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# Modeling Public Health Campaigns for Sexually Transmitted Infections via Optimal and Feedback Control

**Ariel Camacho · Fernando Saldaña · Ignacio Barradas · Silvia Jerez**

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**Abstract** Control of sexually transmitted infections (STIs) poses important challenges to public health authorities. Obstacles for STIs control include low priority in public health programs and disease transmission mechanisms. This work uses a compartmental pair model to explore different public health strategies on the evolution of STIs. Optimal and feedback control are used to model realistic strategies for reducing the prevalence of these infections. Feedback control is proposed to model the reaction of public health authorities relative to an alert level. Optimal control is used to model optimization of available resources for implementing strategies. Numerical simulations are performed using trichomoniasis, gonorrhea, chlamydia and human papillomavirus (HPV) as study cases. HPV is non-curable and it is analyzed only under transmission control such as condom promotion campaigns. Trichomoniasis, gonorrhea, and chlamydia are curable STIs that are modeled here additionally under treatment control. Increased cost-effectiveness ratio (ICER) is employed as a criterion to measure control strategies performance. The features and drawbacks of control strategies under the pair formation process are discussed.

**Keywords** Pair model · Optimal control · Feedback control · Sexually transmitted infections.

## 1 Introduction

Sexually transmitted infections (STIs) constitute a serious public health issue. It has been estimated that the annual direct cost in the US for treating these infections is approximately $ 16 billion (Owusu-Edusei et al., 2013). Implementation of disease control public health strategies is a complex process. Multiple factors are involved, such as available resources as well as geographical and political considerations that change over time. Thus, designing control strategies and determining optimal resource allocation are not straightforward tasks.

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**Although there are over 30 important bacterial, viral and parasitic diseases that can be transmitted by sexual contact (Gerbase et al., 1998), we focus on four of the most common and problematic STIs: trichomoniasis, gonorrhea, chlamydia, and human papillomavirus (HPV) infection. The first three of these infections are curable. In many cases, these infections may go undetected because often they are asymptomatic. Thus, they can lead to severe complications such as pelvic inflammatory disease, ectopic pregnancy, infertility, chronic pelvic pain, neonatal death, and severe disability in infants, among others (Newman et al., 2015). Since 1995, the World Health Organization (WHO) has generated global estimates for the prevalence of trichomoniasis, gonorrhea, and chlamydia every five years (Newman et al., 2015). Hence, the majority of curable STIs' control policies focus on these three infections. Furthermore, according to the Centers for Disease Control and Prevention, HPV is the most common sexually transmitted infection in the United States (CDC, 2013). In addition to its high prevalence, HPV infection is the main etiological factor for the development of cervical cancer and therefore constitutes a serious public health issue. Currently, there is no treatment for the virus itself, but there are vaccines to prevent infection by some of the most common HPV types and treatment for HPV-associated diseases, including genital warts and cervical cancer.**

Despite advances in STI control, the development of effective measures continues to challenge public health authorities (Unemo et al., 2017). Moreover, continuous budget cuts to STI programs pose additional constraints for implementing effective control strategies optimally. Therefore, studies addressing infectious disease control to identify optimal strategies for specific health care goals are of growing importance.

Mathematical modeling offers a theoretical framework to test hypotheses and predict outcomes related to infectious diseases. Spread predominantly by sexual contacts, STIs usually occur among sexual partners. Several mathematical models that study STI dynamics assume that the population is mixed homogeneously, and therefore each sexual contact occurs randomly among individuals (Brauer and Castillo, 2012). For instance, a mathematical model was recently explored to determine optimal strategies to control HPV transmission in Malik et al. (2016), screening and vaccination strategies for HPV in an unscreened population are studied in Milwid et al. (2018), and a syphilis mathematical model is proposed in Gumel et al. (2018).

The previously mentioned works, however, do not consider the pair formation process. Mathematical pair models include the number of sexual partnerships as an explicit variable (Kretzschmar and Dietz, 1998; Heijne et al., 2011; Muller and Bauch, 2010). These models confirmed that partnership duration is an important element in STI epidemiology. In fact, excluding partnerships may potentially bias the model outcome. For a complete review of pair models, see Kretzshmar and Heijne (2017) and the references therein.

Bearing this in mind, in many biological systems questions arise regarding how external forces modify their dynamics. In epidemiological models, input functions are introduced to describe how human efforts (e.g. vaccination) modify the evolution and spread of population diseases. Examples of this approach are Wang (2006) where constant and linear treatment functions are introduced, Zhang and Liu (2008) where a saturated treatment function is considered, and Villaviencio Pulido et al. (2017) where an exponential decay treatment function is studied.

As a first attempt to control an STI, the most simple strategy is to apply constant control efforts (constant control). Constant controls reflect permanent health programs. However, this is not a practical strategy since it does not take into consideration the evolution of the disease. One improvement is to place control efforts according to the prevalence levels. If levels are low, efforts would be decreased in order to minimize the use of resources. In this case, the input function will depend on the infected population variable (feedback control). An example of this approach may be found in a previous work (Saldaña and Barradas, 2019). Nevertheless, feedback functions do not consider the number of resources required to implement the corresponding strategies. As a final improvement, we ask that control efforts optimize a predefined objective function (optimal control). This can be posed as an optimal control problem, a modeling framework that has already been used in biological models (Lenhart and Workman, 2007; Sharomi and Malik, 2017; Camacho and Jerez, 2019). It is important to stress that in this work "resources" and "costs" refer to amounts of economic, human and material resources.

The aim of this work is to discern efficient strategies to control STIs. Here we describe trichomoniasis, gonorrhea, chlamydia and HPV infection dynamics as case studies by incorporating parameters from the literature. To this end, we use pair models to consider pair formation processes (Kretzschmar and Dietz, 1998). We also perform a cost-effectiveness analysis using the increased cost-effectivity ratio (ICER) (Okosun et al., 2011; Cape et al., 2013). A feature in our work is that we employ the ICER as a way to measure different types of control strategies (constant, feedback and optimal control).

The rest of this work is organized as follows. In Section 2 we extend a pair model proposed in Kretzschmar and Dietz (1998) by including two control functions. The first one represents efforts of moving infected people back into the susceptible compartment (treatment) while the second one represents decrement of transmission probability (condom promotion). We find the basic reproduction number $\mathcal{R}_0$ under constant control functions. Next, in Section 3 we introduce an **objective functional that penalizes the presence of infected individuals and the indiscriminate use of the two public health strategies.** Then, we pose an optimal control problem and proceed to characterize the optimal solutions. In Section 4 we present numerical results corresponding to the four STIs considered in this work under different control strategies. This is accompanied by a brief cost-effectiveness analysis to compare STI control strategies. Finally, in Section 5 we discuss the obtained results in this work and we mention our conclusions.

## 2 Sexually Transmitted Infections Pair Model

We consider an epidemic model with non-zero partnership length to study the dynamics of a curable STI in a population based on Kretzschmar and Dietz (1998). The model is constructed under the Susceptible-Infectious-Susceptible ($SIS$) framework. It includes explicitly the number of people in a partnership as a state variable. The total number of single individuals at time $t$ is denoted by $X(t)$ while the total number of pairs of individuals in the population is $P(t)$. Thus, the total population size $N(t)$ at time $t$ is $N(t) = X(t) + 2P(t)$. The basic assumptions that govern the model are the following (Saldaña and Barradas, 2019) (see also Figure 1):

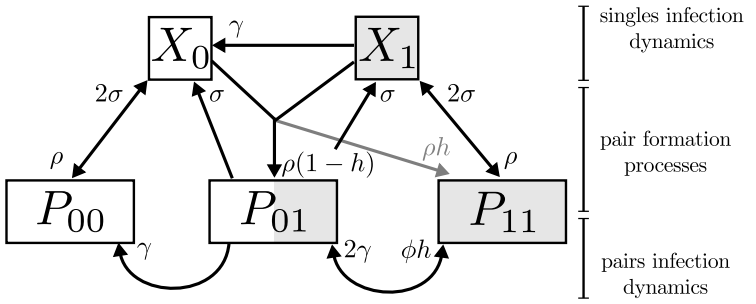


Fig. 1: Schematic representation of the model (1). Single populations are represented by $X$. Pair populations are represented by $P$. The states considered here are susceptible 0 and infected 1. For example, $P_{01}$ is the population of pairs with one susceptible and one infected individuals. Arrows denote the flow between compartments.

$(i)$ Susceptible individuals are recruited as singles into the sexually active population at a constant rate $\nu$, and leave the population by dying or ceasing sexual activity at a constant rate $\mu$.

$(ii)$ At a constant rate $\rho$ per unit of time, single individuals form pairs. These are dissolved when the relationships end at a rate $\sigma$ or when one of the individuals in the pair dies. Since pairs without sexual contact are irrelevant for the spread of the infection, we shall assume that pair formation starts with sexual contact.

$(iii)$ Transmission can only take place within a pair of a susceptible and an infected individual. We consider $\phi$ to be the number of sexual acts per unit of time, and $h \in (0,1)$ the transmission probability per contact.

$(iv)$ We extend the model from Kretzschmar and Dietz (1998) by considering the following. Infected individuals can clear the infection naturally at a rate $\gamma$ due to the immune response. We assume that the recovery rate $\gamma$ increases by a time-dependent function $u_T$ (e.g. treatment of infected individuals). Also, we assume that a time-dependent function $u_C$ decreases the transmission probability $h$ (e.g. condom promotion campaigns). Both functions $u_T$ and $u_C$ represent public health authorities' efforts to reduce the prevalence of the infection.

Such assumptions lead to the following pair model:

$$
\begin{aligned}
X_0' &= \nu + (\sigma+\mu)(2P_{00}+P_{01}) - (\mu+\rho)X_0 + (\gamma+u_T)X_1,\\
X_1' &= (\sigma+\mu)(2P_{11}+P_{01}) - (\mu+\rho)X_1 - (\gamma+u_T)X_1,\\
P_{00}' &= \frac{1}{2}\rho\frac{X_0^2}{X} - (\sigma+2\mu)P_{00} + (\gamma+u_T)P_{01},\\
P_{01}' &= \rho\left(1-h(1-u_C)\right)\frac{X_0X_1}{X} - \left(\sigma+\phi h(1-u_C)+2\mu\right)P_{01}\\
&\quad - (\gamma+u_T)P_{01} + 2(\gamma+u_T)P_{11},\\
P_{11}' &= \frac{1}{2}\rho\frac{X_1^2}{X} + \rho h(1-u_C)\frac{X_0X_1}{X} + \phi h(1-u_C)P_{01} - (\sigma+2\mu)P_{11}\\
&\quad - 2(\gamma+u_T)P_{11},
\end{aligned}
\tag{1}
$$

| Variable | Description |
|---|---|
| $X_0$ | Single susceptible individuals |
| $X_1$ | Single infected individuals |
| $P_{00}$ | Pairs with two susceptible individuals |
| $P_{01}$ | Pairs with a susceptible and an infected individuals |
| $P_{11}$ | Pairs with two infected individuals |
| $X$ | Total number of singles |
| $P$ | Total number of pairs |
| $u_T$ | Public health control: treatment of infected individuals |
| $u_C$ | Public health control: condom promotion |

Table 1: State variables for model (1).

| Parameter | Description | Units |
|---|---|---|
| $\nu$ | Recruitment rate | individuals year$^{-1}$ |
| $\mu$ | Rate of leaving the sexually active population | year$^{-1}$ |
| $\rho$ | Rate of pair formation | year$^{-1}$ |
| $\sigma$ | Separation rate | year$^{-1}$ |
| $\phi$ | Contact frequency within partnerships | year$^{-1}$ |
| $1/\gamma$ | Infectious period in the absence of treatment | year |
| $h$ | Transmission probability per contact | dimensionless |

Table 2: Interpretation and units for the parameters of model (1).

where the derivative is considered with respect to time, and $u_T$ and $u_C$ are time-dependent functions. All the parameters are assumed to be non-negative. Tables 1 and 2 summarize the model variables and parameters.

Before going any further it is important to emphasize the role of the control functions $u$ for $u \in \{u_T, u_C\}$. In our system $u(t)$ represents the impact on the population due to the efforts (decisions, plans or actions) undertaken by the health care system to control the disease at time $t$. In other words, the functions $u_T$ and $u_C$ model public health strategies to reduce the prevalence of the STI. In mathematical terms, the control functions $u$ are non-negative functions that increase the recovery rate of infected individuals or reduce the transmission probability as a consequence of the application of public health strategies. As such, any public health care system has a maximum resource capacity to carry on control strategies. Thus, we assume the following:

$$0 \leq u_T(t) \leq M_T, \qquad 0 \leq u_C(t) \leq M_C \leq 1 \tag{2}$$

for all $t > 0$, where $M_T$ is the maximum increase on the recovery rate $\gamma$ due to treatment and $M_C$ is the maximum decrease on the transmission probability $h$ due to condom promotion and sexual education campaigns.

## 2.1 **Model Reduction**

By adding the equations from (1), note that the total population size $N = X_0 + X_1 + 2(P_{00} + P_{01} + P_{11})$ satisfies $N' = -\mu N + \nu$, from which it is easy to see that the set

$$\Omega = \{(X_0, X_1, P_{00}, P_{01}, P_{11}) \in \mathbb{R}^5_+ \mid X_0 + X_1 + 2(P_{00} + P_{01} + P_{11}) \leq \nu/\mu\}$$

is a positively invariant set under model (1), see Appendix A.

Now, let $X = X_0 + X_1$ be the total number of singles and $P = P_{00} + P_{01} + P_{11}$ the total number of pairs. From (1), observe that the dynamics of singles and pairs are described by the the following system of differential equations:

$$X' = \nu + 2(\sigma + \mu)P - (\mu + \rho)X, \tag{3}$$

$$P' = \frac{1}{2}\rho X - (\sigma + 2\mu)P. \tag{4}$$

The partnership dynamics (3)–(4) has a unique equilibrium point $(X^*, P^*)$:

$$X^* = \frac{\nu(\sigma + 2\mu)}{\mu(\sigma + 2\mu + \rho)}, \qquad P^* = \frac{\nu\rho}{2\mu(\sigma + 2\mu + \rho)}. \tag{5}$$

Let the initial conditions of (3)–(4) be the equilibrium point $(X^*, P^*)$ (5). In this case we say that the pair formation process is at equilibrium. This assumption implies that $X' = 0$ and $P' = 0$, so the total population size is constant with $N = \nu/\mu$. Thus, assuming equilibrium of the pair formation process we may reduce model (1) to the following three-dimensional system:

$$\begin{aligned} X_1' &= (\sigma + \mu)I - (2\mu + \rho + \sigma)X_1 - (\gamma + u_T)X_1, \\ P_{01}' &= \rho\left(1 - h(1 - u_C)\right)X_1\left(1 - \frac{X_1}{X^*}\right) - \left(\sigma + \phi h(1 - u_C) + 2\mu\right)P_{01} \\ &\quad + (\gamma + u_T)\left(I - X_1 - 2P_{01}\right), \\ I' &= \rho h(1 - u_C)X_1\left(1 - \frac{X_1}{X^*}\right) + \phi h(1 - u_C)P_{01} - \mu I - (\gamma + u_T)\, I, \end{aligned} \tag{6}$$

where $I = X_1 + P_{01} + 2P_{11}$ is the total prevalence.

## 2.2 **Basic Reproduction Number**

In this section we analyze the reduced pair model (6) assuming that the control functions $u \in \{u_T, u_C\}$ are constant functions over time. Suppose that the control functions are given by $u_T(t) = u_T^0$ and $u_C(t) = u_C^0$ for all time $t$, where $u_T^0$ and $u_C^0$ are fixed constants that satisfy condition (2). Then, system (6) turns into:

$$\begin{aligned} X_1' &= (\sigma + \mu)I - (2\mu + \rho + \sigma)X_1 - (\gamma + u_T^0)X_1, \\ P_{01}' &= \rho(1 - h(1 - u_C^0))X_1\left(1 - \frac{X_1}{X^*}\right) - (\sigma + \phi h(1 - u_C^0) + 2\mu)P_{01} \\ &\quad + (\gamma + u_T^0)(I - X_1 - 2P_{01}), \\ I' &= \rho h(1 - u_C^0)X_1\left(1 - \frac{X_1}{X^*}\right) + \phi h(1 - u_C^0)P_{01} - \mu I - (\gamma + u_T^0)I. \end{aligned} \tag{7}$$

The basic reproduction number $\mathcal{R}_0$ for pair models is defined as the expected number of secondary infections one typical infectious individual will produce during his/her infectious period, starting in a $P_{11}$ partnership within a completely susceptible population (see Heijne et al., 2013). Thus, the basic reproduction number associated to model (7) is [1]:

$$\mathcal{R}_0 = \frac{h(1 - u_C^0)\left[\rho(\sigma + \mu)(\sigma + 2(\gamma + u_T^0) + 2\mu + \phi) + (\gamma + u_T^0)\phi(\gamma + u_T^0 + \mu + \rho)\right]}{(\mu + \gamma + u_T^0)(\sigma + \phi h(1 - u_C^0) + 2\mu + 2(\gamma + u_T^0))(2\mu + \rho + \sigma + \gamma + u_T^0)}. \tag{8}$$

[1] For details on the computation of $\mathcal{R}_0$ see Saldaña and Barradas (2019).

A triplet $(X_1^*, P_{01}^*, I^*)$ is called an endemic equilibrium point of model (7) if $I^* > 0$ and if the triplet satisfies the following non-linear system:

$$X_1^* = \frac{(\sigma+\mu)I^*}{2\mu+\rho+\sigma+(\gamma+u_T^0)}, \tag{9}$$

$$P_{01}^* = \frac{\rho(1-h(1-u_C^0))X_1^*}{\sigma+\phi h(1-u_C^0)+2\mu+2(\gamma+u_T^0)}\left(1-\frac{X_1^*}{X^*}\right) + \frac{(\gamma+u_T^0)(I^*-X_1^*)}{\sigma+\phi h(1-u_C^0)+2\mu+2(\gamma+u_T^0)}, \tag{10}$$

$$I^* = \frac{\rho h(1-u_C^0)X_1^*}{\mu+(\gamma+u_T^0)}\left(1-\frac{X_1^*}{X^*}\right) + \frac{\phi h(1-u_C^0)P_{01}^*}{\mu+(\gamma+u_T^0)}. \tag{11}$$

System (9)–(11) comes from setting the left-hand side of (7) equal to zero. Assume that $(X_1^*, P_{01}^*, I^*)$ is an endemic equilibrium point. From (9) we can see that $I^* > X_1^* > 0$. In addition, given that $X_1^* \leq X^*$, from equation (10) we deduce that $I^* > P_{01}^* > 0$. In summary, if $(X_1^*, P_{01}^*, I^*)$ is an endemic equilibrium point then

$$I^* > 0, \quad I^* > X_1^* > 0, \quad I^* > P_{01}^* > 0.$$

Substituting the values of $X_1^*$ and $P_{01}^*$ in equation (11) and solving for $I^*$, we get:

$$I^* = (\mathcal{R}_0 - 1)\frac{(\mu+\gamma+u_T^0)(\sigma+\phi h(1-u_C^0)+2\mu+2(\gamma+u_T^0))(2\mu+\rho+\sigma+\gamma+u_T^0)^2X^*}{\rho h(1-u_C^0)(\sigma+2(\gamma+u_T^0)+2\mu+\phi)(\sigma+\mu)^2}. \tag{12}$$

This, in turn, can be used to explicitly determine the values of $X_1$ and $P_{01}$ at the endemic equilibrium. Moreover, when $\mathcal{R}_0 > 1$ all the factors on the right-hand side of expression (12) are positive. Therefore, $I^* > 0$ exists if and only if $\mathcal{R}_0 > 1$. The following result summarizes the role of the basic reproduction number in the dynamics of the disease.

**Theorem 1** *For the constant controls model (7), the disease-free equilibrium $E_0 = (0,0,0)$ always exists and it is locally asymptotically stable if and only if $\mathcal{R}_0 < 1$. For $\mathcal{R}_0 > 1$, the vector $E_1 = (X_1^*, P_{01}^*, I^*)$, where $X_1^*$, $P_{01}^*$ and $I^*$ are given by the solution of system (9)–(11), is the only endemic equilibrium point of model (7) and it is locally asymptotically stable.*

*Proof* It is straightforward to see that $E_0 = (0,0,0)$ is the disease-free equilibrium for model (7). To investigate the local stability of the equilibrium points, we compute the Jacobian matrix of the model (7):

$$J(X_1, P_{01}, I) = \begin{pmatrix} J_{11} & 0 & \sigma+\mu \\ J_{21} & J_{22} & \gamma+u_T^0 \\ J_{31} & \phi h(1-u_C^0) & -(\mu+\gamma+u_T^0) \end{pmatrix},$$

where:

$$J_{11} = 2\mu+\rho+\sigma-(\gamma+u_T^0), \quad J_{21} = \rho(1-h(1-u_C^0))\left(1-\frac{2X_1}{X^*}\right)-(\gamma+u_T^0),$$

$$J_{22} = -(\sigma+\phi h(1-u_C^0)+2\mu+2(\gamma+u_T^0)), \quad J_{31} = \rho h(1-u_C^0)\left(1-\frac{2X_1}{X^*}\right).$$

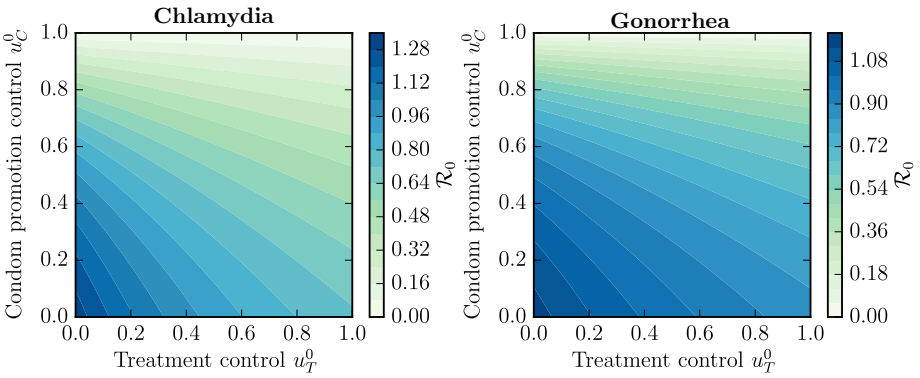


Fig. 2: **Contour plots for $\mathcal{R}_0$ with respect to constant controls $u_T^0$ and $u_C^0$. Model parameter values are found in Table 4.**

The characteristic polynomial for the Jacobian matrix evaluated at the disease-free equilibrium $J(E_0)$ is $P_1(\lambda) = \lambda^3 + a_2\lambda^2 + a_1\lambda + a_0(1-\mathcal{R}_0)$ where:

$$
\begin{aligned}
a_2 &= 2\sigma + 4(\gamma + u_T^0) + 5\mu + \rho + h(1-u_C^0)\phi,\\
a_1 &= (\sigma + 2(\gamma + u_T^0) + 2\mu + h(1-u_C^0)\phi)(\sigma + (\gamma + u_T^0) + 2\mu + \rho)\\
&\quad + ((\gamma + u_T^0) + \mu)(2\sigma + 3(\gamma + u_T^0) + 4\mu + \rho + h(1-u_C^0)\phi),\\
&\quad - h(1-u_C^0)(\rho(\sigma+\mu) + (\gamma + u_T^0)\phi),\\
a_0 &= (\sigma + 2(\gamma + u_T^0) + 2\mu + h(1-u_C^0)\phi)((\gamma + u_T^0) + \mu)(\sigma + (\gamma + u_T^0) + 2\mu + \rho).
\end{aligned}
$$

Note that coefficients $a_i$ are positive for $i = 0, 1, 2$. Thus, $P_1(\lambda)$ is an strictly increasing function for $\lambda \in \mathbb{R}^+$. Furthermore, $P_1(0) > 0$ if and only if $\mathcal{R}_0 < 1$. In consequence, if $\mathcal{R}_0 < 1$, then the roots of the polynomial $P_1(\lambda)$ have negative real part. However, $P_1(\lambda)$ has a unique positive real root if $\mathcal{R}_0 > 1$. Therefore, the disease-free equilibrium is locally asymptotically stable if $\mathcal{R}_0 < 1$, and it is unstable if $\mathcal{R}_0 > 1$.

We have already established that for $\mathcal{R}_0 > 1$ the point $E_1 = (X_1^*, P_{01}^*, I^*)$ is the only endemic equilibrium for model (7). The characteristic polynomial for the Jacobian matrix evaluated at the endemic equilibrium $J(E_1)$ is $P_2(\lambda) = \lambda^3 + b_2\lambda^2 + b_1\lambda + b_0(\mathcal{R}_0 - 1)$ where

$$
b_2 = a_2 > 0, \quad b_1 = a_1 + h(1-u_C^0)\rho(\sigma+\mu)\left(\frac{2X_1^*}{X^*}\right) > 0, \quad b_0 = a_0 > 0.
$$

Seeing that $P_2(0) > 0$ if $\mathcal{R}_0 > 1$, and that $P_2(\lambda)$ is an increasing function of $\lambda$ when $\lambda > 0$, we obtain the local asymptotic stability of $E_1$. □

**To illustrate the behavior of the basic reproduction number (8) with respect to parameter perturbations, we show a contour plot for $\mathcal{R}_0$ in which we vary the values of $u_T^0$ and $u_C^0$ (Figure 2). The numerical values of the model parameters come from two case studies –chlamydia and gonorrhea– that are introduced later in Section 4. We observe in Figure 2 that increasing $u_C^0$ have stronger effects than increasing $u_T^0$ towards reducing $\mathcal{R}_0$. See Supplementary Material, S1 where bifurcation diagrams with respect to $u_T^0$ and $u_C^0$ are shown.**

## 3 Optimal Control Problem

The theoretical results from the previous section allow us to predict qualitative behavior of non-constant control strategies. In this section our objective is to model optimization of resources used by the control strategies. **In order to do that, we propose the following objective functional**

$$J(u_T, u_C) = \int_0^{t_f} I(t) + B_T u_T(t)^2 + B_C u_C(t)^2 dt \tag{13}$$

for a fixed final time $t_f$. **This objective functional has the aim of penalizing the presence of infected individuals, as well as the use of the control functions $u_T$ and $u_C$. The quadratic terms penalize high control levels in comparison with low values of the control functions (Gaff and Schaefer, 2009).** The weight parameters $B_T$ and $B_C$ in (13) balance the impact of the presence of infected people and the use of control. The value of $J$ depends exclusively on $I$, if $B = 0$; whereas, for large values of $B$, $J$ is heavily affected by the use of the control, for $B \in \{B_T, B_C\}$.

We define the set of admissible controls, $D(t_f)$, as the set of Lebesgue measurable functions $u_T$, $u_C$ that satisfy conditions (2) for all time $t \in [0, t_f]$. Thus, the general optimal control problem is:

$$\min_{u_T, u_C \in D(t_f)} J(u_T, u_C) \text{ subject to system (6).} \tag{14}$$

The existence of solutions to the optimal control problem may be proved through standard analytical results. In Appendix B, details are provided for solution existence to the simplified only-treatment model ($u_C \equiv 0$) but similar arguments are valid to the general optimal control problem (14).

Next, we obtain the so-called optimality system in order to find a numerical approximation of optimal control employing the Forward-Backward Sweep Method (see Lenhart and Workman, 2007, Chapter 4). This system corresponds to complementing the reduced model (6) with an adjoint dual system. The optimality system is completed by a characterization of the optimal control solutions in terms of the state and the adjoint variables.

### 3.1 Optimality System

**Theorem 2** *Consider the optimal control problem (14). Given an optimal control vector $(u_T^\dagger, u_C^\dagger)$ and its corresponding state variables $X_1^\dagger$, $P_{01}^\dagger$ and $I^\dagger$, there exist three adjoint variables $\lambda_1(t)$, $\lambda_2(t)$ and $\lambda_3(t)$ that satisfy the system:*

$$u_T^\dagger = \min\left\{M_T, \max\left\{0, \frac{X_1^\dagger\lambda_1 + \lambda_2(2P_{01}^\dagger - I^\dagger + X_1^\dagger) + \lambda_3 I^\dagger}{2B_T}\right\}\right\},$$

$$u_C^\dagger = \min\left\{M_C, \max\left\{0, \frac{\lambda_2\left(X_1^\dagger h\rho\left(\frac{X_1^\dagger}{X^*} - 1\right) - P_{01}^\dagger h\phi\right) + \lambda_3\left(X_1^\dagger h\rho\left(\frac{X_1^\dagger}{X^*} - 1\right) - P_{01}^\dagger h\phi\right)}{2B_C}\right\}\right\},$$

$$X_1^{\dagger\prime} = (\sigma + \mu)I^\dagger - (2\mu + \rho + \sigma)X_1^\dagger - (\gamma + u_T^\dagger)X_1^\dagger,$$

$$P_{01}^{\dagger\prime} = \rho\left(1 - h(1 - u_C^\dagger)\right)X_1^\dagger\left(1 - \frac{X_1^\dagger}{X^*}\right) - \left(\sigma + \phi h(1 - u_C^\dagger) + 2\mu\right)P_{01}^\dagger$$

$$
\begin{aligned}
&+(\gamma+u_T^\dagger)(I^\dagger - X_1^\dagger - 2P_{01}^\dagger),\\
I^{\dagger\prime} &= \rho h(1-u_C^\dagger)X_1^\dagger\left(1-\frac{X_1^\dagger}{X^*}\right)+\phi h(1-u_C^\dagger)P_{01}^\dagger-\mu I^\dagger-(\gamma+u_T^\dagger)I^\dagger,\\
\lambda_1' &= \left(2\mu+\rho+\sigma+\gamma+u_T^\dagger\right)\lambda_1+\left(\gamma+u_T^\dagger-\rho\left(1-h(1-u_C^\dagger)\right)\left(1-\frac{2X_1^\dagger}{X^*}\right)\right)\lambda_2\\
&\quad -h(1-u_C^\dagger)\rho\left(1-\frac{2X_1^\dagger}{X^*}\right)\lambda_3,\\
\lambda_2' &= \left(2\mu+\sigma+2(\gamma+u_T^\dagger)+h(1-u_C^\dagger)\phi\right)\lambda_2-h(1-u_C^\dagger)\phi\lambda_3,\\
\lambda_3' &= -(\mu+\sigma)\lambda_1-(\gamma+u_T^\dagger)\lambda_2+\left(\mu+\gamma+u_T^\dagger\right)\lambda_3-1,\\
&X_1^\dagger(0),\ P_{01}^\dagger(0),\ I^\dagger(0)\ \textit{given},\ \lambda_1(t_f)=\lambda_2(t_f)=\lambda(t_f)=0.
\end{aligned}
\tag{15}
$$

*Proof* Let $H$ be the Hamiltonian function defined by:

$$
\begin{aligned}
H =&\lambda_1\left((\sigma+\mu)I-(2\mu+\rho+\sigma)X_1-(\gamma+u_T)X_1\right)\\
&+\lambda_2\left(\rho(1-h)X_1\left(1-\frac{X_1}{X^*}\right)-(\sigma+\phi h+2\mu)P_{01}+(\gamma+u_T)(I-X_1-2P_{01})\right)\\
&+\lambda_3\left(\rho hX_1\left(1-\frac{X_1}{X^*}\right)+\phi hP_{01}-\mu I-(\gamma+u_T)I\right)+B_Tu_T^2+I.
\end{aligned}
$$

Using the Pontryagin's Maximum Principle (Pontryagin et al., 1965), we get that the following system is satisfied at the optimal control vector $(u_T^\dagger, u_C^\dagger)$:

$$
\begin{aligned}
&\lambda_1=-\frac{\partial H}{\partial X_1},\quad \lambda_2=-\frac{\partial H}{\partial P_{01}},\quad \lambda_3=-\frac{\partial H}{\partial I},\quad \lambda_i(t_f)=0\quad (i=1,2,3),\\
&\left.\frac{\partial H}{\partial u_T}\right|_{u_T=u_T^\dagger}=0,\quad \left.\frac{\partial H}{\partial u_C}\right|_{u_C=u_C^\dagger}=0,
\end{aligned}
$$

from which the system (15) is derived. □

Similar results may be obtained for $u_C \equiv 0$ (only-treatment control is employed) and for $u_T \equiv 0$ (only-condom promotion control is employed). The corresponding optimality systems for these two models can be found in Appendices C and D.

## 4 Numerical Results

In this section we explore model (6) numerically using trichomoniasis, gonorrhea, chlamydia and HPV as case studies. We retrieved from the literature **numerical estimates for some parameters** related to the transmission of these four infections. Parameter values are shown in Tables 3–4. We aim to model an adverse scenario in which a high level of infected population is prevalent. Thus, we consider $I(0) = 7\times10^5$ where half of this population comes from the total of susceptible-infected pairs ($P_{01}(0) = 3\times10^5$). We considered the final time to be $t_f = 20$ years as in Malik et al. (2016).

We analyze the dynamics model (6) for three different families of control functions. The first one is a permanent control program (constant control). The second one is a control program that increases efforts accordingly to higher infected population levels (feedback control). Finally, the third one is a control strategy that aims to minimize the overall cost (optimal control).

## 4.1 **Case Studies**

*Curable STIs: Trichomoniasis, gonorrhea, and chlamydia*

In Figures 3–5 the simulations related to the four STIs considered in this work can be found. The left-hand column plots show the corresponding constant, feedback and optimal controls for each of these STIs, and the right-hand plots show the resulting prevalence dynamics. The three curable STIs considered (trichomoniasis, gonorrhea, and chlamydia) are studied under the effect of both proposed control strategies: the treatment control $u_T$ and the condom promotion control $u_C$.

*Non-curable STI: HPV infection*

As mentioned in the introduction, HPV infection remains as a non-curable STI. Therefore, we only considered the effect of the condom promotion $u_C$ for this disease. At the bottom of Figure 4 we show HPV infection control via condom promotion control.

## 4.2 **Control Strategies**

*Constant*

In practice, a constant control function $u(t) = u^0$ for all time $t$ may not be appropriate. This is because it does not take into account important factors such as the evolution of the prevalence level. Nevertheless, it is useful to predict the global dynamics of model (1) gaining some insight into how other types of control strategies may perform. For the numerical simulations, we employed two constant values that will correspond to the maximum values attainable by the optimal and feedback controls. We considered $u_T^0 = M_T = 1.0$ years $^{-1}$ corresponding to the treatment control, and $u_C^0 = M_C = 0.75$ (dimensionless) for the condom promotion control.

On the left-hand side of Figures 3 and 4 the control functions for the different STIs are shown. In Figures 3 and 4, the constant control strategies allow us to predict the best hypothetical scenario where the maximum decrease of the prevalence level is attained.

*Feedback*

In a more realistic scenario, public health authorities may take decisions on how to control an STI based on the current prevalence at a certain time. In that case, a convenient control strategy is one that only depends on the burden of the infected

| Parameter | Value | Source |
|---|---|---|
| $X_1(0)$ | $1 \times 10^5$ | Assumed |
| $P_{01}(0)$ | $3 \times 10^5$ | Assumed |
| $I(0)$ | $7 \times 10^5$ | Assumed |
| $N$ | $1 \times 10^6$ | Assumed |
| $\rho$ | 5.0 | Heijne et al. (2011) |
| $\sigma$ | 2.0 | Heijne et al. (2011) |
| $\mu$ | 0.111 | Johnson et al. (2001) |
| $\nu$ | $1.111 \times 10^5$ | $N\mu = \nu$ |
| $\phi$ | 52.0 | Johnson et al. (2001) |

Table 3: Population and sexual behavior parameter values.

| Disease | $\gamma$ | $h$ | Source |
|---|---|---|---|
| Trichomoniasis | 0.727 | 0.115 | Johnson and Geffen (2016) |
| Gonorrhea | 1.538 | 0.348 | Johnson and Geffen (2016) |
| Chlamydia | 0.855 | 0.129 | Johnson and Geffen (2016) |
| HPV | 0.5 | 0.073 | Juckett and Hartman-Adams (2010) |

Table 4: Sexual transmitted infection parameter values.

population. These strategies use fewer control efforts when prevalence achieves acceptable levels, whereas it uses maximum efforts when such prevalence is above a critical level. We propose the control function

$$u(t) = \Phi\left(I(t)\right) = \frac{M}{1 + \exp\left\{-k[I(t) - I_{alert}]\right\}}, \tag{16}$$

for $t \in [0, t_f]$, where $I_{alert} > 0$ represents an alert level at which a maximum control reaction speed $k$ is reached, and $u \in \{u_T, u_C\}$ with respective $M \in \{M_T, M_C\}$. This is a standard sigmoid function that saturates at $M$. We incorporated this feedback control $u$ into model (1) following a previous work (Saldaña and Barradas, 2019). Here we employed the following parameters for the feedback function (16): $I_{alert} = 1 \times 10^5$ that corresponds to $10\%$ of the total population, and $k = 1 \times 10^{-4}$. Note that although is not always possible to obtain prevalence data, the World Health Organization periodically estimates the global and regional prevalence of some common sexually transmitted diseases including chlamydia, trichomoniasis and gonorrhea (WHO, 2012b; Newman et al., 2015). Therefore, it is realistic to consider feedback control based on $I(t)$.

In Figures 3 and 4 the feedback controls are also shown on the left-hand side. Note that in all cases the feedback controls begins at its highest possible value $M \in \{M_T, M_C\}$ and then drift to a constant lower value. The lower value is positive since the objective of the feedback control is to act if the prevalence is above the alert level.

*Optimal*

The optimal control solutions were obtained by solving the optimization problems mentioned in Section 3. We obtained solution approximations to the optimality systems by using the Forward-Backward Sweep Method (see Lenhart and Workman, 2007, Chapter 4). For the numerical simulations we used the following weight parameters: $B_T = B_C = 5 \times 10^5$. These values were chosen as a way to compensate for the magnitude of the prevalence level.

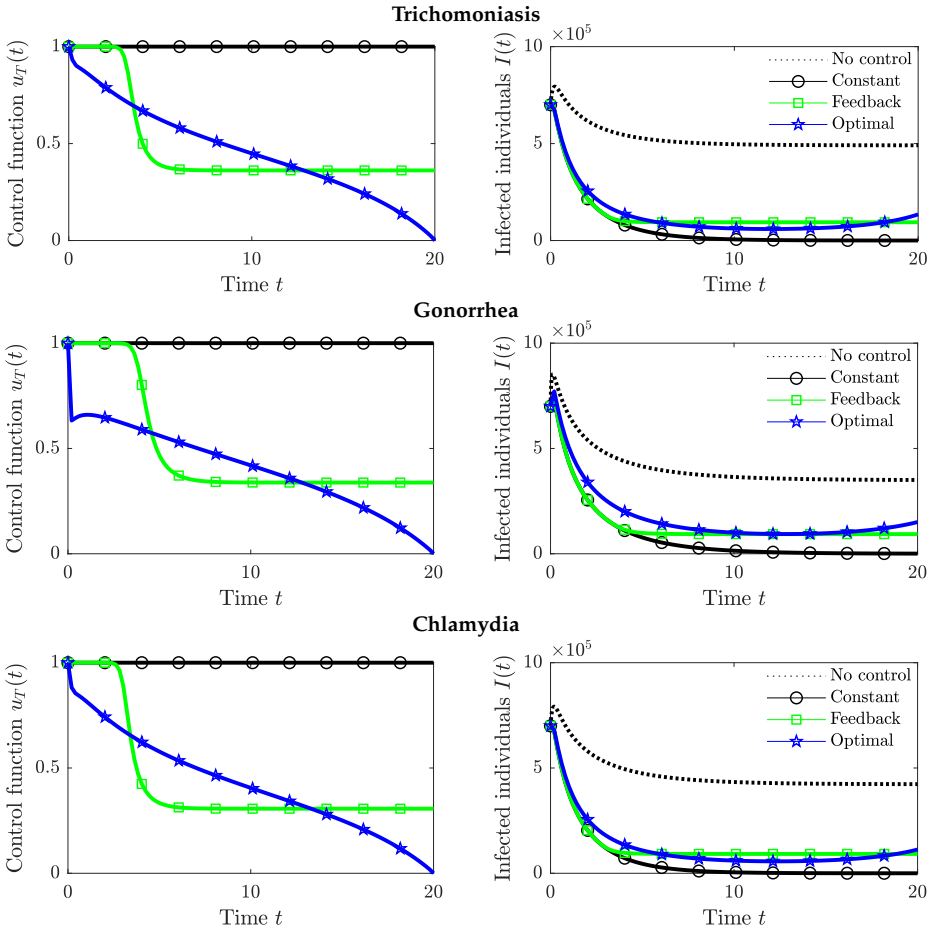


Fig. 3: Only-treatment control strategy ($u_C \equiv 0$) applied to the three curable STIs. Three types of control are considered: constant, feedback, and optimal controls. The final time is $t_f = 20$ years.

In Figures 3– 5 the optimal controls are also present. Note that for the case of the only-treatment model (Figure 3) the optimal control solutions behave in a linear-like manner from the highest value $M_T$ until they reach zero. On the other hand, in the only-condom promotion model (Figure 4) the optimal control solutions have a defined period of time where they have the highest value $M_C$. Then, there is an intermediate period of time where they drop quickly, and finally, there is a period of linear-like behavior. In Figure 5 we tested the simultaneous optimal control strategies and found out that the treatment control has defined convex behavior. In terms of prevalence control, the mixed strategies model (Figure 5) have a better performance than the other two models (Figures 3 and 4).

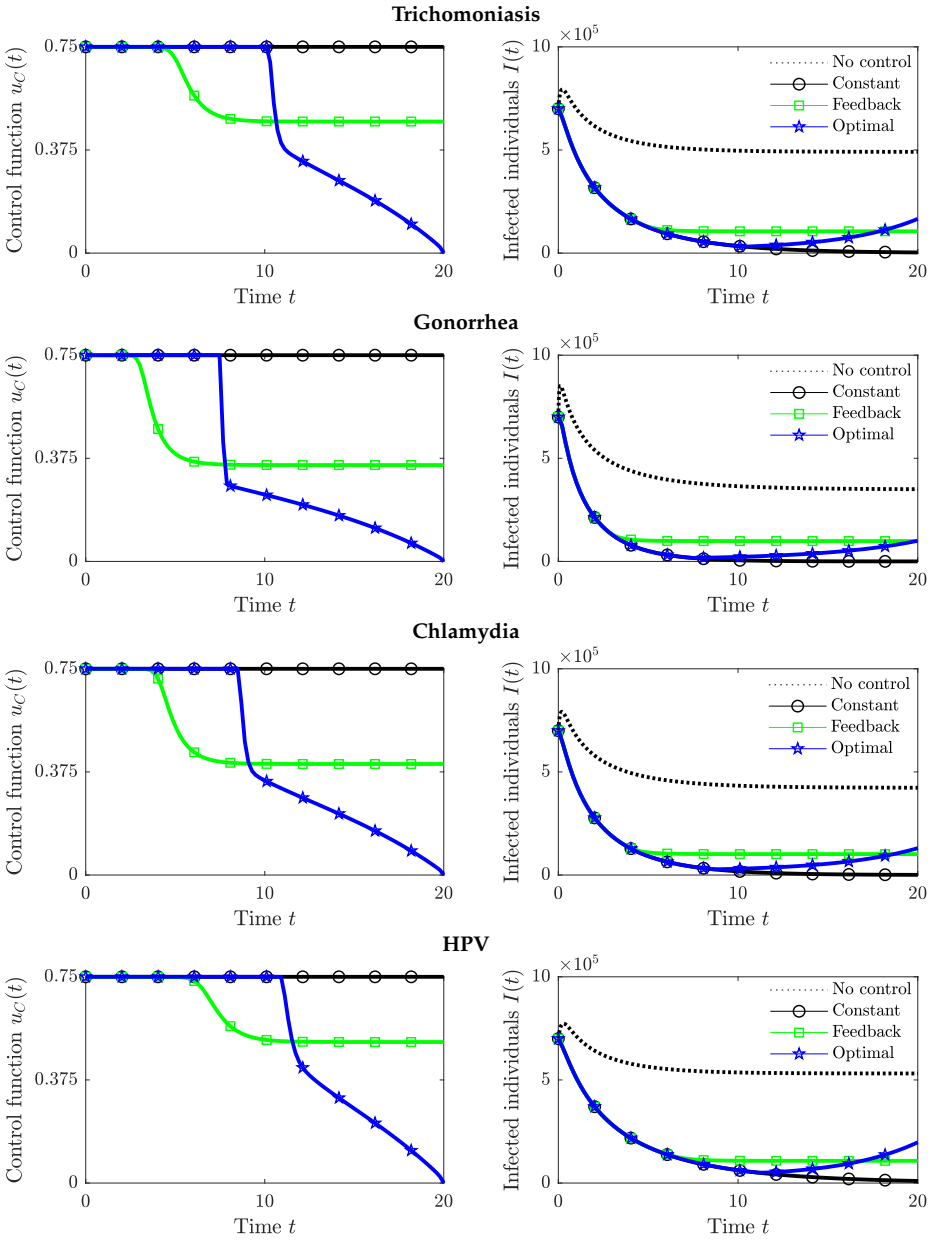


Fig. 4: Only-condom promotion control strategy ($u_T \equiv 0$) applied to the four STIs. Three types of control are considered: constant, feedback, and optimal controls.

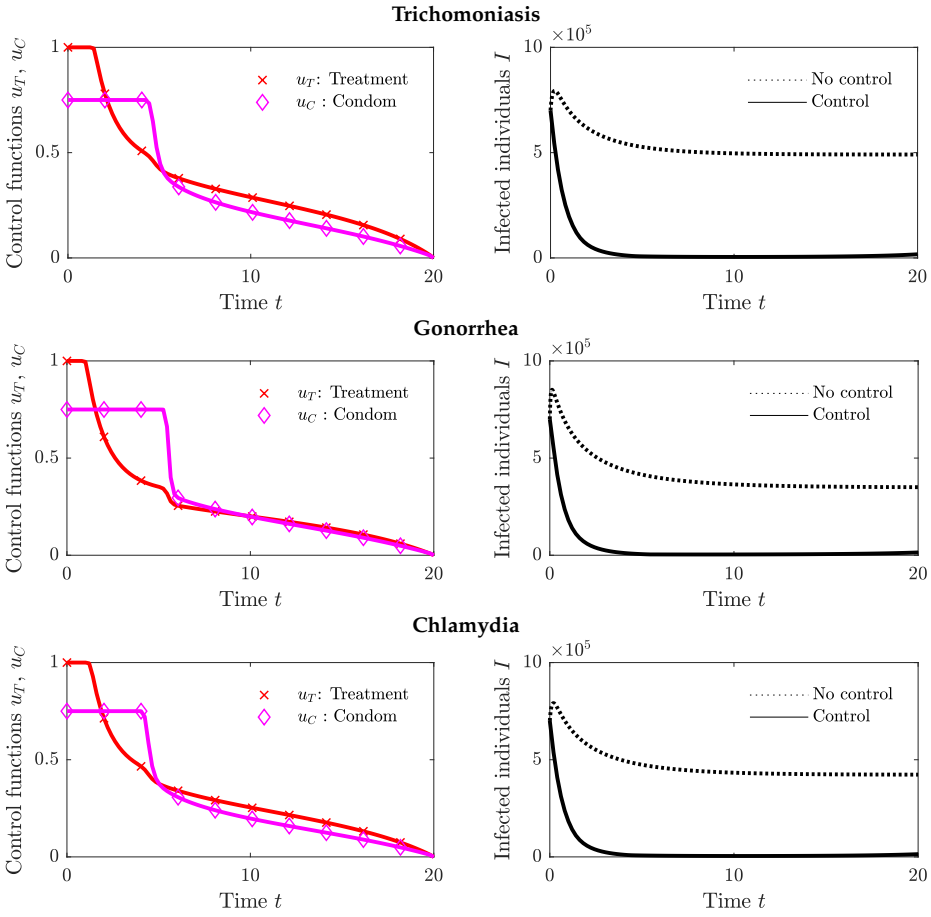


Fig. 5: Treatment and condom promotion optimal control strategies applied simultaneously to the three curable STIs.

### 4.3 **Cost-Effectiveness Analysis**

**To compare different types of control structures (constant, feedback, and optimal controls), we need to define two quantities of interest: the cost of a strategy, and the number of averted individuals by a strategy. Here, we use a cost functional given by:**

$$Cost(u_T, u_C) = \int_0^{t_f} B_T u_T(t)^2 + B_C u_C(t)^2 + A_1 I(t) u_T(t) + A_2 \phi P_{01}(t) u_C(t) dt, \tag{17}$$

**and also an averted functional given by:**

$$Averted(u_T, u_C) = \int_0^{t_f} I_0(t) - I_\dagger(t) dt, \tag{18}$$

**where $I_0$ is the prevalence level under no control, whereas $I_\dagger$ is the prevalence level under control functions $u_T$ and $u_C$.**

**It is noteworthy to mention that many works in the literature refer to objective functional for finding optimal control solutions also as a cost functional, see for instance Okosun et al. (2011); Rodrigues et al. (2014a); Agusto and ELmojtaba (2017) and Nandi et al. (2018). There are few works that employ different objective and cost functionals; for instance, in Sepulveda and Vasilieva (2016); Berhe et al. (2018) and Tilahun et al. (2018), the cost functional is regarded as the objective functional without the terms with no control variables, which only considers inherent control costs. Here, we also make a difference between objective functionals for optimal controls and cost functionals for general strategies. In an attempt to make a fair comparison between optimal control and non-optimal control strategies, we pay attention to the subsequent economic cost that a strategy generates based on the number of individuals affected; similar approaches may be found in Rodrigues et al. (2014b); Otieno et al. (2016) and Momoh and Fügenschuh (2018). Therefore, we want to emphasize that the optimal control solutions that we find satisfy an objective functional (13) that penalizes high levels of control, whereas a cost functional (17) is proposed to incorporate economic cost of applying the control strategies in their respective population compartments. Moreover, in the cost functional (17), the terms whose coefficients are $A_1$ and $A_2$ –$A_1 I u_T$ and $A_2 \phi P_{01} u_C$– measure the frequency of control application, that is, the costs of treating $I u_T$ individuals per year and of condom use among $P_{01} u_C$ susceptible-infected pairs per year, respectively.**

We evaluated the cost-effectiveness of the control strategies for each STI using the increased cost-effectivity ratio (ICER) (Okosun et al., 2011; Cape et al., 2013):

$$ICER(f) = \frac{Cost(f)}{Averted(f)}, \quad ICER(f,g) = \frac{Cost(f) - Cost(g)}{Averted(f) - Averted(g)}, \tag{19}$$

where $f$ and $g$ are assumed to be strategies conformed by pairs of functions $u_T$ and $u_C$, **while** $Cost$ **and** $Averted$ **are the functionals defined by** (17) **and** (18)**, respectively. Observe from equation** (19) **that for individual strategies, it is more desirable to have** $ICER(f)$ **small: low cost and high averted levels. For two strategies,** $ICER(f,g)$ **compares the cost-effectivity of the second strategy** $g$ **with respect the first strategy** $f$**.** The standard method to determine the most cost-effective strategy is as follows:

1. The strategies to be compared are sorted from lowest to highest costs.
2. The ICER for the first strategy, and the ICER between the first and second strategies are computed using (19).
3. If the ICER between the two strategies is negative, eliminate the second strategy: the second strategy has higher cost and lower averted levels.
4. Assume that the ICER between the two strategies is positive.
   - If the first strategy has a lower ICER than the ICER between the two strategies, then eliminate the second strategy: the second strategy has higher averted levels but it is proportionally lower than the first strategy.
   - Otherwise, eliminate the first strategy: the second strategy has higher averted levels proportionally with respect to the first strategy.
5. Repeat the process until only one strategy remains in the list.

**trichomoniasis**

A1=0 A2=0

| | cost | averted | ICER |
|---|---|---|---|
| OT optimal | 2.64E+006 | 5.05E+007 | 0.05 |
| OT feedback | 2.85E+006 | 4.99E+007 | -0.31 |
| OC optimal | 3.23E+006 | 4.97E+007 | |
| OC feedback | 3.25E+006 | 4.64E+007 | |
| mixed | 3.58E+006 | 6.21E+007 | |
| OC constant | 5.63E+006 | 5.35E+007 | |
| OT constant | 1.00E+007 | 5.83E+007 | |
| ↓ | | | |
| OT optimal | 2.64E+006 | 5.05E+007 | 0.05 |
| OC optimal | 3.23E+006 | 4.97E+007 | -0.73 |
| OC feedback | 3.25E+006 | 4.64E+007 | |
| mixed | 3.58E+006 | 6.21E+007 | |
| OC constant | 5.63E+006 | 5.35E+007 | |
| OT constant | 1.00E+007 | 5.83E+007 | |
| ↓ | | | |
| OT optimal | 2.64E+006 | 5.05E+007 | 0.05 |
| OC feedback | 3.25E+006 | 4.64E+007 | -0.15 |
| mixed | 3.58E+006 | 6.21E+007 | |
| OC constant | 5.63E+006 | 5.35E+007 | |
| OT constant | 1.00E+007 | 5.83E+007 | |

| | cost | averted | ICER |
|---|---|---|---|
| ↓ | | | |
| OT optimal | 2.64E+006 | 5.05E+007 | 0.05 |
| mixed | 3.58E+006 | 6.21E+007 | 0.08 |
| OC constant | 5.63E+006 | 5.35E+007 | |
| OT constant | 1.00E+007 | 5.83E+007 | |
| ↓ | | | |
| OT optimal | 2.64E+006 | 5.05E+007 | 0.05 |
| OC constant | 5.63E+006 | 5.35E+007 | 1.00 |
| OT constant | 1.00E+007 | 5.83E+007 | |
| ↓ | | | |
| OT optimal | 2.64E+006 | 5.05E+007 | 0.05 |
| OT constant | 1.00E+007 | 5.83E+007 | 0.95 |
| ↓ | | | |
| OT optimal | 2.64E+006 | 5.05E+007 | 0.05 |

Table 5: **ICER-based cost-effectiveness determination process for trichomoniasis. 'OT': only-treatment, 'OC': only-condom promotion, 'mixed': mixed strategy optimal control.**

**trichomoniasis**

| | | | |
|---|---|---|---|
| **A1=0, A2=0** | | | |
| **OT optimal** | 2.64E+006 | 5.05E+007 | 0.0523 |
| **A1=10, A2=1** | | | |
| **mixed** | 1.82E+007 | 6.21E+007 | 0.2929 |
| **A1=100, A2=10** | | | |
| **OT constant** | 1.40E+008 | 5.83E+007 | 2.3990 |
| | **cost** | **averted** | **ICER** |

**chlamydia**

| | | | |
|---|---|---|---|
| **A1=0, A2=0** | | | |
| **OT optimal** | 2.26E+006 | 4.38E+007 | 0.0516 |
| **A1=10, A2=1** | | | |
| **mixed** | 1.69E+007 | 5.51E+007 | 0.3072 |
| **A1=100, A2=10** | | | |
| **mixed** | 1.40E+008 | 5.51E+007 | 2.5455 |
| | **cost** | **averted** | **ICER** |

**gonorrhea**

| | | | |
|---|---|---|---|
| **A1=0, A2=0** | | | |
| **OC optimal** | 2.35E+006 | 4.04E+007 | 0.0581 |
| **A1=10, A2=1** | | | |
| **mixed** | 1.47E+007 | 4.75E+007 | 0.3090 |
| **A1=100, A2=10** | | | |
| **mixed** | 1.19E+008 | 4.75E+007 | 2.4999 |
| | **cost** | **averted** | **ICER** |

**HPV**

| | | | |
|---|---|---|---|
| **A2=0** | | | |
| **OC optimal** | 3.50E+006 | 5.03E+007 | 0.0695 |
| **A2=1** | | | |
| **OC optimal** | 3.80E+007 | 5.03E+007 | 0.7549 |
| **A2=10** | | | |
| **OC constant** | 3.64E+008 | 5.43E+007 | 6.6894 |
| | **cost** | **averted** | **ICER** |

Table 6: **ICER-based cost-effectiveness analysis. For each STI and for each pair of parameters $(A_1, A_2)$ with values $(0, 0)$, $(10, 1)$ and $(100, 10)$, we show the corresponding most cost-effective strategy. 'OT': only-treatment, 'OC': only-condom promotion, 'mixed': mixed strategy optimal control.**

**As an illustrative example, in Table 5, we gathered the results of the ICER-based cost-effectiveness analysis for trichomoniasis. The same process was performed to the other three STIs, and computations may be found in Supplementary Material, S2. In Table 6, we show the most cost-effective strategies for each STI while varying the weight parameters $(A_1, A_2)$.** We observe in Table 6 that the cost-effectiveness varied among the four STIs considered. **When the values of $A_1$ and $A_2$ were low, optimal controls had the highest cost-effectiveness. For the cases of trichomoniasis and chlamydia, only-treatment optimal control and mixed strategy optimal control had the highest cost-effectivenesses. For the case of gonorrhea, only-condom optimal control and mixed strategy optimal control had the highest cost-effectivenesses. On the other hand, when $A_1$ and $A_2$ were high, constant controls $u_T^0$ and $u_C^0$ showed the highest cost-effectivenesses for trichomoniasis and HPV infection, while mixed strategy optimal control displayed the highest cost-effectivenesses for chlamydia and gonorrhea.**

## 5 Discussions and Conclusions

In this work, we proposed an extension of a pair model (Kretzschmar and Dietz, 1998; Saldaña and Barradas, 2019) to explore STI control under public health strategies. Three different control structures were studied: constant control, feedback control, and optimal control. Constant controls are useful to predict the prevalence evolution through theoretical results, such as the computation of the basic reproduction number $\mathcal{R}_0$. Feedback controls reflect public health strategies that depend on the prevalence levels. Finally, optimal controls are designed to minimize the prevalence levels and the use of the control strategy through time. Here, we characterized optimal solutions using Pontryagin's Maximum Principle and obtained numerical approximations via the Forward-Backward Sweep Method. For the numerical simulations, **and because of being four of the most common and problematic STIs,** we used parameters related to trichomoniasis, gonorrhea, chlamydia and HPV infections. We employed the ICER methodology as a way to contrast the cost-effectiveness of the different strategies considered in this work. We emphasize that our purpose here was to investigate the control of STIs in the form of treatment and condom promotion for pair models with monogamous partnerships.

**Cost-effectiveness analysis compares the costs and health outcomes of alternative strategies. The health gains can be measured using some pertinent health outcome, such as the total number of infections averted. On the other hand, the cost might include direct healthcare costs (e.g. pharmaceutical costs, hospitalization, etc.) and non-healthcare costs (e.g. administrative costs, patient time cost, etc.). The measurement and the evaluation of these resources are not straightforward. Therefore, defining mathematical criteria to compare different types of control is a challenging task. Here, we proposed the cost functional (17) and, considering the lack of additional empirical data, analyzed different scenarios for its weight factors. Our results point out that, when only inherent control cost is considered, optimal control solutions are the most cost-effective strategies. However, when the cost of applying such controls on the population is considered, constant controls may arise as the most cost-effective strategies because they decrease considerably the number of infected individuals.**

As shown in this work, the impact of health public strategies on controlling STI prevalence may be predicted, and improved based on different criteria such as the practicality of implementation (feedback control) or the minimization of an objective functional (optimal control). This work is the first attempt to use optimal control to search for the most efficient way to develop public health strategies for STIs considering the pair formation process **, and also the first one to shown quantitatively the effects of varying cost functional parameters on the cost-effectiveness analysis.**

As future work, concurrency (overlapping of partnerships), sexual risk groups, or studying the relationship between the infectious disease and the pair formation process can be included. HPV infection remains as a non-curable STI, but it could be interesting to include vaccination in the pair model. Also, it could be appropriate to consider a different way to measure the strategies cost.

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**Code availability** The Matlab and Python codes used to run the simulations in this work may be found in https://github.com/arielcam27/STIs_pairModel_control

**Supplementary material**

## Appendix A. Positively invariant sets

Consider the pair model (1):

$$\begin{aligned}
X_0' &= \nu + (\sigma+\mu)(2P_{00}+P_{01}) - (\mu+\rho)X_0 + (\gamma+u_T)X_1,\\
X_1' &= (\sigma+\mu)(2P_{11}+P_{01}) - (\mu+\rho)X_1 - (\gamma+u_T)X_1,\\
P_{00}' &= \frac{1}{2}\rho\frac{X_0^2}{X} - (\sigma+2\mu)P_{00} + (\gamma+u_T)P_{01},\\
P_{01}' &= \rho\left(1-h(1-u_C)\right)\frac{X_0X_1}{X} - \left(\sigma+\phi h(1-u_C)+2\mu\right)P_{01}\\
&\quad - (\gamma+u_T)P_{01} + 2(\gamma+u_T)P_{11},\\
P_{11}' &= \frac{1}{2}\rho\frac{X_1^2}{X} + \rho h(1-u_C)\frac{X_0X_1}{X} + \phi h(1-u_C)P_{01} - (\sigma+2\mu)P_{11}\\
&\quad - 2(\gamma+u_T)P_{11}.
\end{aligned}$$

By adding the equations, note that the total population size $N = X_0 + X_1 + 2(P_{00}+P_{01}+P_{11})$ satisfies $N' = -\mu N + \nu$, and thus

$$N(t) \leq N(0)e^{-\mu t} + \frac{\nu}{\mu}\left(1-e^{-\mu t}\right). \tag{20}$$

If we consider the set

$$\Omega = \{(X_0, X_1, P_{00}, P_{01}, P_{11}) \in \mathbb{R}^5_+ \mid X_0 + X_1 + 2(P_{00}+P_{01}+P_{11}) \leq \nu/\mu\},$$

then, from (20), we get that if $N(0) \in \Omega$ then $N(t) \in \Omega$ for all $t > 0$. We say that $\Omega$ is a positively invariant set under (1).

## Appendix B. Existence of solutions to the optimal control problem

To prove existence of solutions for the only-treatment optimal control problem, we use Theorem 4.1 and Corollary 4.1 from Fleming and Rishel (1975, Chapter III, Section 4). Such result requires the following:

1. The set of solutions of the system (6) (called admissible pairs) is not empty.
2. The set of admissible controls, i.e. functions $u$ satisfying the control conditions (2), is closed and convex.
3. The right-hand side of the system (6) is continuous, bounded from above by a sum of the states and the control, and it can be written as a linear function of the control.
4. Finally, the integrand of (13) is convex in the control, and it is bounded below by $c_1|u|^g - c_2$ with $c_1 > 0$ and $g > 1$.

We can see that $u_T \equiv 0$ is an admissible solution, so the set of admissible pairs is not empty. Since $u_T \in D(t_f)$ (see Section 3 to recall the definition of the set $D$) then the set of admissible controls is closed and convex. Note that the supersolutions of (6), which we are going to denote by $\hat{X}_1$, $\hat{P}_{01}$ and $\hat{I}$, satisfy the following ODE system:

$$\begin{aligned} \widehat{X_1}' &= (\sigma+\mu)\widehat{I}, \\ \widehat{P_{01}}' &= \rho\widehat{X_1} + M\widehat{I}, \\ \widehat{I}' &= \rho\widehat{X_1} + \phi\widehat{P_{01}}, \end{aligned} \tag{21}$$

which is a linear system. Thus, the solutions of system (21) are uniformly bounded for any finite time interval $[0, t_f]$. Let us define

$$f(X_1, P_{01}, I) = \begin{pmatrix} (\sigma+\mu)I - (2\mu+\rho+\sigma)X_1 - (\gamma+u_T)X_1 \\ \rho(1-h)X_1\left(1-\dfrac{X_1}{X^*}\right) - (\sigma+\phi h+2\mu)P_{01} + (\gamma+u_T)(I-X_1-2P_{01}) \\ \rho h X_1\left(1-\dfrac{X_1}{X^*}\right) + \phi h P_{01} - \mu I - (\gamma+u_T)I \end{pmatrix}.$$

It is straightforward to note that there exists a function $g(X_1, P_{01}, I)$ such that

$$f(X_1, P_{01}, I) = g(X_1, P_{01}, I) + u_T \begin{pmatrix} -X_1 \\ I - X_1 - 2P_{01} \\ -I \end{pmatrix}$$

and so the right-hand side of (6) can be written as a linear function of $u_T$. Also, we already have satisfied the continuity of the model. Finally, using the supersolutions system (21) we note that

$$\begin{aligned} \|f(X_1, P_{01}, I)\| &\leq \left\| \begin{pmatrix} 0 & 0 & \sigma+\mu \\ \rho & 0 & M \\ \rho & \phi & P_{01} \end{pmatrix} \begin{pmatrix} X_1 \\ P_{01} \\ I \end{pmatrix} + u_T \begin{pmatrix} -X_1 \\ I - X_1 - 2P_{01} \\ -I \end{pmatrix} \right\| \\ &\leq C\left(\|(X_1, P_{01}, I)\| + \|u_T\|\right) \end{aligned}$$

where $C$ is a constant that depends on the model parameters. Thus, $f$ is bounded from above by a sum of the states and the control. The integrand is $h(I, u_T) = I + Bu_T^2$ and so $h(I, u) = I + Bu_T^2 \geq Bu_T^2$, so choosing $c_2 = 0$, $c_1 = B > 0$ and $g = 2$ we have the following:

**Theorem 3** *There exist an optimal control $u_T$ and state variables $(X_1, P_{01}, I)$ that minimize the objective functional (13) and satisfy the system (6).* □

## Appendix C. Optimality system for the only-treatment model

The corresponding optimality system for the only-treatment control strategy ($u_C \equiv 0$) is given by:

$$u_T = \min\left\{M_T, \max\left\{0, \frac{X_1\lambda_1 + \lambda_2(2P_{01} - I + X_1) + \lambda_3 I}{2B_T}\right\}\right\},$$

$$
\begin{aligned}
X_1' &= (\sigma+\mu)I - (2\mu+\rho+\sigma)X_1 - (\gamma+u_T)X_1,\\
P_{01}' &= \rho(1-h)X_1\left(1-\frac{X_1}{X^*}\right) - (\sigma+\phi h+2\mu)P_{01} + (\gamma+u_T)(I-X_1-2P_{01}),\\
I' &= \rho h X_1\left(1-\frac{X_1}{X^*}\right) + \phi h P_{01} - \mu I - (\gamma+u_T)I,\\
\lambda_1' &= (2\mu+\rho+\sigma+\gamma+u_T)\,\lambda_1 + \left(\gamma+u_T-\rho(1-h)\left(1-\frac{2X_1}{X^*}\right)\right)\lambda_2 - h\rho\left(1-\frac{2X_1}{X^*}\right)\lambda_3,\\
\lambda_2' &= (2\mu+\sigma+2(\gamma+u_T)+h\phi)\,\lambda_2 - h\phi\lambda_3,\\
\lambda_3' &= -(\mu+\sigma)\,\lambda_1 - (\gamma+u_T)\lambda_2 + (\mu+\gamma+u_T)\,\lambda_3 - 1,\\
&X_1(0),\ P_{01}(0),\ I(0) \text{ given},\ \lambda_1(t_f)=\lambda_2(t_f)=\lambda(t_f)=0.
\end{aligned}
$$

## Appendix D. Optimality system for the only-condom promotion model

The corresponding optimality system for the only-condom promotion control strategy ($u_T \equiv 0$) is given by:

$$
\begin{aligned}
u_C &= \min\left\{M_C, \max\left\{0, \frac{\lambda_2\left(X_1 h\rho\left(\frac{X_1}{X^*}-1\right)-P_{01}h\phi\right)+\lambda_3\left(X_1 h\rho\left(\frac{X_1}{X^*}-1\right)-P_{01}h\phi\right)}{2B_C}\right\}\right\},\\
X_1' &= (\sigma+\mu)I - (2\mu+\rho+\sigma)X_1 - \gamma X_1,\\
P_{01}' &= \rho\,(1-h(1-u_C))\,X_1\left(1-\frac{X_1}{X^*}\right) - (\sigma+\phi h(1-u_C)+2\mu)\,P_{01} + \gamma(I-X_1-2P_{01}),\\
I' &= \rho h(1-u_C)X_1\left(1-\frac{X_1}{X^*}\right) + \phi h(1-u_C)P_{01} - \mu I - \gamma I,\\
\lambda_1' &= (2\mu+\rho+\sigma+\gamma)\,\lambda_1 + \left(\gamma-\rho\,(1-h(1-u_C))\left(1-\frac{2X_1}{X^*}\right)\right)\lambda_2\\
&\quad - h(1-u_C)\rho\left(1-\frac{2X_1}{X^*}\right)\lambda_3,\\
\lambda_2' &= (2\mu+\sigma+2\gamma+h(1-u_C)\phi)\,\lambda_2 - h(1-u_C)\phi\lambda_3,\\
\lambda_3' &= -(\mu+\sigma)\,\lambda_1 - \gamma\lambda_2 + (\mu+\gamma)\,\lambda_3 - 1,\\
&X_1(0),\ P_{01}(0),\ I(0) \text{ given},\ \lambda_1(t_f)=\lambda_2(t_f)=\lambda(t_f)=0.
\end{aligned}
$$

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