Optimal vaccine allocation for the control of sexually transmitted infections

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Abstract

The burden of sexually transmitted infections (STIs) poses a challenge due to its large negative impact on sexual and reproductive health worldwide. Besides simple prevention measures and available treatment efforts, prophylactic vaccine is a powerful tool for controlling some viral STIs and their associated diseases. Here, we investigate how prophylactic vaccines are best distributed to prevent and control STIs. We consider sex-specific differences in susceptibility to infection, as well as disease severity outcomes. Different vaccination strategies are compared assuming distinct budged constraints that mimic a scarce vaccine stockpile. Vaccination strategies are obtained as solutions to an optimal control problem subject to a two-sex Kermack-McKendrick-type model, where the control variables are the daily vaccination rates for females and males. One important aspect of our approach relies on conceptualizing a limited but specific vaccine stockpile via an isoperimetric constrain. We solve the optimal control problem via the Pontryagin Maximum Principle and obtain a numerical approximation for the solution using a modified version of the forward-backward sweep method that handles the isoperimetric budget constraint in our formulation. The results suggest that for a limited vaccine supply (**20% − 30%** vaccination coverage), one-sex vaccination, prioritizing females, appears

to be more beneficial than the inclusion of both sexes into the vaccination program. Whereas, if the vaccine supply is relatively large (enough to reach at least **40%** coverage), vaccinating both sexes, with a slightly higher rate for females, is optimal and provides an effective and faster approach to reducing the prevalence of the infection.

Keywords: Epidemic modeling, Optimal control, Vaccine Allocation, Sexually transmitted infections

MSC Classification: 92B05 , 49N90 , 34A34

1 Introduction

According to global estimates of the World Health Organization (WHO), the burden of sexually transmitted infections (STIs) remains high, counting over 350 million new infections annually with one of the four most common STIs – chlamydia, gonorrhea, syphilis, and trichomoniasis World Health Organization (2021). Although the majority of these infections can be cured, when not treated, STIs might lead to serious health consequences. In 2020, the human papillomavirus (HPV) caused over 600,000 new cases of cervical cancer and 342,000 deaths Sung et al (2021). Mother-to-child transmission of syphilis, or congenital syphilis, leads to over 350,000 adverse birth outcomes such as, e.g. early fetal and neonatal deaths, stillbirths, and preterm or low-birth-weight babies Korenromp et al (2019). Negative effects associated with untreated gonorrhea and chlamydia infections include reproductive tract morbidities, such as tubal factor infertility and pelvic inflammatory diseases among women Tsevat et al (2017). Gonorrhea, syphilis, or genital herpes simplex virus infection (HSV) are associated with an increased risk of acquiring or transmitting HIV Unemo et al (2017). Moreover, a recent observational trend study showed that the absolute incidence of STIs cases increased in the last 30 years, especially in sub-Saharan Africa and Latin America Zheng et al (2022) countries. In view of this, more attention should be given to the prevention and control of STIs, particularly in low- and middle-income countries, evaluating the benefits of implementing different public health control strategies.

The spread of STIs can be significantly reduced by a number of non-pharmaceutical interventions including sex abstinence, reduction in the number of sex partners, mutually monogamous relationships, and correct and consistent use of latex condoms Workowski and Bolan (2015). Effective treatment is available for bacterial and parasitic STIs. For example, gonorrhea, syphilis, chlamydia, and trichomoniasis can be treated with antibiotics, often in a single dose World Health Organization (2021); Workowski and Bolan (2015). Viral STIs including HIV, genital HSV, viral hepatitis B, and HPV have limited treatment options, but disease symptoms can be weakened or controlled with systematic treatment World Health Organization (2021); Workowski and

Bolan (2015). Antiviral drugs typically reduce the viral load limiting clinical symptoms, though virus eradication is difficult World Health Organization (2021); Workowski and Bolan (2015). The spread of STIs can also be limited via vaccination, which is the main tool for primary prevention of disease, and one of the most cost-effective public health measures. Therefore, the development of vaccines against STIs is essential to reduce the vast number of infections globally, and their adverse health outcomes Gottlieb et al (2016). Currently, there are vaccines for viral STIs that have been proven to be safe and effective, including vaccines against HPV and hepatitis B virus Gottlieb et al (2016). Major efforts continue in the development of vaccines against other STIs e.g. herpes and HIV, with several vaccine candidates in early clinical development World Health Organization (2021). Nevertheless, as the COVID-19 pandemic has shown, even after successful vaccine development, vaccines usually come on a limited budget and the available stockpile is rarely enough to guarantee the immunization of the entire population Yamey et al (2022). Generally, in addition to non-pharmaceutical interventions, public health authorities rely on a fixed amount of vaccines to control an outbreak, and therefore, optimizing the allocation of scarce vaccines becomes an important problem.

For an effective vaccination program, it is extremely important to identify subgroups within the general population that should be prioritized to be vaccinated Hansen and Day (2011). In the context of STIs, the key allocation problem is to investigate how to effectively distribute a limited vaccine stockpile among individuals, females and males, to minimize the prevalence of the infection in a population Bogaards et al (2015); Heffernan et al (2014); Saldaña et al (2019). Strategic mathematical modeling has already been directed to study resource allocation problems using different approaches such as mixed-integer linear programming models Saif and Elhedhli (2016); Tavana et al (2021), feedback control Camacho et al (2019), analytical insights from compartmental models Bogaards et al (2011); Duijzer et al (2018); Heffernan et al (2014); Gao et al (2021); Vo et al (2021), and optimal control Estadilla et al (2021); Malik et al (2016); Saldaña et al (2019). Here, we focus on optimizing time-dependent control interventions in an epidemiological model, using the optimal control theory (OCT) as a methodology for designing effective vaccination strategies. The OCT has been proven to be a powerful tool in the development and evaluation of intervention strategies to cope with the burden of infectious diseases Bussell et al (2019). For example, several studies have used Kermack-McKendrick-type models coupled with the optimal control theory to devise vaccine prioritization for specific diseases such as influenza Matrajt et al (2013); Shim (2013), dengue Maier et al (2017); Rodrigues et al (2014), and COVID-19 Estadilla et al (2021); Libotte et al (2020); Saldaña and Velasco-Hernández (2021). Nevertheless, to the best of the authors' knowledge, the number of studies investigating vaccine allocation via optimal control theory for STIs is relatively low Brown and White (2011); Camacho et al (2019); Malik et al (2016); Saldaña et al (2019).

In this work, we contribute to the vaccine allocation literature investigating how prophylactic vaccines are best distributed in a population. Assuming sex-specific differences in susceptibility and disease outcomes, the main focus of our study is to investigate under which conditions the inclusion of both sexes into vaccination programs adds to the population-level impact of one-sex-only interventions. Theoretically, high vaccination coverage for one sex might be enough to reach herd immunity and eradicate an STI in a heterosexual population Bogaards et al (2011). Yet, some complications can arise depending on many factors such as (i) the male-to-female sexual infectivity rate is generally higher than that of female-to-male Low et al (2006); Wong et al (2004) (ii) the health risks associated with the infection are considerably higher for females e.g. pelvic inflamatory disease, chronic pelvic pain, ectopic pregnancy, infertility and cervical cancers Low et al (2006); Wong et al (2004). Further, in some cases, there can be a group who is reluctant towards the vaccination; thus, a high vaccination coverage can be difficult to achieve even when targeting one sex-specific group Saldaña et al (2019). Our approach to addressing these issues relies on an optimal control problem, where the cumulative level of infected individuals is minimized under a limited vaccine stockpile and subject to a two-sex epidemic model. One of the main novelties of our approach relies upon modeling the limited vaccine supply using an isoperimetric constrain Kamien and Schwartz (2012).

The rest of this paper is organized as follows. In Section 2, we propose a two-sex Kermack-McKendrick-type model to describe the spread of an STI in a heterosexual population. The model considers prophylactic vaccine strategies that might include both genders. The analysis of equilibria together with the basic and control reproduction numbers are also investigated in Section 2. In Section 3, we formulate an optimal control problem (OCP) to seek optimal sex-specific vaccination programs aiming to minimize the total number of infections in the population. In Section 4, we provide a numerical approximation to the solution of OCP for several realistic vaccine scenarios with budget constraints that mimic a scarce vaccine stockpile insufficient to immunize the total population. We conclude by discussing the implications of our findings for gender-specific vaccination programs against STIs.

2 Methods

2.1 Model formulation

The model stratifies the total population at time t, denoted $N(t)$ according to gender, so $N(t) = N_f(t) + N_m(t)$, where N_f and N_m represent the number of sexually active females and males, respectively. Both populations N_k $(k = f, m)$ are subdivided into mutually exclusive compartments according to infection status as unvaccinated susceptible (S_k), vaccinated susceptible (V_k), and infectious individuals (I_k). Hence, $N_k(t) = S_k(t) + V_k(t) + I_k(t)$, $(k = f, m)$. The transmission dynamics of a sexually transmitted infection in a

heterosexual populations are described by the following system of differential equations:

$$\begin{aligned}
\dot{S}_k &= b_k N_k - (\lambda_{j\to k} + u_k + d_k)S_k + \alpha_k I_k + \theta_k V_k,\\
\dot{V}_k &= u_k S_k - (1-\epsilon_k)\lambda_{j\to k} V_k - (d_k + \theta_k)V_k, \qquad (k, j = f, m, \quad k \neq j) \quad (1)\\
\dot{I}_k &= \lambda_{j\to k}(S_k + (1-\epsilon_k)V_k) - (\alpha_k + d_k)I_k,
\end{aligned}$$

where all the parameters and initial conditions are non-negative.

We assume individuals are recruited into the sexually active population as unvaccinated susceptible at a constant rate b_k proportional to N_k and $1/d_k$ is the average duration of the sexual life for sex $k = f, m$. Prophylactic immunization occurs at a rate u_k. The vaccine reduces the force of infection by a factor $\epsilon_k \in [0, 1]$; thus, ϵ_k is the vaccine effectiveness and the vaccine is 100% effective when $\epsilon_k = 1$. Vaccine-induced immunity wanes at a rate θ_k, thus if $\theta_k = 0$, protection is lifelong. Individuals recover naturally from the infection at a rate α_k. No immunity is assumed after recovery. The acquisition of infection occurs with a sex-specific force of infection given by

$$\lambda_{f\to m} = \frac{\beta_{f\to m} I_f}{N_f}, \quad \lambda_{m\to f} = \frac{\beta_{m\to f} I_m}{N_m}. \tag{2}$$

Here, $\beta_{f\to m}$ ($\beta_{m\to f}$) is the female-to-male (male-to-female) transmission rate. We remark that although system (1) is a minimalist model, it capture the core characteristics of sexually transmitted infections in a heterosexual population under vaccination. For a full description of model parameters, together with their ranges and baseline values see Subsection 4.1 and Table 1.

2.2 Mathematical analysis

From system (1) it is immediate that the total population for sex $k = f, m$ satisfies $\dot{N}_k = (b_k - d_k)N_k$. Since we are interested in studying model (1) over a finite time interval $[0, t_f]$, we assume that the population for both sexes is constant i.e. $N_k(t) = N_k(0) := N_k^*$ for all $t \in [0, t_f]$, so $b_k = d_k$. We stress that the constant population size assumption is standard in epidemic modeling and is based on the fact the time scale of the epidemic process is considerably faster than that of the demographic one for a short time horizon. Therefore, the biologically feasible region for system (1) is

$$\Omega = \left\{(S_k, V_k, I_k) \in \mathbf{R}^3_+ : N_k^* = S_k(t) + V_k(t) + I_k(t), t \in [0, t_f] \ (k = f, m)\right\}$$

Let x_i be an state variable of model (1), then if $x_i = 0$ then $\dot{x}_i \geq 0$. It follows that all solutions of the system (1) with an initial condition in Ω remain in Ω for all $t \geq 0$ and Ω is forward invariant. The basic existence, uniqueness, and continuation results hold for model (1) hold in Ω Wiggins et al (2003).

Therefore system (1) is epidemiologically well-posed Hethcote (2000) and it is sufficient to study its dynamics in Ω.

The disease-free equilibrium (DFE) of model (1) is given by

$$\begin{aligned} E_0 &= (S_f^0, V_f^0, I_f^0, S_m^0, V_m^0, I_m^0) \\ &= \left(\frac{(d_f+\theta_f)N_f^*}{u_f+d_f+\theta_f}, \frac{u_f N_f^*}{u_f+d_f+\theta_f}, 0, \frac{(d_m+\theta_m)N_m^*}{u_m+d_m+\theta_m}, \frac{u_m N_m^*}{u_m+d_m+\theta_m}, 0 \right). \end{aligned}$$

Therefore, the susceptible and vaccinated fractions at equilibrium are

$$s_k^0 = \frac{S_k^0}{N_k^*} = \frac{d_k+\theta_k}{u_k+d_k+\theta_k}, \quad v_k^0 = \frac{V_k^0}{N_k^*} = \frac{u_k}{u_k+d_k+\theta_k}, \quad (k=f,m). \tag{3}$$

Observe that in the absence of vaccination, at the DFE, the whole population remain susceptible. Using the next-generation operator Diekmann et al (1990) and the method of Van den Driessche and Watmough (2002) we obtain the following next-generation matrix

$$\mathbf{K} = \begin{bmatrix} 0 & \dfrac{\beta_{m\to f}(S_f^0 + (1-\epsilon_f)V_f^0)}{(\alpha_m+d_m)N_m^*} \\ \dfrac{\beta_{f\to m}(S_m^0 + (1-\epsilon_m)V_m^0)}{(\alpha_f+d_f)N_f^*} & 0 \end{bmatrix} \tag{4}$$

The control reproduction number is defined as the spectral radius $\rho(\mathbf{K})$, that is, the largest eigenvalue of the next generation matrix. Therefore, the analytic expression for the control reproduction number is

$$R_c(u_f, u_m) = \sqrt{\frac{\beta_{f\to m}(s_m^0 + (1-\epsilon_m)v_m^0)}{(\alpha_f+d_f)} \times \frac{\beta_{m\to f}(s_f^0 + (1-\epsilon_f)v_f^0)}{(\alpha_m+d_m)}}. \tag{5}$$

The notation R_c is used to emphasize that the reproduction number is derived under control measures, in this case, vaccination. The square root in (5) arises since it takes two generations for infected hosts to produce new infected hosts of the same sex Van den Driessche and Watmough (2008). For a biological intuition of R_c observe that an infectious individuals of sex j produces on average $\beta_{j\to k}(s_k^0 + (1-\epsilon_k)v_k^0)$ infections on the opposite sex k $(k, j = f, m,\ k \neq j)$, during his/her infectious period $1/(\alpha_j + d_j)$.

The basic reproduction number in the absence of vaccination, R_0, satisfies

$$R_0 = R_c(0,0) = \sqrt{\frac{\beta_{f\to m}}{(\alpha_f+d_f)} \frac{\beta_{m\to f}}{(\alpha_m+d_m)}} > R_c(u_f, u_m) \text{ for } u_f, u_m > 0. \tag{6}$$

As a direct consequence of Theorem 2 in Van den Driessche and Watmough (2002), we obtain the local stability for the DFE. The result is formalized as follows.

Theorem 1. *The disease-free equilibrium E_0 for model (1) is locally asymptotically stable if $R_c < 1$ and unstable if $R_c > 1$.*

We now investigate the existence of the endemic equilibria of the form $(S_f^\dagger, V_f^\dagger, I_f^\dagger, S_m^\dagger, V_m^\dagger, I_m^\dagger)$ where $0 < I_f^\dagger < N_f^*$, and $0 < I_m^\dagger < N_m^*$ (a straightforward computation can show that $I_f^\dagger = 0$ implies $I_m^\dagger = 0$, and vice-versa). Further, since we are dealing with constant population for both sexes, we can express the endemic equilibria for the susceptible as $S_k^\dagger = N_k^* - V_k^\dagger - I_k^\dagger$ $(k = f, m)$. Then we can solve the equilibrium equations for the vaccinated classes $V_f^\dagger$ and $V_m^\dagger$ in terms of the infected classes $I_m^\dagger$ and $I_m^\dagger$ as

$$V_m^\dagger = \frac{u_m(N_m^* - I_m^\dagger)}{d_m + u_m + \theta_m + (1-\epsilon_m)\beta_{f\to m} I_f^\dagger / N_f^*},$$
$$V_f^\dagger = \frac{u_f(N_f^* - I_f^\dagger)}{d_f + u_f + \theta_f + (1-\epsilon_f)\beta_{m\to f} I_m^\dagger / N_m^*}.$$

Next, defining

$$\delta = d_m + \theta_m + (1-\epsilon_m)u_m,$$
$$\zeta = (\alpha_m + d_m)N_f^* \left((d_m + u_m + \theta_m)N_f^* + (1-\epsilon_m)\beta_{f\to m} I_f^\dagger \right),$$

we can express the infected males as $I_m^\dagger = I_f^\dagger F(I_f^\dagger)$ where

$$F(I_f^\dagger) = \frac{\beta_{f\to m} N_m^* (\delta N_f^* + (1-\epsilon_m)\beta_{f\to m} I_f^\dagger)}{\beta_{f\to m}\delta N_f^* I_f^\dagger + (1-\epsilon_m)(\beta_{f\to m} I_f^\dagger)^2 + \zeta}. \tag{7}$$

Finally, the infected females at the endemic equilibrium $I_f^\dagger$ correspond to the zeros of the following four order polynomial

$$A I_f^\dagger (F(I_f^\dagger))^2 + B F(I_f^\dagger) + C = 0 \tag{8}$$

where

$$A = \beta_{m\to f}^2 (1-\epsilon_f)(N_f^* - I_f^\dagger)$$
$$B = \beta_{m\to f} N_m^* \left(-(\alpha_f + d_f)(1-\epsilon_f) I_f^\dagger + (N_f^* - I_f^\dagger)(d_f + \theta_f + (1-\epsilon_f)u_f) \right)$$
$$C = -(\alpha_f + d_f)(d_f + \theta_f + u_f)(N_m^*)^2$$

In the particular case for which the vaccine efficacy is 100%, that is, $\epsilon_f = \epsilon_m = 1$, we can find a unique endemic equilibrium given by

$$\begin{aligned} \frac{I_f^\dagger}{N_f^*} &= \frac{R_0^2(d_m+\theta_m)(d_f+\theta_f) - (d_m+\theta_m+u_m)(d_f+\theta_f+u_f)}{R_0^2(d_m+\theta_m)(d_f+\theta_f) + \beta_{m\to f}(d_m+\theta_m)(d_f+\theta_f+u_f)/(\alpha_m+d_m)}, \\ \frac{I_m^\dagger}{N_m^*} &= \frac{(\alpha_f+d_f)I_f^\dagger}{\beta_{m\to f}s_f^0(N_f^*-I_f^\dagger)}. \end{aligned} \tag{9}$$

Observe that the above equilibrium only exist if the condition

$$R_0^2(d_m+\theta_m)(d_f+\theta_f) > (d_m+\theta_m+u_m)(d_f+\theta_f+u_f)$$

is fulfilled. This occurs if and only if $R_c > 1$, therefore the classical forward bifurcation occurs when the vaccine is 100% effective and the two-sex epidemic model (1) presents a unique endemic equilibrium. In the general case, it is not possible to obtain a closed-form solution for the endemic equilibria but numerical results indicate that the number of endemic equilibria is at most two. Furthermore, a backward bifurcation can occur if the vaccine effectiveness ϵ_k $(k = f, m)$ is below a certain threshold. Figure 1 depicts the typical dynamics for the endemic equilibria of the infected female class where the backward bifurcation is present. The equilibrium dynamics for the male infected class follow the same qualitative behavior (not shown).

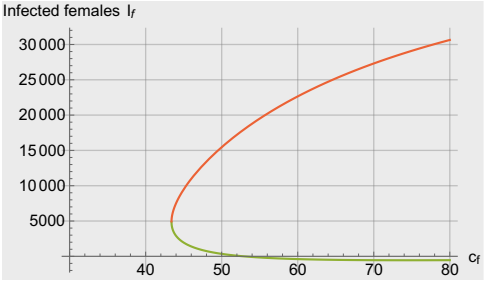


Fig. 1: Endemic equilibria for the infected female sub-population, I_f, as a function of the expected number of sexual contacts that a typical man carries out per year c_f. Vaccine effectiveness for both sexes is 80%. Parameter values are shown in Table 1.

3 Optimal vaccine allocation

In this section, we propose an optimal control problem with an isoperimetric constrain to investigate the best sex-specific vaccine deployment under a limited vaccine budget. For this, we consider time-dependent vaccination rates $u_f(t)$ and $u_m(t)$ per unit of time, thus the controlled model becomes

$$\begin{aligned} \dot{S}_k &= b_k N_k - (\lambda_{j\to k} + u_k(t) + d_k)S_k + \alpha_k I_k + \theta_k V_k, \\ \dot{V}_k &= u_k S_k - (1-\epsilon_k)\lambda_k V_k - (d_k+\theta_k)V_k, \qquad (k,j = f,m, \quad k \neq j) \\ \dot{I}_k &= \lambda_k(S_k + (1-\epsilon_k)V_k) - (\alpha_k + d_k)I_k, \end{aligned} \tag{10}$$

subject to non-negative initial conditions. The vaccination rates will be called controls and denoted by the vector $\mathbf{c}(t) = (u_f(t), u_m(t))^T$.

We conceptualize a limited vaccine supply assuming that the number of vaccines available under the time interval of interest $[0, t_f]$ is fixed with a value W and that all vaccines will be delivered to the population. We further assume that the vaccine stockpile is not enough to vaccine the whole population i.e. $W < N$ since in another case there is no need to optimize vaccine allocation.

This condition can be modeled by the following isoperimetric constraint Kamien and Schwartz (2012); Lenhart and Workman (2007):

$$\int_0^{t_f} u_f(t)S_f(t) + u_m(t)S_m(t)dt = W. \tag{11}$$

The problem for public health officers is to choose an optimal vaccine deployment to minimize the prevalence of the infection, as well as the overall costs of vaccine deployment. In mathematical terms, such a goal can be achieved by minimizing the following objective functional

$$J = \int_0^{t_f} A_1 I_f(t) + A_2 I_m(t) + A_3 u_f^2(t) + A_4 u_m^2(t)dt. \tag{12}$$

The weight parameters A_i $(i = 1, \ldots, 4)$ describe the relative impact of the control or state variables on the value of the objective functional (see Section 4.3). Observe that we have proposed a quadratic cost functional. This assumption is commonly justified by arguing that the quadratic terms penalize high levels of control administration in comparison with the cost of low levels Saldaña et al (2019). We follow this approach but we remark that this formulation is the most mathematically convenient, as for such L_2-type functionals, the optimal controls can be easily obtained via Pontryagin's Maximum Principle.

The control set is defined by

$$\mathcal{U} = \{\mathbf{c}(t) : u_k(t) \text{ bounded and Lebesgue measurable on } [0, t_f],\ k = f, m\}, \tag{13}$$

with bounds

$$0 \leq u_f(t), u_m(t) \leq u_{max}, \quad \forall t \in [0, t_f]. \tag{14}$$

Observe that besides the budgetary constrain (11), the vaccination rates should be constrained (due to logistic limitations) under a maximum vaccination rate u_{max} per unit of time e.g. daily vaccination rate.

To obtain an approximation for the maximum vaccination rate u_{max}, let us consider a population $M(t)$ where no individuals has been immunized. If the vaccination rate, u, is proportional to population size, we have $M'(t) = -uM(t)$, and $M(0) = 1$ for a normalized population. It follows that $M(t) = \exp(-ut)$ are the individuals that have not been vaccinated at time t. Therefore, the fraction of vaccinated individuals at time t, that is, the vaccination coverage, $V_c(t)$, is $V_c(t) = 1 - \exp(-ut)$. For a fixed time horizon t_f, we have

$$V_c(t_f) = 1 - \exp(-ut_f) \quad \text{or} \quad u = -\ln(1 - V_c(t_f))/t_f. \tag{15}$$

Considering a very optimistic case in which health authorities achieve a vaccination coverage $V_c(t_f) = 80\%$ of the population in $t_f = 1$ year, we obtain that the constant vaccination rate $u \approx 1.60$ per year. Therefore, we choose a maximum daily vaccination rate as $u_{max} = 1.60/365$.

Given the special structure of (11), we can convert the isoperimetric constrain (11) into a fixed endpoint constrain Kamien and Schwartz (2012), by defining

$$Z(t) = \int_0^t u_f(s)S_f(s) + u_m(s)S_m(s)ds. \tag{16}$$

The additional state variable, $Z(t)$, represents the cumulative number of vaccines that have been given at time t, and satisfies

$$\dot{Z}(t) = u_f(t)S_f(t) + u_m(t)S_m(t) \quad Z(0) = 0, \quad Z(t_f) = W. \tag{17}$$

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

$$\min_{\mathbf{c} \in \mathcal{U}} J(\mathbf{c}) \text{ subject to model (10) coupled with constrain (17).} \tag{18}$$

An application of the Fillipov-Cesari theorem (Fleming and Rishel, 1975, Chapter III, Theorem 4.1) gives conditions to assert existence of an optimal control pair

$$\mathbf{c}^*(t) = (u_f^*(t), u_m^*(t))^T$$

and corresponding optimal state solutions

$$\mathbf{X}^*(t) = (S_f^*(t), V_f^*(t), I_f^*(t), S_m^*(t), V_m^*(t), I_m^*(t), Z^*(t))^T$$

for the OCP (18). The proof is standard for L_2-type objective functionals and we omit it. Proofs of such statements can be found in Camacho et al (2019); Saldaña et al (2019); Sepulveda-Salcedo et al (2020). We now use Pontryagin maximum principle to state the necessary criterion satisfied by an optimal control Fleming and Rishel (1975); Kamien and Schwartz (2012).

Theorem 2. *If $\mathbf{X}^*(t)$ and $\mathbf{c}^*(t)$ are optimal for the OCP (18), then there exist a constant λ_0 and piecewise differentiable functions $\lambda(t) = (\lambda_1, \ldots, \lambda_7)$, where for all $t \in [0, t_f]$ we have $(\lambda_0, \lambda(t)) \neq (0, \mathbf{0})$, such that for every $t \in [0, t_f]$*

$$H(t, \mathbf{X}^*(t), \mathbf{c}^*(t), \lambda(t)) \leq H(t, \mathbf{X}^*(t), \mathbf{c}(t), \lambda(t)) \tag{19}$$

for all admissible controls $\mathbf{c} \in \mathcal{U}$, where the Hamiltonian function H is defined by

$$\begin{aligned} H(t, \mathbf{X}, \mathbf{c}, \lambda) = \lambda_0 &\left[A_1 I_f + A_2 I_m + A_3 u_f^2 + A_4 u_m^2\right] + \\ &\lambda_1 \left[b_f N_f - (\lambda_{m\to f} + u_f + d_f)S_f + \alpha_f I_f + \theta_f V_f\right] + \\ &\lambda_2 \left[u_f S_f - (1-\epsilon_f)\lambda_{m\to f} V_f - (d_f + \theta_f)V_f\right] + \\ &\lambda_3 \left[\lambda_{m\to f}(S_f + (1-\epsilon_f)V_f) - (\alpha_f + d_f)I_f\right] + \\ &\lambda_4 \left[b_m N_m - (\lambda_{f\to m} + u_m + d_m)S_m + \alpha_m I_m + \theta_m V_m\right] + \\ &\lambda_5 \left[u_m S_m - (1-\epsilon_m)\lambda_{f\to m} V_m - (d_m + \theta_m)V_m\right] + \\ &\lambda_6 \left[\lambda_{f\to m}(S_m + (1-\epsilon_m)V_m) - (\alpha_m + d_m)I_m\right] + \\ &\lambda_7 \left[u_f S_f + u_m S_m\right]. \end{aligned} \tag{20}$$

Except at points of discontinuity of $\mathbf{c}^*(t)$, the adjoint variable $\lambda(t)$ satisfies

$$
\begin{aligned}
\dot{\lambda}_1 &= \lambda_1 \left(\frac{\beta_{m\to f} I_m^*}{N_m^*} + u_f^* + d_f \right) - \lambda_2 u_f^* - \lambda_3 \frac{\beta_{m\to f} I_m^*}{N_m^*} - \lambda_7 u_f^*, \\
\dot{\lambda}_2 &= -\lambda_1 \theta_f + \lambda_2 \left[(1-\epsilon_f) \frac{\beta_{m\to f} I_m^*}{N_m^*} + (d_f + \theta_f) \right] - \lambda_3 (1-\epsilon_f) \frac{\beta_{m\to f} I_m^*}{N_m^*}, \\
\dot{\lambda}_3 &= -\lambda_0 A_1 - \lambda_1 \alpha_f + \lambda_3 (\alpha_f + d_f) + \lambda_4 \frac{\beta_{f\to m}}{N_f^*} S_m^* + \lambda_5 (1-\epsilon_m) \frac{\beta_{f\to m}}{N_f^*} V_m^* \\
&\quad - \lambda_6 \frac{\beta_{f\to m}}{N_f^*} (S_m^* + (1-\epsilon_m) V_m^*), \\
\dot{\lambda}_4 &= \lambda_4 \left(\frac{\beta_{f\to m} I_f^*}{N_f^*} + u_m^* + d_m \right) - \lambda_5 u_m^* - \lambda_6 \frac{\beta_{f\to m} I_f^*}{N_f^*} - \lambda_7 u_m^*, \\
\dot{\lambda}_5 &= -\lambda_4 \theta_m + \lambda_5 \left[(1-\epsilon_m) \frac{\beta_{f\to m} I_f^*}{N_f^*} + (d_m + \theta_m) \right] - \lambda_6 (1-\epsilon_m) \frac{\beta_{f\to m} I_f^*}{N_f^*}, \\
\dot{\lambda}_6 &= -\lambda_0 A_2 + \lambda_1 \frac{\beta_{m\to f}}{N_m^*} S_f^* + \lambda_2 (1-\epsilon_f) \frac{\beta_{m\to f}}{N_m^*} V_f^* - \lambda_3 \frac{\beta_{m\to f}}{N_m^*} (S_f^* + (1-\epsilon_f) V_f^*) \\
&\quad - \lambda_4 \alpha_m + \lambda_6 (\alpha_m + d_m), \\
\dot{\lambda}_7 &= 0.
\end{aligned}
\tag{21}
$$

Furthermore,

$$
\lambda_0 = 1 \quad or \quad \lambda_0 = 0. \tag{22}
$$

Last, the following transversality conditions are satisfied:

$$
\lambda_i(t_f) = 0 \quad i = 1, \ldots, 6, \quad \lambda_7(t_f) = free. \tag{23}
$$

The adjoint variables $\lambda_i(t)$ $(i = 1, \ldots, 6)$ have a classical interpretation in OCP as the marginal valuation of the associated state variable at time t Kamien and Schwartz (2012). The value of the constant λ_0 in the Hamiltonian (20) is either 0 or 1. If $\lambda_0 = 1$, then the OCP (18) would have a solution in which the objective matters Kamien and Schwartz (2012). In this scenario, the Hamiltonian function has the standard form, and minimization of the objective functional (12) is equivalent to minimization of H as a function of $\mathbf{c}(t)$ along the optimal path. This is not always possible for OCPs that include an isoperimetric constrain Fleming and Rishel (1975). This results from the fact that the controlled system,(10) coupled with (17), has more endpoint conditions than differential equations. Hence, the system is over-determined and the optimization problem may become unfeasible. If $\lambda_0 = 0$, one can handle the OCP finding an admissible control $\mathbf{c}^*(t)$ that satisfies the isoperimetric constrain (11). However, such control will neglect the value of the objective functional Sepulveda-Salcedo et al (2020). Problems in which $\lambda_0 = 0$ are called abnormal Fleming and Rishel (1975) and the optimal control usually presents a bang-bang structure since H is a linear function in the control. A feasible control, in this case, is to start vaccinating with the maximal effort at the initial phase and to continue vaccinating with maximal effort to deploy all the vaccines at a time $\hat{t} \in (0, t_f)$ Hansen and Day (2011); Sepulveda-Salcedo et al (2020).

In our context, we cannot disregard the value of the objective functional since is essential to find the optimal vaccine deployment. Hence, hereafter we assume $\lambda_0 = 1$. In these conditions, we can use the first-order optimality conditions to obtain the following characterization of the optimal controls:

$$u_f^*(t) = \min\left\{\max\left\{0, \frac{(\lambda_1 - \lambda_2 - K)S_f^*}{2A_3}\right\}, u_{max}\right\}, \tag{24}$$

$$u_m^*(t) = \min\left\{\max\left\{0, \frac{(\lambda_4 - \lambda_5 - K)S_m^*}{2A_4}\right\}, u_{max}\right\}. \tag{25}$$

The constant $K \in \mathrm{R}$ comes from the solution of the last equation in the adjoint system (21), which implies $\lambda_7 = K$, where K should be chosen to fulfill the condition $Z(t_f) = W$.

4 Numerical Results

Here, we complement the analytical results in the previous sections with the numerical computation of the optimal control. To obtain the optimal control solutions we must solve the optimality system which is a boundary value problem involving the state equations (10), coupled with the fixed endpoint constrain (17), and the adjoint system (21). The characterization of the optimal control (24)-(25) has to be substituted in the latter equations to get a system that only depends on the state and adjoint variables. Observe that although the model variables for the controlled system (10) have free end conditions, the additional state variable $Z(t)$ has a specified endpoint (17). Therefore, the forward-backward sweep method (FBSM) cannot be applied directly to solve the optimality system Lenhart and Workman (2007). Instead, we need to find the value K for the adjoint variable $\lambda_7 = K$ such that $Z(t_f) = W$. To this end, we consider an adapted FBSM that takes as an input a guess for K, and solves the corresponding OCP. The solution obtained by the implementation of FBSM is denoted as $\varphi(K)$, and the corresponding final value for the auxiliary function Z that computes the number of cumulative vaccinated individuals is denoted $Z_K(t_f)$. The adapted FBSM is an iterative process that seeks the value of K that minimizes the difference $Z_K(t_f) - W$. We use the classical secant method to solve this outer iterative process which usually involves several iterations of the FBSM.

4.1 Model parameters

We retrieved the baseline values for some of our model parameters using sexual behavior data from United States of America (USA) and estimations from previous studies on STIs. Rather than studying a single disease, our approach is to investigate a set of scenarios of interest that might be plausible for the most common STIs. The selection of parameters is outlined as follows.

The sexually active life expectancy has been estimated to be on average higher for males than for females Lindau and Gavrilova (2010). In particular, the sexually active life expectancy for males is 34.7 years with a 95% confidence interval $(34.1, 35.3)$. Thus, $1/d_m \in (34.1, 35.3)$ years. The sexually active life expectancy for females is 30.7 years with a 95% confidence interval $(30, 31.4)$. Thus, $1/d_f \in (30, 31.4)$ years. In 2020, is was estimated in the USA that the percentage of female population is 50.52 percent compare to 49.48 percent male population United Nations (2020). Therefore, $N_f^* = 0.5052N$ and $N_m^* = 0.4948N$. For simplicity, we assume that the total population is $N = 100,000$.

The parameter $\beta_{m\to f} = c_m p_{m\to f}$ is the transmission rate from males to females, where c_m is the expected number of sexual contacts with men that a typical woman

carries out per unit of time and $p_{m\to f}$ is the probability of female infection given contact with an infectious male. Likewise, the transmission rate from females to males $\beta_{f\to m} = c_f p_{f\to m}$, is the product of the expected number of sexual contacts with women that a typical man carries out per unit of time c_f and the probability of male infection given contact with an infectious female $p_{f\to m}$. To obtain the conservation of total sex contacts, the mixing function should satisfy the following condition Busenberg and Castillo-Chavez (1991):

$$c_f N_m^* = c_m N_f^*. \tag{26}$$

Observe that if $N_f^* \neq N_m^*$ then the parameters c_f and c_m can differ substantially. Under our conditions, if we assume that c_f is fixed, we can obtain $c_m = 0.4948c_f/0.5052 = 0.9794c_f$. Men and women in good health report frequent sex (once or more weekly) Lindau and Gavrilova (2010). In our study, we assume that the expected number of sexual contacts that a typical man carry out follows a triangular distribution $c_f \sim Tri(0, 100, 52)$ per year Lindau and Gavrilova (2010). Furthermore, there is evidence that the male to female sexual infectivity rate is generally greater than that for female to male Low et al (2006); Wong et al (2004). For example, for genital herpes HSV-2, estimations indicate that $p_{m\to f} \approx 4p_{f\to m}$ Heffernan et al (2014). Therefore, we set $p_{m\to f} > p_{f\to m}$, and we propose $p_{m\to f} \sim Tri(0, 1, 0.70)$, and $p_{f\to m} \sim Tri(0, 1, 0.40)$.

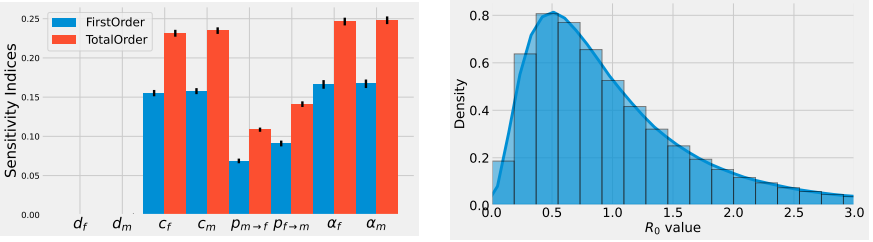
According to the WHO, to be approved, vaccines are required to have a high efficacy rate of at least 50% World Health Organization (2021). Current vaccines against STIs have been proven to be highly effective to prevent infection e.g. vaccines against HPV, and hepatitis B virus Gottlieb et al (2016). In this study, we consider vaccine efficacy between 60%-95% for both sexes ($\epsilon_f, \epsilon_m \in [0.60, 0.95]$). The average infectious period might vary substantially in STIs, depending on the disease ranging, from a few days up to several months Workowski and Bolan (2015). As a consequence, we assume $1/\alpha_k \in [10, 100]$ days ($k = f, m$). Regarding the duration of vaccine-induced immunity, we assume that the protection last from at least one year and can be maintained up to 30 years, hence $1/\theta_k \in [1, 30]$ years ($k = f, m$). Model parameters are summarized in Table 1.

Parameters	**Values – ranges**	**Units**
Female's sexually active life expectancy $1/d_f$	30.7– $(30, 31.4)$	*year*
Male's sexually active life expectancy $1/d_m$	34.7– $(34.1, 35.3)$	*year*
Average number of sexual contacts for males c_f	52– $Tri(0, 100, 52)$	$year^{-1}$
Average number of sexual contacts for females c_m	50– $Tri(0, 97, 50)$	$year^{-1}$
Probability of female infection $p_{m\to f}$	0.70– $Tri(0, 1, 0.70)$	*dimensionless*
Probability of male infection $p_{f\to m}$	0.40– $Tri(0, 1, 0.40)$	*dimensionless*
Vaccine efficacy ϵ_k	0.80– $(0.60, 0.95)$	*dimensionless*
Duration of the infectious period $1/\alpha_k$	20– $(10, 100)$	*days*
Vaccination rates u_k	0.50– $(0.0, 1.60)$	$year^{-1}$
Duration of vaccine-induced protection $1/\theta_k$	20– $(1, 30)$	*year*

Table 1: Baseline model (1) parameters ($k = f, m$). References for the parameter values are given in the main text. The total population is assumed to be $N = 100,000$ with a gender distribution $N_f^* = 0.5052N$ and $N_m^* = 0.4948N$.

4.2 Global sensitivity analysis for the reproduction numbers

Here, a global sensitivity analysis is performed to provide a quantitative measure of the contributions of the model parameters on the reproduction numbers R_0 and R_c. We use a variance-based sensitivity analysis classically referred as the Sobol method which is, so far, one of the most powerful techniques among current global sensitivity analysis methods Zhang et al (2015). Sobol sensitivity analysis determines the contribution of input parameters to the overall variance of a model outcome of interest, in our case, the reproduction numbers. In particular, the so-called first-order Sobol indices measure the contribution to the output variance by a single model input alone. Whereas, the total-order index measures the contribution to the output variance caused by a model input, including both its first-order effects and all higher-order interactions Saltelli et al (2008). We perform numerical experiments (100,000 samples) using SALib, an open-source library written in Python for performing sensitivity analyses Herman and Usher (2017). The ranges used for the parameters are listed in Table 1.



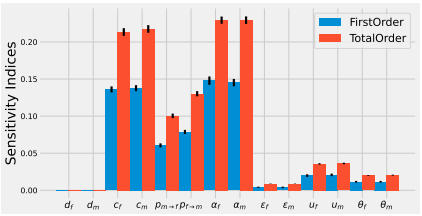
(a) (b)

Fig. 2: (a) First (blue) and total (red) Sobol's indices for the basic reproduction number R_0. The ranges for the parameters are listed in Table 1. The vertical black lines in the indices represent 95% confidence intervals. (b) Histogram for the distribution of R_0. The solid line represents a kernel density estimation for the continuous distribution.

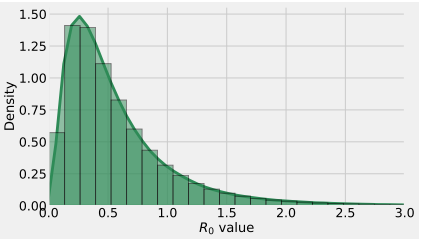
Figure 2 (a) shows the first (blue) and total (red) Sobol's indices for the basic reproduction number R_0. The dark marks on top of the bars in Fig. 1 represent 95% confidence intervals for the sensitivity indices. Notice that they are very small. Observe that the expected number of sexual contacts c_k together with the recovery rates α_k $(k = f, m)$ are the parameters that contribute the most to the variability of R_0. Whereas, the contribution to the variability of R_0 given by the mortality rates d_k $(k = f, m)$ is practically zero. Figure 2 (b) shows a histogram for the distribution of R_0. The solid line represents a kernel density estimation for the continuous distribution. Observe that although in most cases R_0 value is below 1, in some extreme scenarios R_0 can be as high as 3.

Figure 3 (a) shows the first (blue) and total (red) Sobol's indices for the control reproduction number R_c. As in the case for R_0, the parameters c_k and α_k $(k = f, m)$ contribute the most to the variance of R_c. Figure 3 (b) shows a histogram for the

distribution of R_c. Observe that the distribution for R_c is more close to low values in comparison with the R_0 distribution (see Figure 2 (b)). Hence, even though the vaccine parameters (ϵ_k, u_k, θ_k) are not the most influential parameters on R_c, they still can significantly reduce the value of R_c.



(a)



(b)

Fig. 3: (a) First (blue) and total (red) Sobol's indices for the control reproduction number R_c. The ranges for the parameters are listed in Table 1. The vertical black lines in the indices represent 95% confidence intervals. (b) Histogram for the distribution of R_c. The solid line represents a kernel density estimation for the continuous distribution.

4.3 Vaccination scenarios

We investigate several vaccination scenarios to evaluate the optimal sex-specific vaccine deployment among the population. The time horizon for our simulations is 365 days, that is, $t_f = 365$ days and $t \in [0, t_f]$. In the objective functional (12), the parameters A_1 and A_2 balance the cost of the reduction in health and well-being of infected females and males, respectively. These costs related to pain and suffering are sometimes referred to as morbidity costs Muennig and Bounthavong (2016). On the other hand, A_3 and A_4 represent the costs of vaccine deployment in females and males, respectively.

In real-life scenarios, the monetary costs and side effects of a vaccination program are typically small compared with the potential losses that an outbreak can inflict. Hence, we assume $A_1, A_2 > A_3, A_4$. Furthermore, females are more severely affected by STIs because of anatomical physiological characteristics. So in a heterosexual setting, women bear the largest burden Workowski and Bolan (2015). The classical example is HPV infection. While HPV infection can lead to cervical cancer and death in women, the infection in men rarely leads to severe health problems (penile cancer from HPV might happen but the rate is far lower than the rate for cervical cancer) Sung et al (2021). Therefore, $A_1 > A_2$. In particular, for the numerical simulations, we assume $A_1 = 10$, $A_2 = 1$. The cost of vaccine deployment is assumed to be the same for both sexes, and are fixed as $A_3 = A_4 = A_2/2$. Initial conditions are set as follows. $I_f(0) = I_m(0) = 10$, $V_f(0) = V_m(0) = 0$, and $S_f(0) = N_f^* - I_f(0) - V_f(0)$, $S_m(0) = N_m^* - I_m(0) - V_m(0)$. These conditions represent a starting vaccination roll-out program where no individuals in the population have been vaccinated. Regarding the vaccine stockpile, we consider three cases corresponding to supply of vaccines for 20% ($W = 0.2N$), 30% ($W = 0.3N$) and 40% ($W = 0.4N$) of the total population.

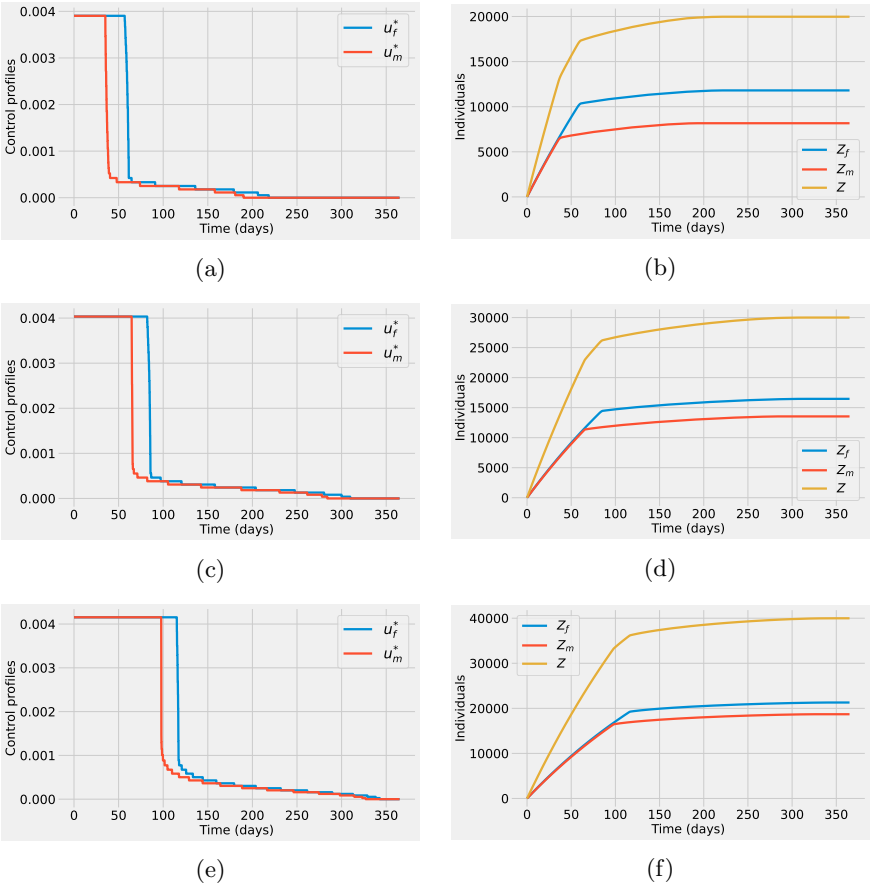


Fig. 4: First column: Optimal time-dependent vaccination rates for females $u_f^*(t)$ (blue) and males $u_f^*(t)$ (red). Second column: Cumulative number of vaccinated females (blue) and vaccinated males (red) computed from the optimal states corresponding to the optimal controls on the first column. The total cumulative number of vaccines administered, $Z(t)$, is shown in yellow. For both columns the supply of vaccines correspond to 20% (a)-(b) (first row), 30% (c)-(d) (second row) and 40% (e)-(f) (third row) of the total population. Baseline parameter values are listed in Table 1. Initial conditions are $I_f(0) = I_m(0) = 10$, $V_f(0) = V_m(0) = 0$, and $S_f(0) = N_f^* - I_f(0) - V_f(0)$, $S_m(0) = N_m^* - I_m(0) - V_m(0)$.

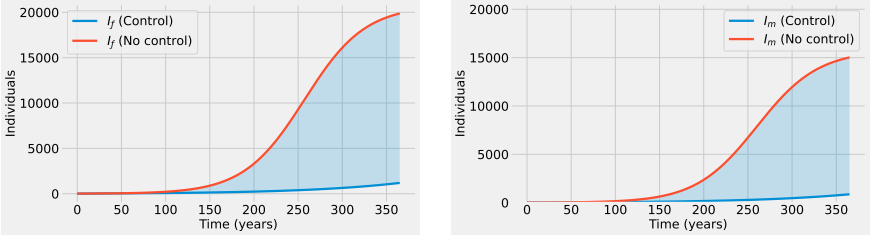
To better quantify the gender-specific optimal vaccine deployment we define

$$Z_f(t) = \int_0^t u_f(s)S_f(s)ds, \quad Z_m(t) = \int_0^t u_m(s)S_m(s)ds. \tag{27}$$

Observe that $Z_f(t)$ and $Z_m(t)$ represent the cumulative number of vaccinated females and males, respectively, at time t, and $Z(t) = Z_f(t)+Z_m(t)$ for all $t \in [0, t_f]$. Furthermore, since vaccinated individuals can still get infected, it follows that $Z_f(t) \geq V_f(t)$, $Z_m(t) \geq V_m(t)$ for all $t \in [0, t_f]$.

The first column in Figure 4 shows the optimal control solutions, that is, the optimal time-dependent vaccination rates for females $u_f^*(t)$ (blue) and males $u_m^*(t)$ (red). The second column shows the sex-specific optimal vaccine deployment using cumulative vaccinated individuals. The cumulative number of vaccinated females $Z_f(t)$ (blue), males $z_m(t)$ (red) are obtained from the optimal states corresponding to the optimal controls on the first column. The variable $Z(t)$ that represents the total cumulative number of vaccines administered is also shown. Observe that $Z(t_f) = W$ for each of the cases investigated: $W = 0.2N^*$ (first row), $W = 0.3N^*$ (second row) and $W = 0.4N^*$ (third row). For all cases (see Figure 4 (a), (c), (e)), the optimal control solutions suggest that health officers must allocate as much vaccines as possible at the early phase of the outbreak. After a significant fraction of the population is immunized, then reduce quickly the vaccination rate to low levels and keep it like that for a long period of time. Finally, gradually decrease vaccine deployment to zero.

One important result from plots (a), (c), (d) in Figure 4 is that although the vaccination rate for females should be higher than the one for males, this difference is relatively small. Hence, under these conditions men should be included in vaccination programs together with females. Figure 4 (b), (d), (f) shows, as expected from the optimal controls, that the cumulative number of vaccinated females is above the one for males. Nevertheless, the key point to notice is that the difference on the sex-specific cumulative vaccination increases as the vaccine stockpile reduces (note that the difference is bigger in Figure 4 (b) in comparison with Figure 4 (f)). In other words, for a very limited vaccine supply, one sex-vaccination can be more beneficial than the inclusion of both sexes into the vaccination program.



(a) (b)

Fig. 5: (a) Number of infected females as a function of time without control (red line) and with optimal vaccination rates corresponding to the case $W = 0.3N$ (blue line). (b) Number of infected males as a function of time without control (red line) and with optimal control (blue line). The integral of the shaded area represents the number of infections averted by the optimal vaccination rates.

We remark that for all the scenarios explored, the implementation of the vaccination program manage to significantly reduce the prevalence of the infection in

comparison with the no control case. Figure 5 deploys the number of infected individuals without control (red solid line) and under the application of the optimal vaccination rates (blue solid line) corresponding to the case $W = 0.3N$ (see Figure 4 (c)). Females and males are presented in Figure 5 (a) and (b), respectively. The integral of the shaded area corresponds to the number of infections averted by the vaccination programs.

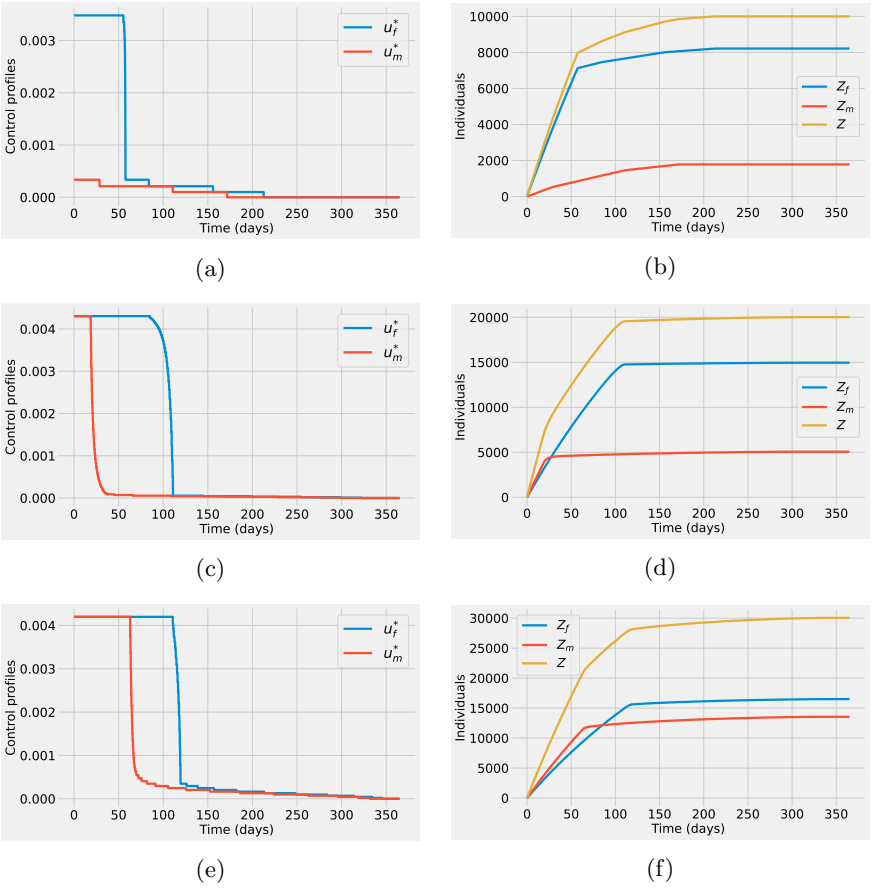


Fig. 6: First column: Optimal time-dependent vaccination rates for females $u_f^*(t)$ (blue) and males $u_f^*(t)$ (red). Second column: Cumulative number of vaccinated females (blue), males (red) computed from the optimal states corresponding to the optimal controls on the first column. The total cumulative number of vaccines administered, $Z(t)$, is shown in yellow. For both columns the supply of vaccines correspond to 20% (first row), 30% (second row) and 40% (third row) of the total population. Baseline parameter values are listed in Table 1. Initial conditions $I_f(0) = I_m(0) = 10$, $V_f(0) = 10000$, $V_m(0) = 0$, and $S_f(0) = N_f^* - I_f(0) - V_f(0)$, $S_m(0) = N_m^* - I_m(0) - V_m(0)$.

The results in Figure 4 were derived for a starting vaccination roll-out program. Another scenario of interest is when a single-sex vaccination strategy is already established. In this context, public health authorities would like to evaluate if it is better to increase coverage in the existing single-sex program or to vaccinate both sexes simultaneously Bogaards et al (2011). We assume $V_f(0) = 10000$, hence, a substantial number of females have already been vaccinated, and $V_m(0) = 0$, i.e. no vaccinated males. This scenario mimics HPV vaccination programs in several countries which are currently directed at females only Bruni et al (2021). Other model parameters are fixed as show in Table 1, except the total vaccine stockpile W that now counts 10000 vaccines less (the ones that are already delivered for females). The optimal control profiles together with the cumulative vaccinated individuals for these conditions are shown in Figure 6. From the optimal controls (see Figure 6 (a), (c), (d)) it is clear that for a scenario of very limited vaccine stockpile, i.e. $W < 0.3N^*$, vaccine administration should continue prioritizing the female-only target population. However, if the stockpile is relatively large, i.e. $W > 0.4N^*$, the inclusion of males in the vaccination program is the optimal strategy to effectively eliminate the epidemic in the population.

5 Discussion

The prevention and control of sexually transmitted infections have extensive public health benefits including the reduction of preventable deaths of newborns, and improved sexual and reproductive health World Health Organization (2021). Vaccine development and successful implementation of effective immunization programs are critical actions to progress in the control of STIs Gottlieb et al (2019). Nevertheless, due to cost and logistical challenges, vaccine stockpile is typically limited and not enough to achieve a high-immunization coverage, particularly in low-middle-income settings Yamey et al (2022). Data reports significant sex-specific differences on biological risks for STI acquisition, the clinical manifestation of the infection, and their potential for transmission to the opposite sex Hook (2012); Wong et al (2004). Hence, determining optimal sex-specific vaccination programs against STIs is a challenging task that deserves more attention. A major example are HPV vaccination programs which were introduced in several countries for young girls. These early female-only HPV immunization programs have been found to be cost-effective when cervical cancer prevention is the main objective (see Brisson et al (2020) and the references therein) . Yet, a number of studies e.g. Elfström et al (2016); Stanley (2012) have suggested that if rather than to prevent cervical cancer alone, the aim is to reduce all HPV-associated diseases, then the inclusion of males can be cost-effective. Currently, more than 30% of the HPV programs are gender-neutral (GN), i.e. with both females and males receiving the vaccine. However, 79% of GN programs are from high-income countries whereas only 21% from upper-middle-income countries Bruni et al (2021).

In this study we investigate under which conditions the inclusion of both males and females into vaccination programs adds to the population-level impact of female-only interventions. Considering sex-specific differences in transmissibility and severity in disease outcomes, we compare various vaccination strategies against STI transmission for different realistic settings described by distinct budget constraints associated with the vaccine supply. The vaccination strategies are obtained as solutions to an optimal control problem aiming to reduce the total prevalence of the infection subject

to a minimalist two-sex Kermack-McKendrick-type model. The control variables are the daily vaccination rates for females and males, respectively, that mimic a prophylactic vaccine with effectiveness not necessarily equal to 100%. One important aspect of our approach relies upon modeling a limited but specific vaccine stockpile via an isoperimetric constrain Kamien and Schwartz (2012). We solve the optimal control problem via the Pontryagin Maximum Principle and obtain a numerical approximation for the solution using a modified version of the FBSM which handles the isoperimetric budget constraint in our formulation.

We considered two main scenarios regarding the current immunization coverage in the population (i) a starting vaccination roll-out program where no individuals in the population have been vaccinated (see Figure 4) and (ii) a female-only vaccination strategy which is already established and has reached around 20% coverage in females (see Figure 6). The second scenario is relevant for public health authorities who would like to evaluate if it is better to increase coverage in the existing female-only program or to vaccinate both sexes simultaneously. Each of these scenarios is further sub-divided according to the total vaccine supply available W which is incorporated via the isoperimetric constrain (11). The simulations for the first scenario show that although the vaccination rate for females should be higher than the one for males, this difference is relatively small if the vaccine supply is relatively large (enough to reach at least 40% coverage). Hence, under these conditions, vaccinating both sexes, with a slightly higher rate for females, is optimal and provides an effective and faster approach to reducing the prevalence of the infection. However, the difference on the sex-specific vaccine distribution increases as the vaccine stockpile reduces. In other words, for a very limited vaccine supply (30% coverage or less), female-only vaccination can be more beneficial than the inclusion of both sexes into the vaccination program. Furthermore, for the case in which a female-only program is already ongoing, vaccine administration should continue prioritizing the female-only target population and males should only be included is the vaccine stockpile is very large. Since the male-to-female sexual infectivity rate is generally higher than that of female-to-male, prioritizing female vaccination might seem counter intuitive, because vaccinating super-spreaders (in this case males) is usually effective to reduce the prevalence of the infection. Yet, this may be due to the fact that the health risks associated with STIs are considerably higher for females in comparison with men. This is considered in the solution of our optimal control problem using the weight parameters in the objective functional.

As with the majority of studies, we considered some simplifying modeling assumptions that can be improved in further studies. First, we assumed that single-dose vaccination is enough to reach full immunity. Nevertheless, a two-dose series is often needed and there might be a delay of some days (or weeks) to achieve full immunity. Second, we assumed that susceptible individuals are easily identified for a prophylactic vaccine that lacks therapeutic effects and in therefore not effective in already infected individuals. In the contrary case, some vaccines can be misdirected in the infected population. Finally, we have considered a heterosexual population but inclusion of individuals with another sexual orientation can play a key role in disease dynamics. Future investigations are necessary to validate if the principal properties of the optimal vaccination policies drawn from this study are affected when these assumptions are relaxed.

Competing interests

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

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