B_2 \tilde{I}_f(t) dt, \quad (6)$$

where

$$L(S) = A_1(w_1\mu_f + w_2\mu_m) + A_2(u_1\tilde{S}_f(t) + u_2\tilde{S}_m(t)) + A_3\alpha(\tilde{U}_f(t) + \tilde{S}_f(t)). \quad (7)$$

The parameters A_i ($i = 1, 2, 3$) are positive constants associated with the relative costs of vaccination and screening, and parameters B_j ($j = 1, 2$) represent the medical and social costs associated with the illness. The terms $(w_1\mu_f + w_2\mu_m)$ and $(u_1\tilde{S}_f(t) + u_2\tilde{S}_m(t))$ count the number of vaccinations given prior and after sexual initiation, respectively, and $\alpha(\tilde{U}_f(t) + \tilde{S}_f(t))$ counts the number of individuals that are screened.

The costs attributable to the vaccination includes the price of the vaccine, the cost of delivery, as well as other administration associated costs. It is logical to expect that delivering the vaccine to school boys and girls is cheaper than vaccination of the sexually active individuals; hence, $A_1 < A_2$. Since the costs of screening and follow up are uncertain, for simplicity, we assume that $A_3 \approx A_1$; that is, the costs associated with screening and juveniles vaccination are of the same magnitude. Moreover, it is also considered that unaware infected females are at greater risk of developing HPV-induced cervical cancer than aware infected females; therefore, it can be expected that $B_1 \geq B_2$. Under these considerations, as a base case, we assume $A_1 = 1, A_2 = 5, A_3 = 1, B_1 = 15, B_2 = 10$. Moreover, a time horizon of $T = 100$ years is chosen because in this time frame the majority of the benefits and cost of vaccination can be recognized (Elbasha and Dasbach, 2010). To perform a cost-effectiveness analysis, we use the following algorithm:

1. The list of strategies with their corresponding costs and effectiveness is sorted from lowest to highest costs. Let S_A and S_B be the first and the second elements of the sorted list, respectively.
2. The $ACER(S_A)$ of the first element of the list S_A is computed.
3. The $ICER(S_A, S_B)$ between the first two elements of the list S_A, S_B is computed.
4. The following conditions are assessed:
 - If $ICER(S_A, S_B) \leq 0$, then S_A has higher effectiveness than S_B ; hence, we keep S_A and remove S_B .
 - If $ICER(S_A, S_B) \geq ACER(S_A)$, then S_B has higher effectiveness than S_A , but in proportion is less cost-effective than S_A ; hence, we keep S_A and remove S_B .
 - If $0 < ICER(S_A, S_B) < ACER(S_A)$, then S_B has higher effectiveness than S_A and is in proportion more cost-effective than S_A ; hence, we keep S_B and remove S_A .
5. We return to STEP 2 until we find the most cost-effective strategy.

To fairly compare the proposed strategies, we set the values for the screening and vaccination rates in such a way that the value of the effective reproduction number $\mathcal{R}_e(c)$ is the same for all the strategies. Then, we compute the corresponding costs and the total infection averted over the time horizon for each intervention. These data allow us to compute both the ICER and the ACER using the algorithm proposed above and rank the interventions in order of increasing cost-effectiveness ratios. The results are summarized in Table 2.

The results of the cost-effectiveness analysis suggest that the strategy S_4 (female’s vaccination) is the most cost-effective intervention and S_2 (vaccination before sexual initiation) is the strategy with the second-best performance. These results coincide with several studies that have analyzed HPV transmission at the population level finding that vaccination of pre-adolescent girls is both highly effective and highly cost-effective to reduce the disease burden caused by HPV, see Seto et al. (Seto et al., 2012) and the references therein. However, regardless of the independence of the cost function (6) from infected males, the third most cost-effective strategy is S_5 (male’s vaccination). This result is somehow unexpected; however, it could be explained by the fact that for a heterosexual population, the eradication of the infection can be achieved by vaccinating a considerable proportion of a single-sex. On the other hand, the strategy with the worst performance is S_7 (vaccination of sexually active individuals with female’s screening), thus, even assuming a medium duration of protection for the vaccine (20 years), it is plausible to vaccinate individuals before sexual debut avoiding the potential of an HPV infection.

The simulations of the HPV model showing the effects of strategy S_4 , which is the most cost-effective control strategy according to the results in Table 2, are illustrated in Fig. 3. The simulations show that the number of infected individuals decreases to zero after an approximate time of 40 years. Furthermore, the fraction of vaccinated females increases until it reaches a value of 0,62, whereas the fraction of vaccinated males is maintained at zero.

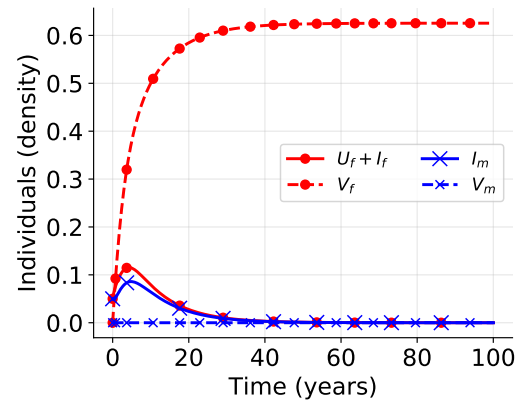


Figure 3: Dynamics of model (1) state variables under intervention S_4 with fixed constant controls $w_1 = 0,3$ and $u_1 = 0,127$

COST-EFFECTIVENESS ANALYSIS FOR OPTIMAL CONTROLS

In the previous sections, we analysed the qualitative properties of the HPV model (1) and performed a cost-effectiveness analysis for constant control policies. Constant control analysis is helpful to understand the mean behavior of the model. However, such a constant control scheme disregards the changing dynamics of the infection and thereby can be a fragile strategy.

For monetary and time resources, as well as disease elimination, it is essential to find the right time and the right

Strategy	$C(S_i)$	$E(S_i)$	Rank
$S_1 (w_1 = 0,03, w_2 = 0,03, u_1 = 0,05, u_2 = 0,05, \alpha = 0,1)$	\$ 70.33	31.77	# 7
$S_2 (w_1 = 0,81 w_2 = 0,81)$	\$ 47.86	31.04	# 2
$S_3 (u_1 = 0,068, u_2 = 0,05)$	\$ 69.07	31.71	# 6
$S_4 (w_1 = 0,3, u_1 = 0,127)$	\$ 49.24	32.43	# 1
$S_5 (w_2 = 0,3, u_2 = 0,119)$	\$ 55.07	31.86	# 3
$S_6 (w_1 = 0,66 w_2 = 0,6, \alpha = 0,4)$	\$ 59.50	31.99	# 5
$S_7 (u_1 = 0,046, u_2 = 0,05, \alpha = 0,2)$	\$ 73.30	32.01	# 8
$S_8 (w_1 = 0,15, u_1 = 0,1, \alpha = 0,3)$	\$ 58.03	32.65	# 4

TABLE 2: CONTROL STRATEGIES WITH FIXED CONSTANT CONTROLS TOGETHER WITH THEIR COSTS (USING (6)) AND CUMULATIVE LEVEL OF INFECTION AVERTED. THE RANKING OF THE STRATEGIES IS ACCORDING TO THE COST-EFFECTIVENESS ALGORITHM. FOR ALL THE STRATEGIES, THE VALUE OF THE EFFECTIVE REPRODUCTION NUMBER IS $\mathcal{R}_e(c) = 0,9$

amount of control administration. Therefore, it is valuable to incorporate time-dependent screening and vaccination into our model and explore the most cost-effective strategy via the optimal control theory.

Including time-dependent controls $c(t) = (w_1(t), w_2(t), u_1(t), u_2(t), \alpha(t))$ and considering

$$S_f = 1 - U_f - I_f - V_f, \quad S_m = 1 - I_m - V_m$$

we obtain the following five-dimensional control model for HPV dynamics:

$$\begin{aligned} \dot{U}_f &= (S_f + \varepsilon V_f)(1 - p)\beta_m I_m - (\gamma_f + \alpha(t) + \mu_f)U_f, \\ \dot{I}_f &= (S_f + \varepsilon V_f)p\beta_m I_m + \alpha(t)U_f - (\gamma_f + \mu_f)I_f, \\ \dot{V}_f &= w_1(t)\mu_f + u_1(t)S_f - \varepsilon\beta_m V_f I_m - (\mu_f + \theta)V_f, \\ \dot{I}_m &= (\beta_f U_f + \tilde{\beta}_f I_f)(S_m + \varepsilon V_m) - (\gamma_m + \mu_m)I_m, \\ \dot{V}_m &= w_2(t)\mu_m - (\beta_f U_f + \tilde{\beta}_f I_f)\varepsilon V_m + u_2(t)S_m - (\mu_m + \theta)V_m. \end{aligned} \tag{8}$$

Here, the controls are subject to constraints

$$0 \leq w_1(t), w_2(t), u_1(t), u_2(t), \alpha(t) \leq 1. \tag{9}$$

The control model (8) is defined on a finite time interval $[0, T]$ and the set of admissible controls, denoted $D(T)$, is defined as the set of all possible Lebesgue measurable functions which for almost all $t \in [0, T]$ satisfy constraints (9).

For an optimal control problem, it is necessary to define a quantitative criterion to evaluate the performance of the admissible controls. In mathematical terms, this quantitative criterion leads to the definition of an objective functional, and an optimal control is one that minimizes (or maximizes) this functional. For the control model (8) and the set of admissible controls $D(T)$, we want to minimize the overall impact of the infection and the level of efforts that would be needed to control the infection over T years. Thus, we consider system (8) together with the following objective functional

$$\begin{aligned} J(c) &= \int_0^T B_1 U_f + B_2 I_f + \\ &\frac{1}{2} (A_1 (w_1^2 + w_2^2) + A_2 (u_1^2 + u_2^2) + A_3 \alpha^2) dt. \end{aligned} \tag{10}$$

It is generally assumed that the quadratic terms penalize high levels of control administration (to avoid costly interventions) because increasing the availability of vaccines and other resources often leads to a waste" (Sharomi and Malik,

2017). Nevertheless, it is important to mention that the sum of weighted squares of the controls is probably the most common form of the objective functional in the literature due to its mathematical convenience. In particular, for functionals of these type, it is possible, by virtue of the Pontryagin maximum principle, to obtain the optimal controls as explicit functions of the state and adjoint variables.

For the sake of simplicity and comparison, in this paper the objective functional (10) considers the sum of weighted squares of the controls and also uses the same weight parameters of the cost function (6).

The general optimal control problem is to find optimal vaccination and screening rates

$$c^* = (w_1^*(t), w_2^*(t), u_1^*(t), u_2^*(t), \alpha^*(t))$$

such that

$$J(c^*) = \min_{c \in D(T)} J(c) \tag{11}$$

subject to the dynamics of the HPV control model (8).

Theorem 4.1 in (Fleming and Rishel, 1975, Chapter III) ensures the existence of an optimal control and the corresponding solution for this problem. Proofs of such statements can be found in (Camacho and Jerez, 2019; Saldaña *et al.*, 2019).

Here, we must clarify the following: (i) Although optimal controls c^* are expected to be more cost-effective than constant controls, this is not known *a priori* because c^* minimize the objective functional (10) and the ICER measures the cost using (6); (ii) The cost function (6) can also be used as an objective functional for the optimal control; however, generally speaking, an optimal control problem could have multiple goals and therefore, the objective functional may include other factors besides costs.

Characterization of the optimal controls

Here, we obtain the optimality system that corresponds to complement the control model (8) with a dual system for adjoint variables. Then, we can achieve the characterization of the optimal controls in terms of the state and adjoint variables.

The Pontryagin maximum principle converts the optimal control problem (11) into a problem of minimizing pointwise

the Hamiltonian

$$H = B_1 U_f + B_2 I_f + \frac{1}{2} [A_1 (w_1^2 + w_2^2) + A_2 (u_1^2 + u_2^2) + A_3 \alpha^2] + \psi_1 \dot{U}_f + \psi_2 \dot{I}_f + \psi_3 \dot{V}_f + \psi_4 \dot{I}_m + \psi_5 \dot{V}_m \quad (12)$$

with respect to the controls. Here, ψ_i for $i = 1, \dots, 5$ are adjoint variables which satisfy the following system of differential equations:

$$\begin{aligned} \dot{\psi}_1 &= -B_1 + [(1-p)\beta_m I_m + \gamma_f + \alpha^* + \mu_f] \psi_1 + (p\beta_m I_m - \alpha^*) \psi_2 \\ &\quad + u_1^* \psi_3 - \beta_f [(1-I_m - V_m) + \varepsilon V_m] \psi_4 + \beta_f \varepsilon V_m \psi_5, \\ \dot{\psi}_2 &= -B_2 + (1-p)\beta_m I_m \psi_1 + (p\beta_m I_m + \gamma_f + \mu_f) \psi_2 + u_1^* \psi_3 \\ &\quad - \tilde{\beta}_f [(1-I_m - V_m) + \varepsilon V_m] \psi_4 + \tilde{\beta}_f \varepsilon V_m \psi_5, \\ \dot{\psi}_3 &= [(1-p)\psi_1 + p\psi_2] (1-\varepsilon) \beta_m I_m + (\varepsilon \beta_m I_m + u_1^* + \mu_f + \theta) \psi_3, \\ \dot{\psi}_4 &= -\beta_m ((1-U_f - I_f - V_f) + \varepsilon V_f) [(1-p)\psi_1 + p\psi_2] + \\ &\quad \varepsilon \beta_m V_f \psi_3 + (\beta_f U_f + \tilde{\beta}_f I_f + \gamma_m + \mu_m) \psi_4 + u_2^* \psi_5, \\ \dot{\psi}_5 &= (\beta_f U_f + \tilde{\beta}_f I_f) ((1-\varepsilon)\psi_4 + \varepsilon \psi_5) + (u_2^* + \theta + \mu_m) \psi_5, \end{aligned} \quad (13)$$

with transversality conditions $\psi_k(T) = 0$ for $k = 1, \dots, 5$. For this control problem, applying the maximum principle from, we obtain the following characterization for the optimal controls:

$$\begin{aligned} w_1^*(t) &= \min \left\{ 1, \max \left\{ 0, -\frac{\mu_f}{A_1} \psi_3(t) \right\} \right\}, \\ w_2^*(t) &= \min \left\{ 1, \max \left\{ 0, -\frac{\mu_m}{A_1} \psi_5(t) \right\} \right\}, \\ u_1^*(t) &= \min \left\{ u_{max}, \max \left\{ 0, -\frac{1}{A_2} (1-U_f(t) - I_f(t) - V_f(t)) \psi_3(t) \right\} \right\}, \\ u_2^*(t) &= \min \left\{ u_{max}, \max \left\{ 0, -\frac{1}{A_2} (1-I_m(t) - V_m(t)) \psi_5(t) \right\} \right\}, \\ \alpha^*(t) &= \min \left\{ \alpha_{max}, \max \left\{ 0, \frac{1}{A_3} (\psi_1(t) - \psi_2(t)) U_f(t) \right\} \right\}. \end{aligned} \quad (14)$$

The control model (8), the system of differential equations for the adjoints (13) and the control characterization above form the optimality system. The optimality system will allow us to obtain time-dependent versions of the control strategies $S_1 - S_8$. To achieve this, we solve numerically such system using the forward-backward sweep method described in (Lenhart and Workman, 2007, Chapter 4). The time-dependent profiles for the control strategies (denoted $S_i^*(t)$, $i = 1, 2, \dots, 8$) are shown in Fig. 4.

Cost-effectiveness analysis for time-dependent control strategies

Next, we want to determine the most cost-effective of the time-dependent control strategies $S_i^*(t)$ ($i = 1, 2, \dots, 8$) illustrated in Fig. 4. As in the case of constant controls, we need to compare the costs and the effectiveness of the interventions. This is done using the cost-effectiveness algorithm presented in section . The results of this analysis can be found in Table 3.

The results presented in Table 3 indicate that $S_4^*(t)$ is the most cost-effective strategy. This result coincides with the results for the constant control case (see Table 2). Hence, female's vaccination is the intervention with the best performance for control of HPV infection. Nevertheless, for time-dependent control strategies, the second most cost-effective intervention is female's vaccination and screening, $S_8^*(t)$;

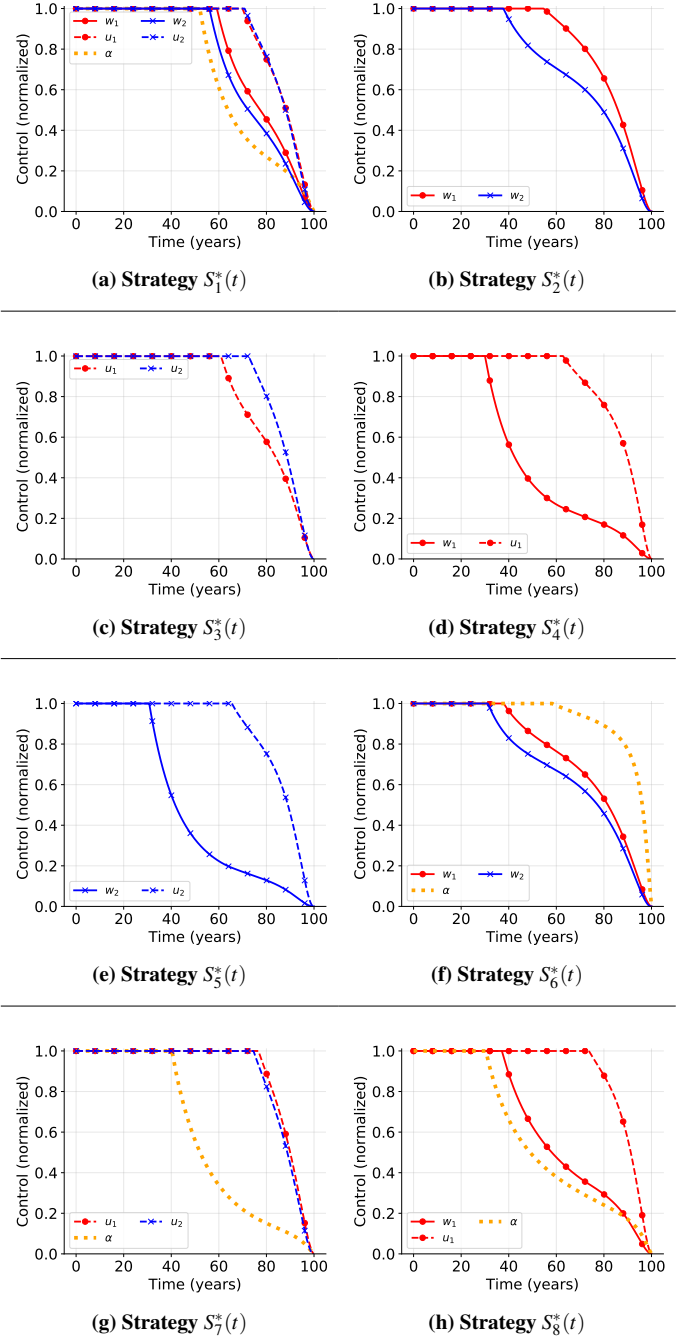


Figure 4: Time-dependent profiles of the control strategies derived from the optimal control problem (11).

Strategy	$C(S_i^*)$	$E(S_i^*)$	Rank
$S_1^*(t)$	\$ 64.48	31.76	#8
$S_2^*(t)$	\$ 48.65	30.86	#3
$S_3^*(t)$	\$ 64.04	31.69	#7
$S_4^*(t)$	\$ 47.92	32.39	#1
$S_5^*(t)$	\$ 53.69	31.82	#4
$S_6^*(t)$	\$ 59.23	31.85	#5
$S_7^*(t)$	\$ 64.36	31.99	#6
$S_8^*(t)$	\$ 50.80	32.61	#2

TABLE 3: COSTS (USING (6)), CUMULATIVE LEVEL OF INFECTION AVERTED, AND RANK ACCORDING TO THE COST-EFFECTIVENESS ALGORITHM FOR THE CONTROL STRATEGIES WITH TIME-DEPENDENT CONTROL STRATEGIES DERIVED FROM (11)

whereas for constant control strategies, vaccination prior to sexual initiation, S_2 , is the second most cost-effective intervention. Therefore, the rankings for the constant and the time-dependent control case differ. Moreover, it is uncertain if the time-dependent control strategies outperforms the constant control strategies as expected. Thus, we use the ICER and ACER to compare constant control strategies S_i (see Table 2) against the time-dependent control strategies $S_i^*(t)$ (see Fig. 4).

First, we compare the most cost-effective control strategies with constant and time-dependent controls, that is, S_4 versus $S_4^*(t)$. For this, we need the following computations:

$$ACER(S_4^*(t)) = \frac{47,92}{32,39} = 1,479,$$

$$ICER(S_4^*(t), S_4) = \frac{49,24 - 47,92}{32,43 - 32,39} = 33,00.$$

These computations imply that $ICER(S_4^*(t), S_4) > ACER(S_4^*(t))$. Hence, although strategy S_4 has higher effectiveness than strategy $S_4^*(t)$, in proportion, S_4 is less cost-effective than $S_4^*(t)$. In particular, the value of $ICER(S_4^*(t), S_4)$ shows a cost saving of \$ 33 for strategy $S_4^*(t)$ over strategy S_4 . Consequently, in this case, the time-dependent control outperform the constant control.

Next, we compare the second most cost-effective constant control strategy S_2 against the second most cost-effective time-dependent control strategy $S_8^*(t)$. The cost-effective ratios are:

$$ACER(S_2) = \frac{47,86}{31,04} = 1,54,$$

$$ICER(S_2, S_8^*(t)) = \frac{50,80 - 47,86}{32,61 - 31,04} = 1,87.$$

Clearly, $ICER(S_2, S_8^*(t)) > ACER(S_2)$. Thus, the comparison shows a cost saving of \$ 1,87 for strategy S_2 over strategy $S_8^*(t)$. Therefore, in this case, the constant control outperform the time-dependent control.

Finally, we compare the third most cost-effective control strategies, that is, S_5 against $S_2^*(t)$. The cost-effectiveness ratios are calculated as follows:

$$ACER(S_2^*(t)) = \frac{48,65}{30,86} = 1,57,$$

$$ICER(S_2^*(t), S_5) = \frac{55,07 - 48,65}{31,86 - 30,86} = 6,42.$$

The comparison between strategies S_5 and $S_2^*(t)$ shows a cost saving of \$ 6,42 for strategy $S_2^*(t)$ over strategy S_5 . Hence, in this case, the time-dependent control outperform the constant control.

On the whole, the intervention with the best performance is the time-dependent strategy $S_4^*(t)$ (see Fig. 5 for the simulations of the HPV model showing the effects of strategy S_4^*). Nevertheless, generally speaking, time-dependent control strategies obtained by the solution of the optimal control problem are not always more cost-effective than constant control strategies.

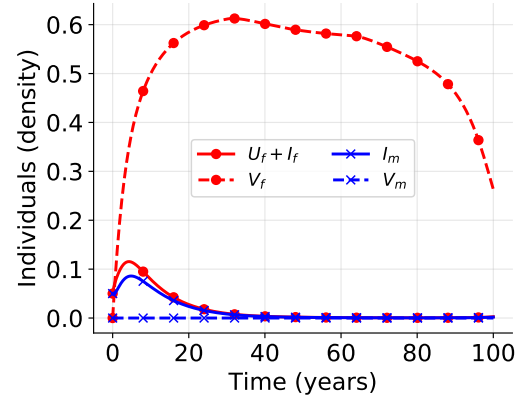


Figure 5: Simulations of the HPV model showing the effects of the time-dependent control strategy $S_4^*(t)$ with optimal controls w_1^* and u_1^* illustrated in Fig. 4 (d).

DISCUSSION AND CONCLUDING REMARKS

Data from clinical trials indicate that HPV vaccines are highly effective in preventing HPV associated diseases. Nevertheless, so far the question whether it is better, in terms of health and cost, to vaccinate females only, males only, or both sexes, remains a controversy. Some studies have shown that males' vaccination alongside females' vaccination, can be cost-effective, particularly if female vaccination coverage is low to moderate and if all potential health benefits of HPV vaccination are considered (Chesson et al., 2011). Moreover, in circumstances where the immunization coverage in females is likely to be low, it is more optimal to vaccinate males than hard-to-reach females. However, in the majority of countries recommending HPV vaccination, the preferred strategy is vaccination of young adolescent girls aged 9-14 (Brisson et al., 2016).

This work aimed to assess the cost-effectiveness of HPV healthcare interventions. We proposed constant control strategies based on combinations of the five controls incorporated in our model and used cost-effectiveness ratios to identify which strategy delivers the best effectiveness for the money invested. Comparisons of the cost-effectiveness of the proposed constant control strategies consistently show that females' vaccination, including pre-adolescent girls and adult women, is the most cost-effective strategy. Then, the next strategy with the best performance is the vaccination of school-boys and -girls before sexual initiation. Furthermore, the third most cost-effective strategy is males' vaccination. This result is unexpected because the cost function (6) does not depend on the presence of HPV infected males. Therefore, a very adequate choice to balance cost and protection is increasing vaccine uptake among all eligible females and extending coverage to high-risk males sub-groups. In general, the aforementioned results are qualitatively similar to the results in previous studies with respect to the finding that including young boys in existing female-only vaccination programs would further decrease HPV associated diseases and is cost-effective (Bogaards et al., 2015; Brown and Jane White, 2011; Elbasha and Dasbach, 2010; Soe et al., 2018). Nevertheless, our results differ from those of (Smith et al., 2011) that suggest that extending HPV vaccination programs to include males will provide some incremental

benefits, but up to three-quarters of the maximum possible vaccination-conferred benefit to males will be achieved by existing female-only vaccination programs.

Secondly, we considered the control parameters to be time-dependent and formulated an optimal control problem. We used the Pontryagin maximum principle to derive the necessary conditions for the optimal control and obtained numerical approximations via the forward-backward sweep method. This allowed us to obtain time-dependent versions of the control strategies. As in the case for constant controls, we used cost-effectiveness ratios to identify the strategy with the best performance to control HPV infection. The results confirm that the females' vaccination is the most cost-effective strategy. For this intervention, the numerical computations (see Fig. 4 (b)) indicate that initially, the vaccination rates should be applied at the maximum level and after approximately half of the time interval, these rates should gradually be reduced reaching zero at the final time. An important limitation of this study is that we simplified the natural history of HPV infection. Hence, several extensions are possible for example, including compartments related to the development of cervical intraepithelial neoplasia (CIN) and cervical cancer stages in females. Moreover, type-specific HPV infection can also be considered (Elbasha and Dasbach, 2010).

The objective functional (10) of the optimal control problem considers the sum of weighted squares in the controls. This penalizes high levels of control administration but differs from the costs derived from function $C(S)$. Therefore, when comparing constant against time-dependent control policies, it is not known *a priori* which of the strategies is the most cost-effective. Therefore, we used the ICER-ACER methodology to compare constant against time-dependent control strategies that are optimal in the sense that they minimize functional (10). The results indicate that time-dependent controls are not always more cost-effective than constant controls. Therefore, one must be very careful with the election of the objective functional for optimal control problems in epidemiology.

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