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ORIGINAL ARTICLE

A Dynamic Model to Assess Human Papillomavirus Vaccination Strategies in a Heterosexual Population Combined with Men Who have Sex with Men

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Abstract

Vaccination is effective in preventing human papillomavirus (HPV) infection. It is imperative to investigate who should be vaccinated and what the best vaccine distribution strategy is. In this paper, we use a dynamic model to assess HPV vaccination strategies in a heterosexual population combined with gay, bisexual, and other men who have sex with men (MSM). The basic reproduction numbers for heterosexual females, heterosexual males and MSM as well as their average for the total population are obtained. We also derive a threshold parameter, based on basic reproduction numbers, for model analysis. From the analysis and numerical investigations, we have several conclusions. (1) To eliminate HPV infection, the priority of vaccination should be given to MSM, especially in countries that have already achieved high coverage in females. The heterosexual population gets great benefit but MSM only get minor benefit from vaccinating heterosexual females or males. (2) The best vaccination strategy is to vaccinate MSM firstly as many as possible, then heterosexual females, lastly heterosexual males. (3) Given a fixed vaccination coverage of MSM, distributing the remaining vaccines to only heterosexual females or males leads to a similar prevalence in the total population. This prevalence is lower than that when vaccines are distributed to both genders. The evener the distribution, the higher the prevalence in the total population. (4) Vaccination becomes less effective in reducing the prevalence as more vaccines are given. It is more effective to allocate vaccines to a region with lower vaccination coverage. This study provides information that may help policymakers formulate guidelines for vaccine distribution to reduce HPV prevalence on the basis of vaccine availability and prior vaccination coverage. Whether these guidelines are affected when the objective is to reduce HPV-associated cancer incidence remains to be further studied.

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Extended author information available on the last page of the article

Keywords HPV · Sexual transmission · MSM · Dynamic model · Vaccination strategy

1 Introduction

Human papillomavirus (HPV) is a group of common viruses mainly transmitted through sexual contact. Most sexually active people acquire HPV infection at some point of their lives, and some of them may be repeatedly infected. Most HPV infections will clear up without any intervention within several months after acquisition and about 90% clear up within 2 years (WHO 2019a). However, a small proportion of HPV infections with certain types can persist and progress to cancer. There are more than 100 types of HPV, among which at least 14 can cause cancer and are known as high-risk types. The others are low-risk types. In the high-risk-type group, the well-known types are HPV types 16 and 18, which cause 70% of cervical cancers and pre-cancerous cervical lesions (WHO 2019a). According to the US CDC data from 2013 to 2017, about 45,300 HPV-associated cancers occur each year, among which about 25,400 are in women and 19,900 are in men. Cervical cancer is the most common HPV-associated cancer in women, and oropharyngeal cancers are the most common in men. In the low-risk-type family, the most known types are HPV types 6 and 11, which cause 90% of genital warts and most RRP (recurrent respiratory papillomatosis). Although the infection with low-risk types rarely results in death, it may cause significant occurrence of disease and greatly affect people's life (WHO 2019a).

Vaccination is effective in preventing HPV infection. Three prophylactic vaccines against HPV infection are available. The bivalent, quadrivalent and 9-valent vaccine protect people from HPV types 16/18, 16/18/6/11 and 16/18/6/11/31/33/45/52/58, respectively. All these three vaccines have been proved to be safe, highly immunogenic and can induce strong protection against HPV and its sequelae (European Medicines Agency 2015; Schiller et al. 2012; Sankaranarayanan et al. 2016; Drolet et al. 2015). HPV vaccine was first licensed in 2006 in USA, and since then more than 100 countries have introduced HPV vaccine into their national schedule, among which many are developed countries (WHO 2019b). Vaccinating girls between ages of 9–14 is typically recommended by the WHO (2019a). In most countries, HPV vaccination programs only target pre-adolescent girls (and may also include catch-up programs for older females), but some countries, such as the USA and Australia, have begun to include boys (Centers for Disease Control and Prevention 2011; Georgousakis et al. 2012). The target population of HPV vaccination varies with time in many countries. In the US, from 2006 to 2009 routine vaccination was recommended for girls at age 11 or 12, and the series could be started at age 9. HPV vaccine was also recommended for women through age 26 who were not vaccinated previously. The reason for setting age 11 or 12 years as the target age group is that HPV vaccines are more effective if injected before potential exposure to HPV. In 2009, CDC added recommendation that males may be vaccinated at age 9–26 years. Although some adults aged 27 through 45 years might benefit from the vaccine if they have not been adequately vaccinated, the public health benefit of vaccination in this age range is minimal (Meites et al. 2019). In 2011, the recommendation for females was the same as before, but for males it changed.

Routine vaccination was recommended for boys at age 11 or 12, and series could be started at age 9. Vaccination was also recommended for males through age 21 who were not vaccinated before. Vaccination was specially recommended for gay, bisexual, and other men who have sex with men (MSM) through age 26 (Markowitz et al. 2018). Some other countries have also emphasized HPV vaccination for MSM, including UK, Australia, Ireland, etc. (Australian Government 2018; UK 2020; Ireland 2018). MSM constitute about 5.43% (95% CI 4.79% to 6.07%) of sexually active male population (Chen et al. 2013; Grey et al. 2016). Many studies show that HPV-related diseases are more common in MSM, especially in HIV-positive MSM, than in other populations (World Health Organization and Others 2017; Van Aar et al. 2013; Supindham et al. 2015; Yang et al. 2012; Gerend et al. 2016). There are also some papers suggesting that the government needs to offer HPV vaccine to MSM (Sauvageau and Dufour-Turbis 2016; Kirby 2015). How to choose the target population for HPV vaccination and what is the best strategy of vaccine distribution need to be further investigated.

Mathematical models have been widely used to investigate the spread and control of infectious diseases (Hethcote 2000; Brauer et al. 2008). Since HPV vaccine became available, mathematical models have been developed to study the epidemiological and economic consequences of HPV vaccination. For example, Elbasha formulated two-sex HPV vaccination models to assess the impact of HPV vaccine against HPV infection in heterosexual population (Elbasha 2006, 2008). The author found that if the reproduction number is greater than one, then the disease-free equilibrium is unstable and there exists a unique endemic equilibrium which is globally asymptotically stable; if the reproduction number is less than one, the disease-free equilibrium is globally asymptotically stable and HPV infection is predicted to be eliminated. Based on this model, Ribassin-Majed and Lounes developed another model to investigate the impact of quadrivalent HPV vaccine on the prevalence of HPV types 6/11 in French heterosexual males and females. Assuming the HPV vaccine coverage among females was 30%, the model suggested that after applying vaccination for 10 years, the prevalence of HPV types 6/11 in females would be halved and the prevalence in males could be reduced by one quarter. They also showed that HPV types 6/11 could be eradicated if vaccine coverage in females is kept above 12% (Ribassin-Majed et al. 2014). Another model considering the vaccination against multiple HPV types, also formulated by Elbasha, demonstrated that if interactions among HPV types are synergistic, mass vaccination might reduce the prevalence of types which are not even included in the vaccine (Elbasha and Galvani 2005). Some models have also been used to investigate the impact of HPV vaccine on HPV infection and cervical cancer (Sharomi and Malik 2017), the effect of treatment and vaccination on HPV transmission dynamics (Omame et al. 2018). Smith et al. included age structure in an HPV model (Smith et al. 2011). Llamazares and Smith addressed the question of whether the provincial health care in Canada should pay for voluntary adult vaccination (Llamazares and Smith 2008). Riesen et al. investigated the consequences of regional heterogeneity in HPV vaccine uptake on the transmission in Switzerland (Riesen et al. 2017). All these dynamic models only considered the heterosexual population.

In this article, we will develop a dynamic model to investigate the vaccine distribution strategy for preventing HPV infection in a heterosexual population combined with MSM. In Sect. 2, we formulate the mathematical model. Sections 3 and 4 are

devoted to the analysis of the model without and with vaccination. We define the basic reproduction numbers for heterosexual females, heterosexual males and MSM, and provide their biological explanations. We also derive a threshold parameter and use it to study the stability of the equilibrium points. In Sect. 5, we conduct numerical simulations to evaluate the influence of HPV vaccination on the prevalence of HPV infection and investigate the best vaccine distribution strategy. Section 6 is our conclusion and discussion.

2 Model Formulation

In this section, we develop a mathematical model to study the transmission of HPV infection in a heterosexually active population with sexually active MSM. The population is divided into three subgroups, namely, heterosexual females, heterosexual males and MSM. We use subscripts f, m and M to denote them, respectively. Note that MSM may also have sex with heterosexual females. In each subgroup, the population is divided into three classes: susceptible (S_k), vaccinated (V_k) and infectious individuals (I_k), where $k = f, m, M$.

In the absence of vaccination, we assume that humans become sexually active and enter the susceptible compartment S_k with the recruitment rate Λ_k. They leave all compartments at a rate μ_k. Susceptible individuals are infected by HPV with the force of infection λ_k. Upon infection, the host moves to the infectious compartment I_k. Infected people can clear infection at a rate δ_k. Recovery from many virus infections can provide protection against future exposure and reinfection. However, for HPV a number of studies have shown that reinfection is common. For example, the Ref. Ranjeva et al. (2017) shows that there is no evidence for homologous immunity in men. Instead, it finds that infection with one HPV type strongly increases the risk of infection with that type for years afterward. The paper Moscicki et al. (2012) shows that the prevalence rates in men are steady across all ages, which suggests that men following recovery do not develop protection against reinfection. The study Trottier et al. (2010) shows that reinfection with the same HPV type is also common in women. Natural immunity does not play a role in controlling the extent of reinfections. For MSM, a recent study finds no evidence of HPV16 natural immunity protecting against subsequent HPV16 infection (Beachler et al. 2018). In view of these studies, we developed models based on the SIS (susceptible–infected–susceptible) structure, which was also used in some other HPV modeling studies such as Ref. Ribassin-Majed et al. (2014).

In the model with vaccination, we assume that a fraction ($\phi_k, k = f, m, M$) of susceptibles are vaccinated and that vaccine-induced immunity doesn't wane during the sexually active period. Vaccine offers a degree of protection τ regardless of the sexual orientation. Thus, the probability of a vaccinated person getting infected and moving to the infected compartment I_k is $1 - \tau$ with $0 \leq \tau \leq 1$. We also assume that all infected individuals, vaccinated or not, can clear infection and become susceptible at a rate δ_k . The model is described by the following system of differential equations.

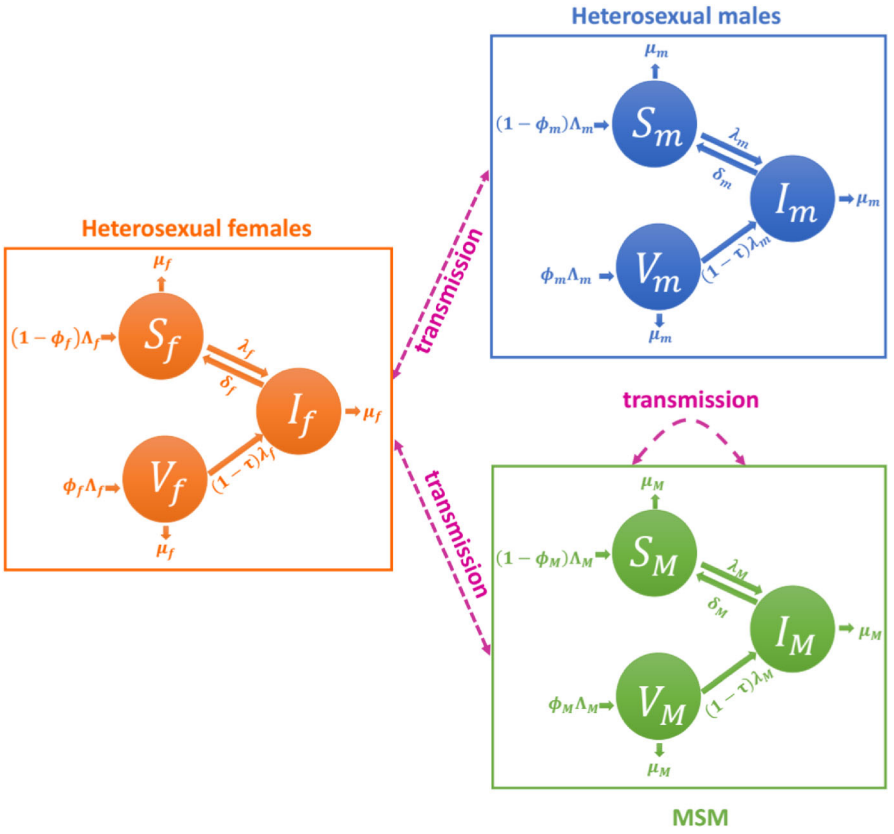

Fig. 1 Flow diagram of the model of HPV infection with vaccination. Each group (heterosexual females, males and MSM, denoted by f, m and M, respectively) is divided into three classes: susceptible, infectious and vaccinated, denoted by S, I and V, respectively. In addition to the transmission within their own group, MSM are also assumed to infect heterosexual females (Color figure online)

A schematic diagram of the model is shown in Fig. 1.

$$\begin{cases} S'_f(t) = (1-\phi_f)\Lambda_f - \lambda_f S_f + \delta_f I_f - \mu_f S_f, \\ V'_f(t) = \phi_f \Lambda_f - (1-\tau)\lambda_f V_f - \mu_f V_f, \\ I'_f(t) = \lambda_f S_f + (1-\tau)\lambda_f V_f - (\delta_f + \mu_f) I_f, \\ S'_m(t) = (1-\phi_m)\Lambda_m - \lambda_m S_m + \delta_m I_m - \mu_m S_m, \\ V'_m(t) = \phi_m \Lambda_m - (1-\tau)\lambda_m V_m - \mu_m V_m, \\ I'_m(t) = \lambda_m S_m + (1-\tau)\lambda_m V_m - (\delta_m + \mu_m) I_m, \\ S'_M(t) = (1-\phi_M)\Lambda_M - \lambda_M S_M + \delta_M I_M - \mu_M S_M, \\ V'_M(t) = \phi_M \Lambda_M - (1-\tau)\lambda_M V_M - \mu_M V_M, \\ I'_M(t) = \lambda_M S_M + (1-\tau)\lambda_M V_M - (\delta_M + \mu_M) I_M. \end{cases} \tag{1}$$

The force of infection is given by

$$\lambda_f = \frac{c_{mf}\beta_{mf}I_m + c_{Mf}\beta_{Mf}I_M}{N_f}, \quad \lambda_m = \frac{c_{fm}\beta_{fm}I_f}{N_m},$$
$$\lambda_M = \frac{c_{MM}\beta_{MM}I_M + c_{fM}\beta_{fM}I_f}{N_M},$$

where $N_k = S_k + V_k + I_k$, $k = f, m, M$. Descriptions of all the variables and parameters of system (1) can be found in Table 1.

If we take the sum of S_k, V_k and I_k in system (1), we get $N_k' = \Lambda_k - \mu_k N_k$, $k = f, m, M$. Thus, the equilibrium of N_k is Λ_k/μ_k. At equilibrium, we analyze the limiting system where N_k in (1) is replaced by its equilibrium. The domain of the system is

$$D = \{(S_f, V_f, I_f, S_m, V_m, I_m, S_M, V_M, I_M) \in \Re_+^9 : S_k + V_k + I_k \leq \Lambda_k/\mu_k, k = f, m, M\}.$$

It can be verified that D is positively invariant for system (1). The model is both epidemiologically and mathematically well posed (see "Appendix A").

Remark 1 For sexually transmitted diseases, the number of partners for one individual per unit of time can be considered as a constant. Thus, it is reasonable to model transmission by the standard incidence $c\beta\frac{S}{N}I$, where c is the contact rate, β is the transmission probability per contact, and S, I, N represent susceptible, infected and total population, respectively (Martcheva 2015). In an entirely susceptible population (i.e., $S/N = 1$), $c\beta$ represents the number of secondary cases generated by one infectious individual (i.e., $I = 1$) per unit time. Similarly, one can use $c_m\beta_m\frac{S_f}{N_f}I_m$ and $c_f\beta_f\frac{S_m}{N_m}I_f$ to describe the new infection of females and males, respectively, where the subscript m (or f) in parameters c and β represents the transmission from male to female (or from female to male). In some two-sex models (Elbasha 2006; Ribassin-Majed et al. 2014; Sharomi and Malik 2017; Omame et al. 2018), $c_f\beta_m\frac{I_m}{N_m}S_f$ and $c_m\beta_f\frac{I_f}{N_f}S_m$ were used to model the infection of females and males, respectively. If the model only involves heterosexual population, these two methods of modeling infection are equivalent in view of the consistency condition $c_f N_f = c_m N_m$ (Elbasha 2006; Sharomi and Malik 2017; Omame et al. 2018). Our model includes heterosexual populations and MSM and we also assume that MSM can have sex with heterosexual females. Thus, $c_f N_f = c_m N_m$ does not hold in our model. We follow the first method to describe the force of infection. For example, we use $c_{mf}\beta_{mf}\frac{S_f}{N_f}I_m$ to describe the number of secondary infected heterosexual females generated by infectious heterosexual males per unit of time. Using this rate, $c_{mf}\beta_{mf}$ represents the number of secondary infected heterosexual females generated by one infectious heterosexual male in an entirely susceptible heterosexual female population per unit of time. Similar explanation can be given for the force of infection induced by heterosexual female and MSM.

Table 1 Description of variables and parameters

Symbol	Description	Baseline	Unit	Range	Source
Subscripts					
f	Heterosexual female				
m	Heterosexual male				
M	MSM				
k	Gender/sexual orientation ($k = f, m, M$)				
Variables					
$S_k(t)$	Susceptible sexually active population of gender k				
$V_k(t)$	Vaccinated sexually active population of gender k				
$I_k(t)$	Infected sexually active population of gender k				
$N_k(t)$	Total size of sexually active population of gender k				
λ_k	Force of infection for gender k				
Parameters					
Λ_f (Λ_m)	New recruits into heterosexually active females (males)	10^5	person/year	[80,000, 120,000]	Example
Λ_M	New recruits into sexually active MSM	5000	person/year	[4000, 6000]	See text
μ_k	Exit rate from the sexually active population of gender k	$\frac{1}{10}$	1/year	$\left[\frac{1}{12}, \frac{1}{8}\right]$	See text
c_{mf}	The average number of heterosexual female partners for one heterosexual male per year	2.5	person/year	[2.1, 2.9]	See text
c_{Mf}	The average number of heterosexual female partners for one MSM per year	0.4	person/year	[0.3, 0.5]	See text
c_{fm}	The average number of heterosexual male partners for one heterosexual female per year	1.8	person/year	[1.4, 2.2]	See text
c_{MM}	The average number of MSM partners for one MSM per year	2.8	person/year	[2.4, 3.2]	See text
c_{fM}	The average number of MSM partners for one heterosexual female per year	0.2	person/year	[0.02, 0.4]	See text
β_{mf}	Transmission probability per partnership from heterosexual male to heterosexual female	0.25	1/person	[0.15, 0.3]	See text
β_{Mf}	Transmission probability per partnership from MSM to heterosexual female	0.05	1/person	[0.03, 0.07]	See text

Table 1 continued

Symbol	Description	Baseline	Unit	Range	Source
β_{fm}	Transmission probability per partnership from heterosexual female to heterosexual male	0.7	1/person	[0.6, 0.8]	See text
β_{MM}	Transmission probability per partnership from MSM to MSM	0.75	1/person	[0.6, 0.89]	See text
β_{fM}	Transmission probability per partnership from heterosexual female to MSM	0.14	1/person	[0.1, 0.18]	See text
δ_k	Recovery rate from infection for gender k	0.55	1/year	[0.5, 0.6]	Marino et al. (2008)
τ	Degree of protection by vaccine	0.9	None	[0.8, 0.95]	Ribassin-Majed et al. (2014)
ϕ_k	Percentage of new recruits vaccinated for gender k	Varied	None		
v	Amount of vaccines ($v = \phi_f \Lambda_f + \phi_m \Lambda_m + \phi_M \Lambda_M$)	Varied	person/year		
$dummy$	Parameter for comparison in PRCC	1	None	[1, 10]	See text

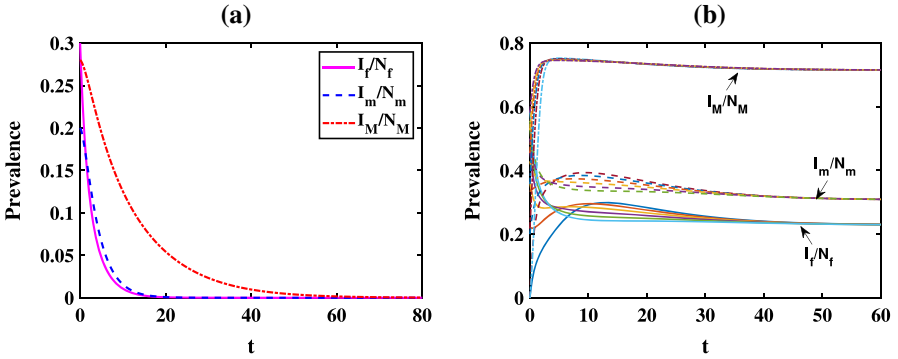

Fig. 2 Predicted dynamics of the prevalence by model (2). The threshold R_0 for **a** and **b** is 0.8615 and 3.2308, respectively. Panel **a** shows that the disease dies out and **b** shows that the solutions converge to the same endemic equilibrium given different initial conditions. Parameter values are **a**: $\beta_{mf} = 0.08$, $\beta_{Mf} = 0.04$, $\beta_{fm} = 0.25$, $\beta_{MM} = 0.2$, $\beta_{fM} = 0.05$; **b**: $\beta_{mf} = 0.25$, $\beta_{Mf} = 0.05$, $\beta_{fm} = 0.7$, $\beta_{MM} = 0.75$, $\beta_{fM} = 0.14$. The other parameters are the same: $\Lambda_f = \Lambda_m = 100{,}000$, $\Lambda_M = 5000$, $\mu_f = \mu_m = \mu_M = 0.1$, $c_{mf} = 2.5$, $c_{Mf} = 0.4$, $c_{fm} = 1.8$, $c_{MM} = 2.8$, $c_{fM} = 0.2$, $\delta_f = \delta_m = \delta_M = 0.55$ (see text for description). The initial condition for **a** is $(S_f, V_f, I_f, S_m, V_m, I_m, S_M, V_M, I_M) = (3{,}500{,}000, 0, 1{,}500{,}000, 4{,}000{,}000, 0, 1{,}000{,}000, 180{,}000, 0, 70{,}000)$ (Color figure online)

3 Analysis of the Model Without Vaccination

We start the analysis by considering the model in the absence of vaccination. In this case, $\phi_k = 0$ and $V_k \equiv 0$ for $k = f, m, M$. The model reduces to the following

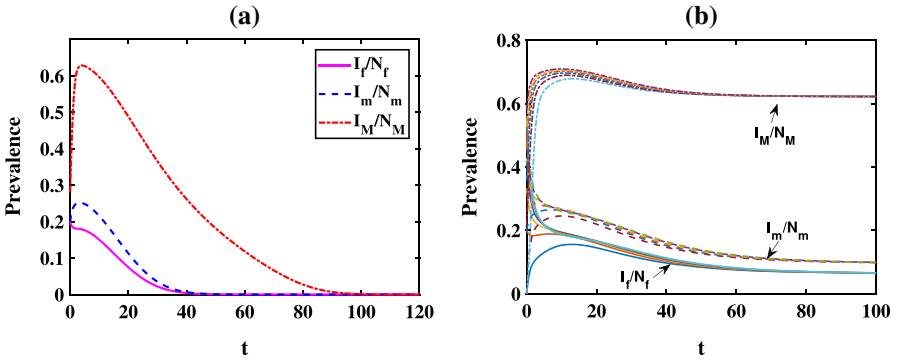

Fig. 3 Predicted dynamics of the prevalence by model (1) with vaccination. The threshold R_0 for panel **a** and **b** is 0.6138 and 2.6492, respectively. The proportion of vaccination for each group is **a**: $\phi_f = 0.7$, $\phi_m = 0.5$, $\phi_M = 0.9$; **b**: $\phi_f = 0.3$, $\phi_m = 0.15$, $\phi_M = 0.2$. The other parameters are the same: $\Lambda_f = \Lambda_m = 100{,}000$, $\Lambda_M = 5000$, $\mu_f = \mu_m = \mu_M = 0.1$, $c_{mf} = 2.5$, $c_{Mf} = 0.4$, $c_{fm} = 1.8$, $c_{MM} = 2.8$, $c_{fM} = 0.2$, $\beta_{mf} = 0.25$, $\beta_{Mf} = 0.05$, $\beta_{fm} = 0.7$, $\beta_{MM} = 0.75$, $\beta_{fM} = 0.14$, $\delta_f = \delta_m = \delta_M = 0.55$, $\tau = 0.9$. The initial condition for **a** is $(S_f, V_f, I_f, S_m, V_m, I_m, S_M, V_M, I_M) = (3{,}200{,}000, 800{,}000, 1{,}000{,}000, 3{,}500{,}000, 500{,}000, 1{,}000{,}000, 150{,}000, 30{,}000, 70{,}000)$ (Color figure online)

$$\begin{cases} S_f'(t) = \Lambda_f - \lambda_f S_f + \delta_f I_f - \mu_f S_f, \\ I_f'(t) = \lambda_f S_f - (\delta_f + \mu_f) I_f, \\ S_m'(t) = \Lambda_m - \lambda_m S_m + \delta_m I_m - \mu_m S_m, \\ I_m'(t) = \lambda_m S_m - (\delta_m + \mu_m) I_m, \\ S_M'(t) = \Lambda_M - \lambda_M S_M + \delta_M I_M - \mu_M S_M, \\ I_M'(t) = \lambda_M S_M - (\delta_M + \mu_M) I_M, \end{cases} \tag{2}$$

where λ_f, λ_m and λ_M are the same as before, and $N_k = S_k + I_k,\ k = f, m, M$.

3.1 Basic Reproduction Numbers

We define

$$R_{0,mf} = \frac{c_{mf}\beta_{mf}}{\delta_m + \mu_m}, \quad R_{0,Mf} = \frac{c_{Mf}\beta_{Mf}}{\delta_M + \mu_M}, \quad R_{0,fm} = \frac{c_{fm}\beta_{fm}}{\delta_f + \mu_f},$$
$$R_{0,MM} = \frac{c_{MM}\beta_{MM}}{\delta_M + \mu_M}, \quad R_{0,fM} = \frac{c_{fM}\beta_{fM}}{\delta_f + \mu_f}.$$

From Remark 1, we know that $c_{mf}\beta_{mf}$ represents the number of secondary infected heterosexual females generated by one infected heterosexual male in an entirely susceptible heterosexual female population per unit of time. Multiplying it by $1/(\delta_m + \mu_m)$, the duration of heterosexual males in the infectious stage, leads to the basic reproduction number $R_{0,mf}$, i.e., the total number of secondary infected heterosexual females generated by one infected heterosexual male during the whole

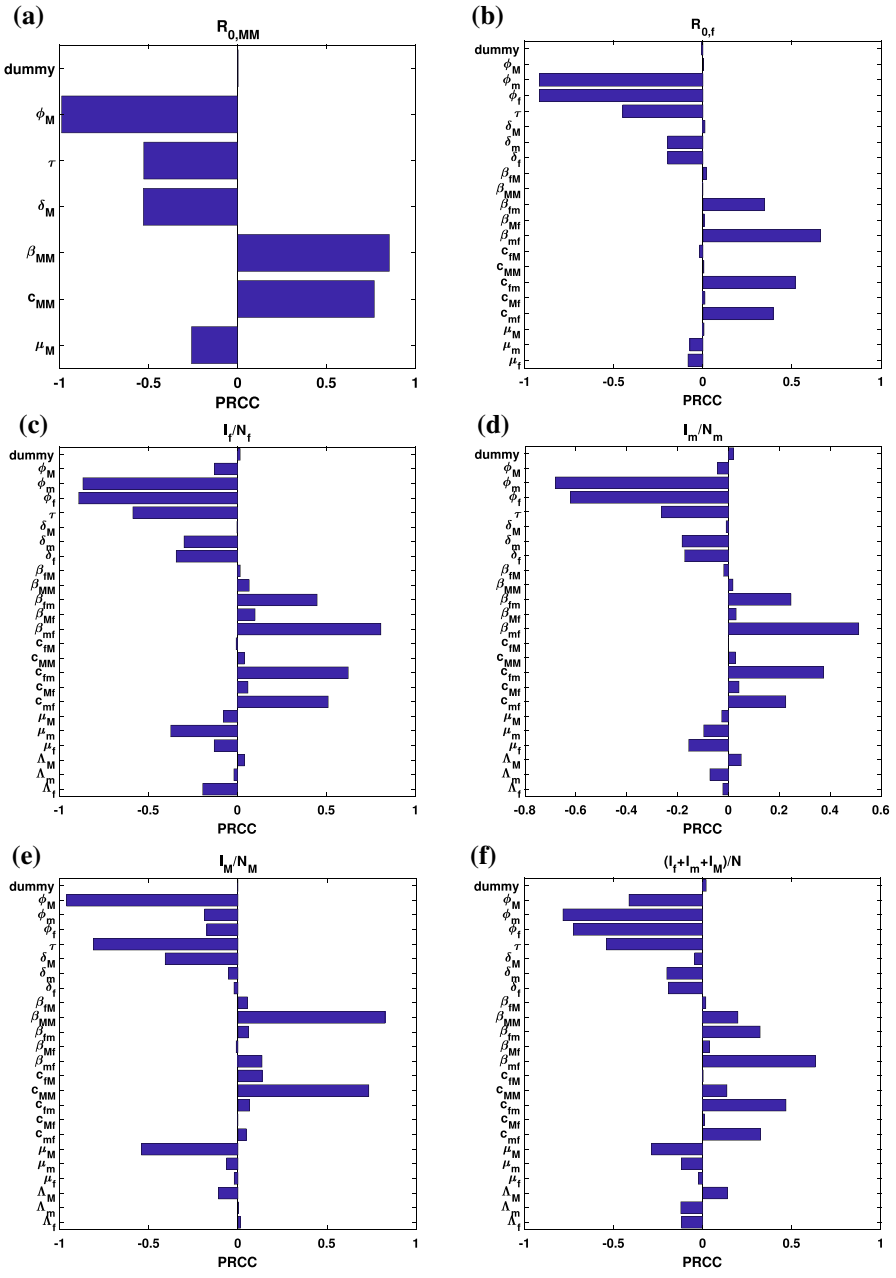

Fig. 4 Sensitivity analysis using PRCC. In the analysis of $R_{0,f}$, we choose 0.5, 0.5, 0.92 as base values for ϕ_f, ϕ_m, ϕ_M, respectively, and [0.01, 0.99], [0.01, 0.99], [0.88, 0.99] as their ranges. In other panels, we choose 0.5, 0.5, 0.5 as base values for ϕ_f, ϕ_m, ϕ_M, respectively, and [0.01, 0.99], [0.01, 0.99], [0.01, 0.99] as their ranges. The other parameters are from Table 1. The initial conditions for **c**–**f** are the same as those in Fig. 2a, and the end time is 40 years (Color figure online)

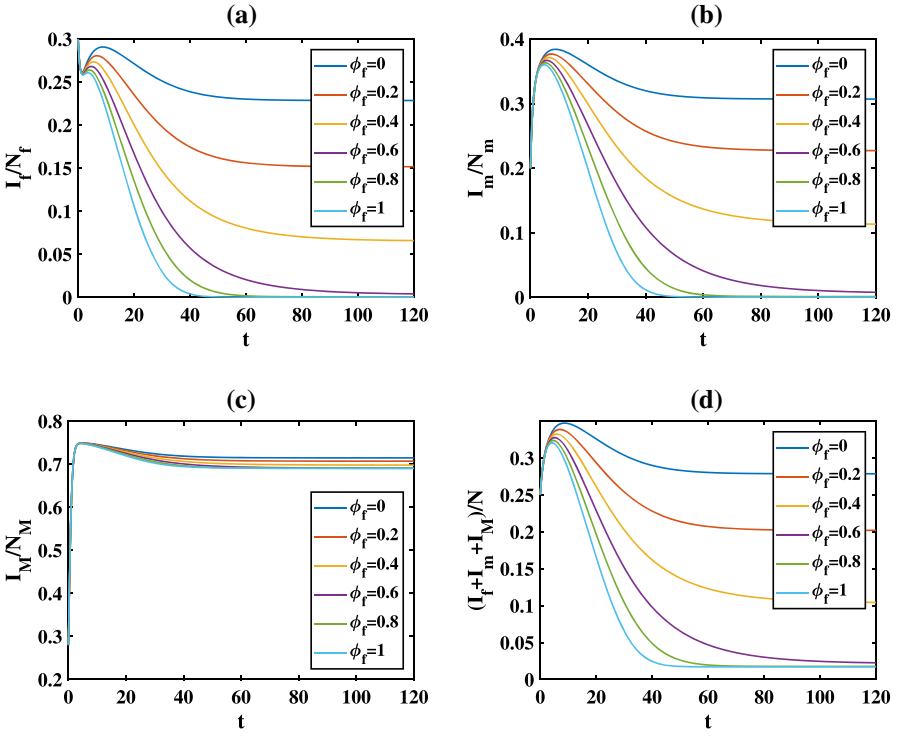

Fig. 5 The influence of only vaccinating females on the prevalence in **a** heterosexual females, **b** heterosexual males, **c** MSM, and **d** the total population. The proportion of female vaccination ϕ_f is varying and $\phi_m = \phi_M = 0$. The other parameters are the same as those in Fig. 3. The initial conditions for all the four graphs are the same as those in Fig. 2a (Color figure online)

infectious period in an entirely susceptible heterosexual female population. We have similar explanations for $R_{0,Mf}$, $R_{0,fm}$, $R_{0,MM}$ and $R_{0,fM}$.

System (2) always has the disease-free equilibrium (DFE) $E_0 = (S_f^0, 0, S_m^0, 0, S_M^0, 0)$, where $S_f^0 = \frac{\Lambda_f}{\mu_f}$, $S_m^0 = \frac{\Lambda_m}{\mu_m}$, $S_M^0 = \frac{\Lambda_M}{\mu_M}$. By linearizing system (2) at the DFE and studying its local asymptotic stability (see next section), we derive the following threshold parameter

$$R_0 = \max\left\{R_{0,MM},\, R_{0,fm}R_{0,mf} + R_{0,fM}\frac{1}{1-R_{0,MM}}R_{0,Mf}\right\}$$

with $R_{0,MM} \neq 1$. We will show that R_0 also determines the existence of the endemic equilibrium.

When $R_{0,MM} < 1$, according to transmission routes, we define

$$R_{0,f} = R_{0,fm}R_{0,mf} + R_{0,fM}\sum_{n=0}^{\infty} R_{0,MM}^n R_{0,Mf},$$

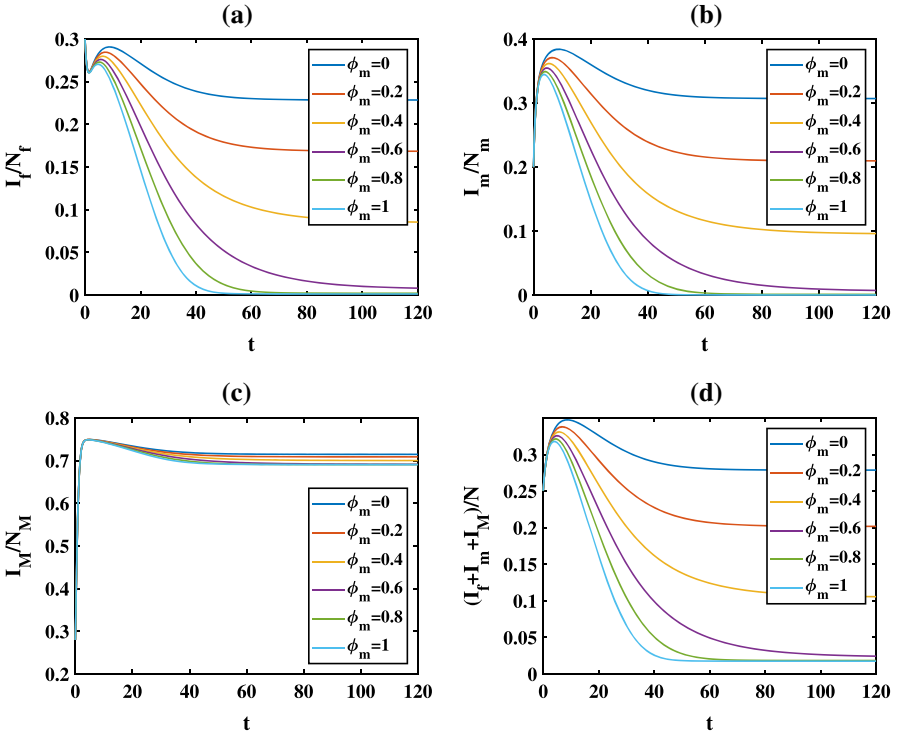

Fig. 6 The influence of only vaccinating heterosexual males on the prevalence. The parameter ϕ_m is varying but $\phi_f = \phi_M = 0$. The other parameters are the same as those in Fig. 3. The initial conditions for all the four graphs are the same as those in Fig. 2a (Color figure online)

$$R_{0,m} = R_{0,mf}\left(1 + R_{0,fM}\sum_{n=0}^{\infty} R_{0,MM}^{n} R_{0,Mf}\right) R_{0,fm},$$
$$R_{0,M} = R_{0,MM} + R_{0,Mf}(1 + R_{0,fm}R_{0,mf})R_{0,fM}.$$

$R_{0,f}$ is the basic reproduction number for heterosexual females, which can be explained as follows. From the biological meaning of $R_{0,fm}$, $R_{0,mf}$, $R_{0,fM}$, $R_{0,MM}$ and $R_{0,Mf}$ explained above, we know that $R_{0,fm}R_{0,mf}$ is the number of secondary infected heterosexual females generated by one infected heterosexual female through heterosexual males in an entirely susceptible heterosexual female and heterosexual male population during the infected heterosexual female's whole infectious period. Similarly, $R_{0,fM}\sum_{n=0}^{\infty} R_{0,MM}^{n} R_{0,Mf}$ is the number of secondary infected heterosexual females generated by one infected heterosexual female through MSM in an entirely susceptible heterosexually female and MSM population during the infected heterosexual female's whole infectious period. Thus, $R_{0,fm}R_{0,mf}+R_{0,fM}\sum_{n=0}^{\infty} R_{0,MM}^{n} R_{0,Mf}$ is the number of secondary infected heterosexual females generated by one infected heterosexual female in an entirely susceptible population during the infected heterosexual female's whole infectious period. This explains that $R_{0,f}$ is the basic

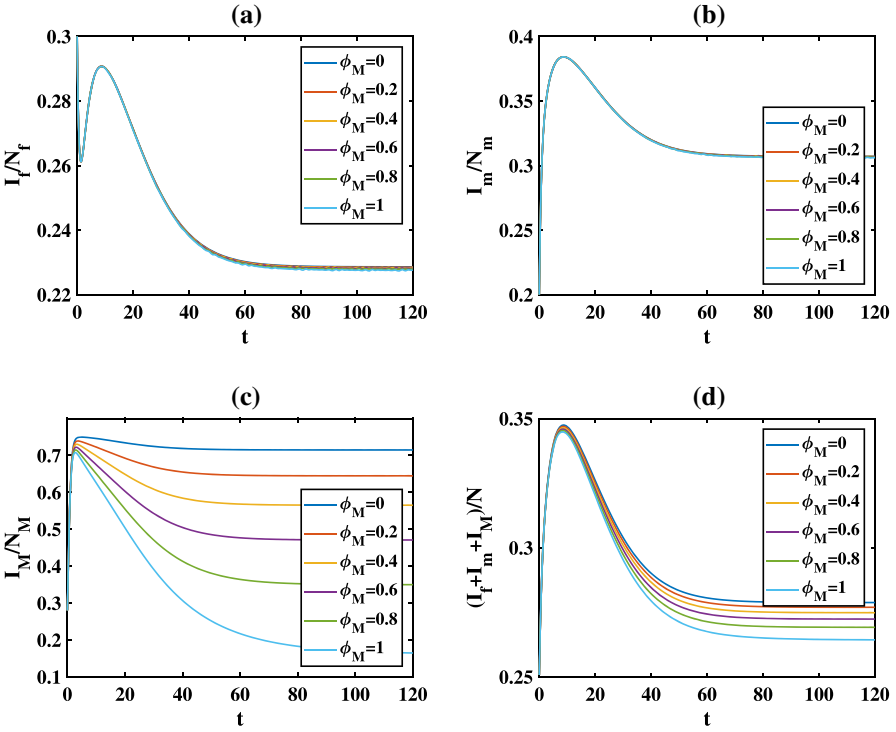

Fig. 7 The influence of only vaccinating MSM on the prevalence (ϕ_M is varying but $\phi_f = \phi_m = 0$). The other parameters are the same as those in Fig. 3. The initial conditions for all the four graphs are the same as those in Fig. 2a (Color figure online)

reproduction number for heterosexual females. Similarly, we can explain that $R_{0,m}$ is the basic reproduction number for heterosexual males and $R_{0,M}$ is the basic reproduction number for MSM.

When $R_{0,MM} < 1$, we further define

$$\overline{R}_0 = \frac{R_{0,f} + R_{0,m} + R_{0,M}}{3}$$

to be the average basic reproduction number, which represents the average number of secondary cases generated by one infectious individual during the whole infectious period in an entirely susceptible population.

We have the following results regarding these basic reproduction numbers. Propositions 1 and 3 are proved in "Appendices B, C," respectively. Proposition 2 is trivial by calculating the sum of series when $R_{0,MM} < 1$. From Proposition 2, we also have that when $R_{0,MM} < 1$, $R_0 = \max\{R_{0,MM}, R_{0,f}\}$.

Proposition 1 *If $R_{0,MM} > 1$, then the infection of MSM is uniformly weakly endemic.*

Proposition 2 *If $R_{0,MM} < 1$, then $R_{0,f} = R_{0,fm}R_{0,mf} + R_{0,fM}\frac{1}{1-R_{0,MM}}R_{0,Mf}$.*

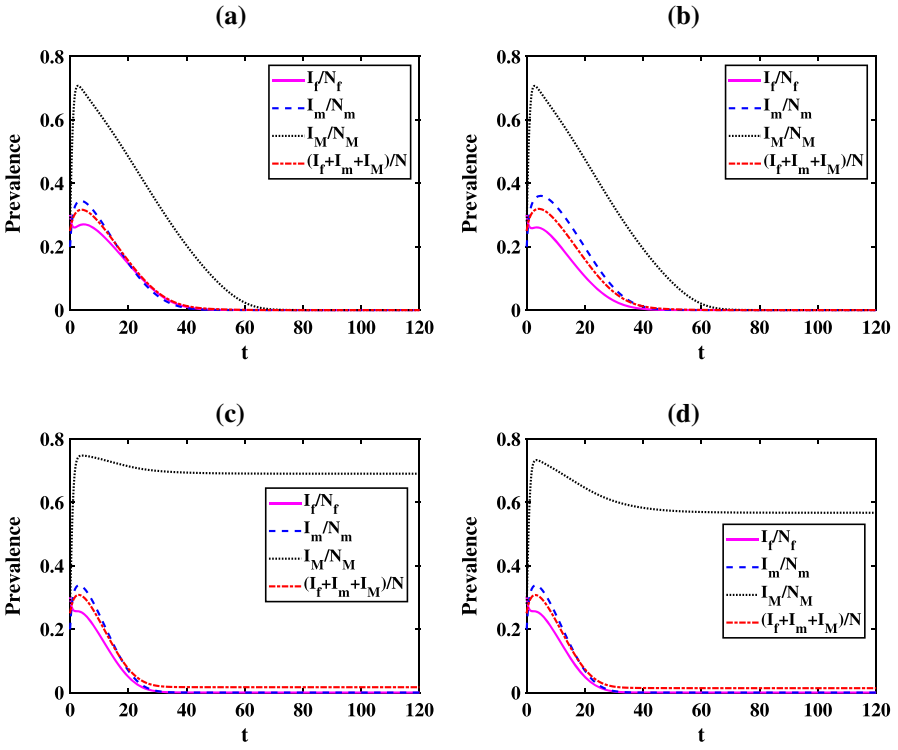

Fig. 8 The influence of vaccinating different groups on the prevalence. **a**: $\phi_m = \phi_M = 1$, $\phi_f = 0$; **b**: $\phi_f = \phi_M = 1$, $\phi_m = 0$; **c**: $\phi_f = \phi_m = 1$, $\phi_M = 0$; **d**: $\phi_f = \phi_m = 1$, $\phi_M = 0.3$. The other parameters are the same as those in Fig. 3. The initial conditions for all the four graphs are the same as those in Fig. 2a. The graphs in **a** and **b** show that the disease will die out if MSM and either heterosexual males or females are all vaccinated. The graphs in **c** and **d** show the disease won't die out even when all heterosexual females and males are vaccinated but MSM are not sufficiently vaccinated (Color figure online)

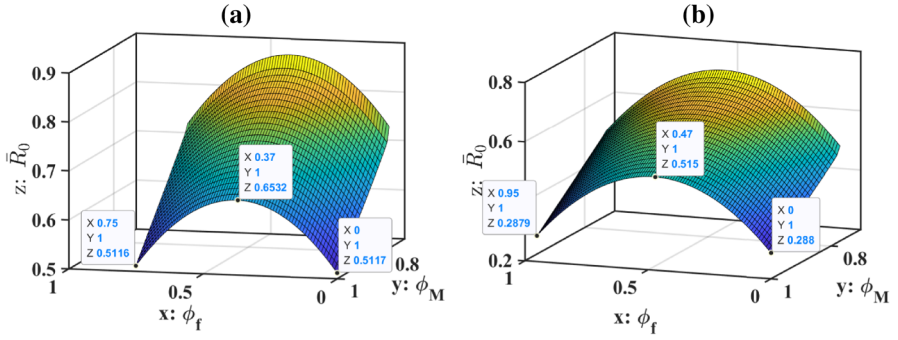

Fig. 9 The average basic reproduction number with different vaccine distributions. The total amount of vaccine is fixed in **a**: $v = 80{,}000$ and **b**: $v = 100{,}000$. The vaccination proportion of heterosexual males ϕ_m can be calculated according to ϕ_f, ϕ_M, and the total vaccine amount v (Sect. 5.4). The other parameters are the same as those in Fig. 3 (Color figure online)

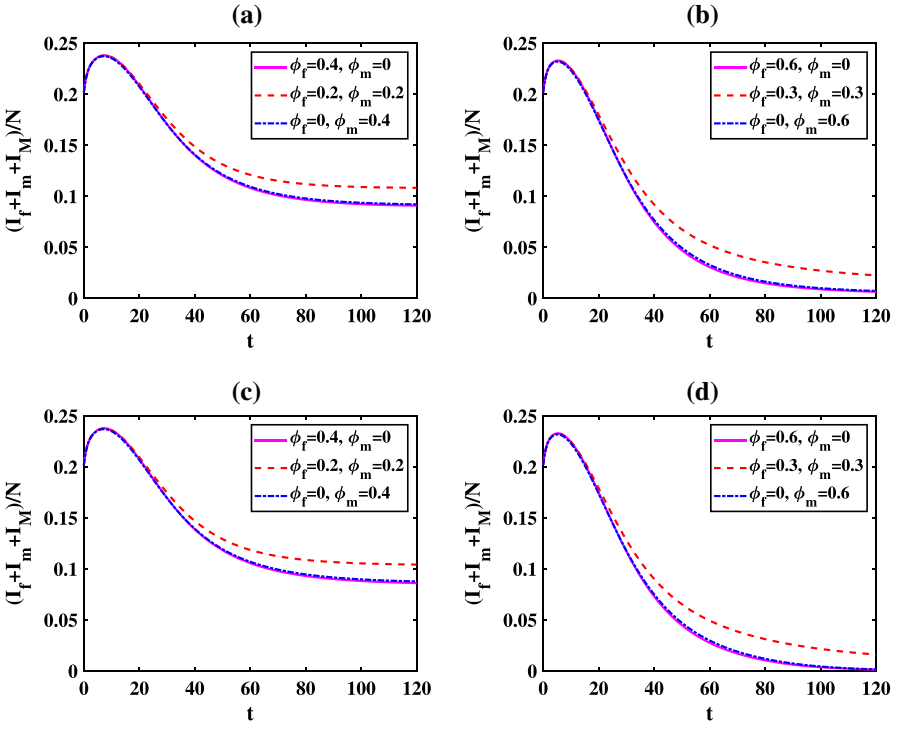

Fig. 10 Prevalence in the total population with different vaccine distributions. The vaccination proportion of MSM is fixed in **a**, **b**: $\phi_M = 0.8$ and **c**, **d**: $\phi_M = 0.9$. The other parameters are the same as those in Fig. 3. The initial conditions for all the four graphs are the same as those in Fig. 3a (Color figure online)

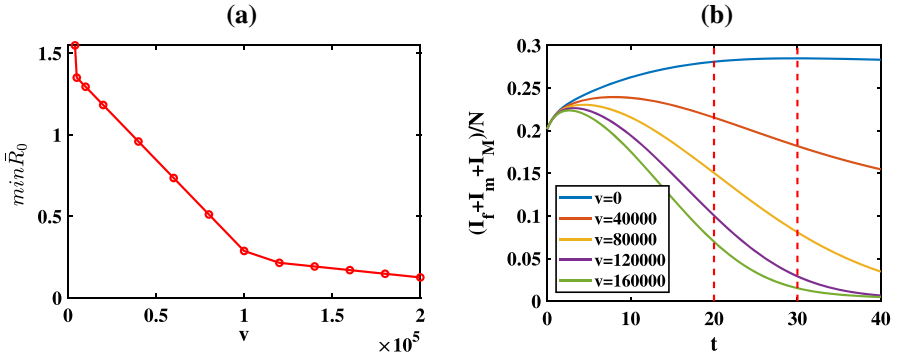

Fig. 11 The effect of increasing vaccine availability. Panel **a** shows the change of the minimum of the average basic reproduction number as the vaccine availability increases. Panel **b** shows the prevalence change in the total population with a fixed vaccine amount applying the best vaccination strategy. The other parameters for **b** are the same as those in Fig. 3. The initial condition for **b** is the same as that in Fig. 3a (Color figure online)

Proposition 3 *If $R_{0,MM} < 1$, then $R_{0,f} < 1$ is a sufficient condition for $R_{0,m} < 1$ and $R_{0,M} < 1$.*

3.2 Equilibria and Stability

For the stability of the disease-free equilibrium and existence of the endemic equilibrium, we have the following results. Theorems 1 and 3 are proved in the online supplementary material. Theorem 2 is proved in "Appendix D."

Theorem 1 (i) *Suppose that $R_{0,MM} \neq 1$. When $R_0 < 1$, the DFE E_0 is locally asymptotically stable; when $R_0 > 1$ and $R_{0,fm}R_{0,mf} + R_{0,fM}\dfrac{1}{1-R_{0,MM}}R_{0,Mf} \neq 1$, E_0 is unstable. Here the second inequality is actually $R_{0,f} \neq 1$ when $R_{0,MM} < 1$.*
(ii) *When $R_{0,MM} = 1$, E_0 is unstable.*

Considering the limiting system, in which $N_k = \Lambda_k/\mu_k$ is a constant, we have the following global result.

Theorem 2 *Suppose that $R_{0,MM} \neq 1$. When $R_0 \leq 1$, the DFE E_0 is globally asymptotically stable.*

Theorem 3 (i) *Suppose that $R_{0,MM} \neq 1$. When $R_0 > 1$, the endemic equilibrium exists;*
(ii) *When $R_{0,MM} = 1$, the endemic equilibrium exists.*

Because of the complexity of the model, it is challenging to analytically study the uniqueness and stability of the endemic equilibrium. According to the numerical simulations under different initial conditions shown later (Fig. 2b), the endemic equilibrium might also be unique and globally asymptotically stable when it exists.

4 Analysis of the Model with Vaccination

In this section, we study model (1) with vaccination.

4.1 Basic Reproduction Numbers

We define

$$
\begin{aligned}
R_{0,mf}(\phi_f) &= \frac{c_{mf}\beta_{mf}}{\delta_m + \mu_m}[(1-\phi_f) + (1-\tau)\phi_f],\\
R_{0,Mf}(\phi_f) &= \frac{c_{Mf}\beta_{Mf}}{\delta_M + \mu_M}[(1-\phi_f) + (1-\tau)\phi_f],\\
R_{0,fm}(\phi_m) &= \frac{c_{fm}\beta_{fm}}{\delta_f + \mu_f}[(1-\phi_m) + (1-\tau)\phi_m],\\
R_{0,MM}(\phi_M) &= \frac{c_{MM}\beta_{MM}}{\delta_M + \mu_M}[(1-\phi_M) + (1-\tau)\phi_M],
\end{aligned}
$$

$$R_{0,fM}(\phi_M) = \frac{c_{fM}\beta_{fM}}{\delta_f + \mu_f}[(1-\phi_M) + (1-\tau)\phi_M].$$

To explain $R_{0,mf}(\phi_f)$, we rewrite it as

$$R_{0,mf}(\phi_f) = \frac{c_{mf}\beta_{mf}(1-\phi_f)}{\delta_m + \mu_m} + \frac{c_{mf}\beta_{mf}(1-\tau)\phi_f}{\delta_m + \mu_m}.$$

Recall that $\frac{c_{mf}\beta_{mf}}{\delta_m + \mu_m}$, i.e., $R_{0,mf}$ defined in Sect. 3.1, is the total number of secondary infected heterosexual females generated by one infected heterosexual male during the whole infectious period in an entirely susceptible heterosexual female population. Because $(1-\phi_f)$ is the proportion of unvaccinated in the susceptible heterosexual female population, the two terms in the right side of the above equation $R_{0,mf}(\phi_f)$ represent the contribution from unvaccinated (with transmission probability β_{mf}) and vaccinated (with reduced transmission probability $\beta_{mf}(1-\tau)$) susceptible heterosexual females, respectively. Similarly, we can explain $R_{0,Mf}(\phi_f)$, $R_{0,fm}(\phi_m)$, $R_{0,MM}(\phi_M)$ and $R_{0,fM}(\phi_M)$. When $\phi_f = \phi_m = \phi_M = 0$, they are reduced to the corresponding basic reproduction numbers defined in Sect. 3.1.

By setting the right-hand sides of the equations in system (1) to zero, we know that system (1) always has a DFE given by $\overline{E}_0 = (\overline{S}_f^0, \overline{V}_f^0, 0, \overline{S}_m^0, \overline{V}_m^0, 0, \overline{S}_M^0, \overline{V}_M^0, 0)$, where

$$\overline{S}_k^0 = (1-\phi_k)\frac{\Lambda_k}{\mu_k}, \quad \overline{V}_k^0 = \phi_k\frac{\Lambda_k}{\mu_k}, \quad k = f, m, M.$$

By linearizing system (1) around the DFE $\overline{E}_0$, we derive the following threshold quantity for the DFE to be locally asymptotically stable

$$R_0(\phi_f, \phi_m, \phi_M) = \max\left\{R_{0,MM}(\phi_M),\ R_{0,fm}(\phi_m)R_{0,mf}(\phi_f) + R_{0,fM}(\phi_M)\frac{1}{1-R_{0,MM}(\phi_M)}R_{0,Mf}(\phi_f)\right\}$$

with $R_{0,MM}(\phi_M) \neq 1$. As in the model without vaccination, we can define the *basic reproduction numbers* for heterosexual females, heterosexual males and MSM according to the transmission routes. When $R_{0,MM}(\phi_M) < 1$, we let

$$\begin{aligned} R_{0,f}(\phi_f, \phi_m, \phi_M) &= R_{0,fm}(\phi_m)R_{0,mf}(\phi_f) + R_{0,fM}(\phi_M) \\ &\quad \times \sum_{n=0}^{\infty} R_{0,MM}(\phi_M)^n R_{0,Mf}(\phi_f), \\ R_{0,m}(\phi_f, \phi_m, \phi_M) &= R_{0,mf}(\phi_f)(1 + R_{0,fM}(\phi_M) \\ &\quad \times \sum_{n=0}^{\infty} R_{0,MM}(\phi_M)^n R_{0,Mf}(\phi_f))R_{0,fm}(\phi_m), \end{aligned}$$

$$R_{0,M}(\phi_f, \phi_m, \phi_M) = R_{0,MM}(\phi_M) + R_{0,Mf}(\phi_f)(1 + R_{0,fm}(\phi_m R_{0,mf}(\phi_f))) \times R_{0,fM}(\phi_M).$$

$R_{0,k}(\phi_f, \phi_m, \phi_M)$ is the number of secondary infected individuals of gender k ($k = f, m, M$) generated by one infectious individual of gender k in an entirely susceptible population. It defines the basic reproduction number for gender k. We also define

$$\overline{R}_0(\phi_f, \phi_m, \phi_M) = \frac{R_{0,f}(\phi_f, \phi_m, \phi_M) + R_{0,m}(\phi_f, \phi_m, \phi_M) + R_{0,M}(\phi_f, \phi_m, \phi_M)}{3}$$

to be the *average basic reproduction number* when $R_{0,MM}(\phi_f, \phi_m, \phi_M) < 1$. It gives the average number of secondary cases generated by one infectious individual in an entirely susceptible population during the whole infectious period.

We have the following similar results as in Propositions 1–3. The proof is omitted.

Proposition 4 *If $R_{0,MM}(\phi_M) > 1$, then the infection of MSM is uniformly weakly endemic.*

Proposition 5 *If $R_{0,MM}(\phi_M) < 1$, then $R_{0,f}(\phi_f, \phi_m, \phi_M) = R_{0,fm}(\phi_m)R_{0,mf}(\phi_f) + R_{0,fM}(\phi_M)\frac{1}{1-R_{0,MM}(\phi_M)}R_{0,Mf}(\phi_f)$.*

Proposition 6 *If $R_{0,MM}(\phi_M) < 1$, then $R_{0,f}(\phi_f, \phi_m, \phi_M) < 1$ is a sufficient condition for $R_{0,m}(\phi_f, \phi_m, \phi_M) < 1$ and $R_{0,M}(\phi_f, \phi_m, \phi_M) < 1$.*

4.2 Equilibria and Stability

We have the following results on the local stability of the DFE. The proof is also omitted.

Theorem 4 (i) *Suppose that $R_{0,MM}(\phi_M) \neq 1$. When $R_0(\phi_f, \phi_m, \phi_M) < 1$, the DFE $\overline{E}_0$ is locally asymptotically stable; when $R_0(\phi_f, \phi_m, \phi_M) > 1$ and $R_{0,fm}(\phi_m)R_{0,mf}(\phi_f) + R_{0,fM}(\phi_M)\frac{1}{1-R_{0,MM}(\phi_M)}R_{0,Mf}(\phi_f) \neq 1$, $\overline{E}_0$ is unstable.* (ii) *When $R_{0,MM}(\phi_M) = 1$, $\overline{E}_0$ is unstable.*

Concerning the global stability of the DFE $\overline{E}_0$, it is challenging to find a proper Lyapunov function. However, using the Theorem by Castillo-Chavez and Song (2004) [also in Martcheva (2015)], we have the following result. The proof is given in "Appendix E." It is also challenging to analytically study the endemic equilibrium of the model with vaccination. From the simulations under different initial conditions (Fig. 3b), the endemic equilibrium might exist, be unique and also stable.

Proposition 7 *When $R_{0,MM}(\phi_M) \neq 1$, there is no backward bifurcation for system (1).*

Table 2 Best strategy for vaccine distribution

v	ϕ_f	ϕ_m	ϕ_M	$\min \overline{R}_0$
4000	0	0	0.8	1.5482
5000	0	0	1	1.3506
10,000	0.05	0	1	1.2947
20,000	0.15	0	1	1.1828
40,000	0.35	0	1	0.9590
60,000	0.55	0	1	0.7357
80,000	0.75	0	1	0.5116
100,000	0.95	0	1	0.2879
120,000	1	0.15	1	0.2152
140,000	1	0.35	1	0.1928
160,000	1	0.55	1	0.1705
180,000	1	0.75	1	0.1481
200,000	1	0.95	1	0.1257

5 Numerical Investigations

5.1 Parameter Setting and Simulation

Most of the parameter values are chosen from previous modeling papers and epidemiological literature. Since the transmission probability of HPV is much lower once people settle down and have fixed lifetime sexual partner, we focus on the period before settling down. The average age of the first sexual intercourse is around 18 (Wikipedia 2020), and the average first marriage age is around 28 (The Spruce 2019). Thus, we set $\mu_f = \mu_m = \mu_M = \frac{1}{10}$ year^{-1} as the base value with the range $\left[\frac{1}{12}, \frac{1}{8}\right]$ for sensitivity analysis. According to a survey by Nectar Sleep (Insider 2018), the average number of sexual partners is 26 for men and 19 for women before settling down. However, studies have also shown that men often increase their "number," while women decrease theirs when asked. Thus, in our simulation we assume that the average number of sexual partners for heterosexual males and females before settling down is 25 and 20, respectively. This number for MSM is assumed to be 32. We also assume that the probability for a heterosexual female to have MSM as sexual partner is $1/10$, and that the probability for an MSM to have heterosexual female as sexual partner is $1/8$. Therefore, we choose the following base values with unit person/year for parameters.

$$c_{mf} = \frac{25}{10} = 2.5, \quad c_{Mf} = \frac{32 \times \frac{1}{8}}{10} = 0.4, \quad c_{fm} = \frac{20 \times (1 - \frac{1}{10})}{10} = 1.8,$$
$$c_{MM} = \frac{32 \times (1 - \frac{1}{8})}{10} = 2.8, \quad c_{fM} = \frac{20 \times \frac{1}{10}}{10} = 0.2$$

We also set a range [2.1, 2.9] for c_{mf}, [0.3, 0.5] for c_{Mf}, [1.4, 2.2] for c_{fm}, [2.4, 3.2] for c_{MM}, and [0.02, 0.4] for c_{fM} for sensitivity analysis. According to Moscicki et al.

(2012), the per-partnership probability was estimated to be $0.05 - 0.28$ for male-to-female transmission and $0.19 - 0.81$ for female-to-male transmission. Because we investigate the period before people settle down, we choose $\beta_{mf} = 0.25$ and $\beta_{fm} = 0.7$ as the base value with unit person^{-1}, and set a range $[0.15, 0.3]$ for β_{mf} and $[0.6, 0.8]$ for β_{fm}. The probability of transmission per-partnership depends on the number of sexual contacts and the probability of successful transmission per contact. The sexual contacts between heterosexual females and MSM are much fewer than that between heterosexual females and males. Thus, we choose $\beta_{Mf} = 0.2\beta_{mf} = 0.05$, $\beta_{fM} = 0.2\beta_{fm} = 0.14$ as their base values, and set a rage $[0.03, 0.07]$ for β_{Mf} and $[0.1, 0.18]$ for β_{fM}. Transmission between MSM is more common than other groups. We choose $\beta_{MM} = 0.75$ as its base value and $[0.6, 0.89]$ as its range. Lastly, as an example, we assume that new recruits into sexually active females and males per year are 100,000, that is $\Lambda_f = \Lambda_m = 100{,}000$ with unit person/year. According to Chen et al. (2013), the percentage of MSM among adult men ranged from 4.79 to 6.07%. We choose the new recruits into sexually active MSM to be $100{,}000 \times 5\% = 5000$, i.e., $\Lambda_M = 5000$. The values for the remaining few parameters are from the previous literature (Table 1). According to the Refs. Revzina and Diclemente (2005), Dunne et al. (2006), the reported prevalence of HPV for females and males falls into the range of 14–90% and 1.3–72.9%, respectively. These are the prevalences before introducing HPV vaccines. Thus, we checked the prevalence predicted by our model without vaccination. Using the model parameters, the prevalence in heterosexual females, heterosexual males and MSM is 23%, 30.9% and 71.6%, respectively (Fig. 2b), which are within the above ranges.

In the model without vaccination, we showed that the DFE always exists and is stable when $R_0 < 1$ in Sect. 3.2. In Fig. 2a with $R_0 = 0.8615$, we see that the prevalence in each subgroup converges to zero, which means that the disease dies out. In Theorem 3 we only proved the existence of the endemic equilibrium. However, the simulations in Fig. 2b with $R_0 = 3.2308$ and different initial conditions suggest that the endemic equilibrium might be unique and stable when $R_0 > 1$. For the model with vaccination, we have similar results. Figure 3a with $R_0 = 0.6138$ shows that the prevalence in each subgroup goes to zero, while Fig. 3b with $R_0 = 2.6492$ shows that the system converges to a positive steady state under various initial conditions.

5.2 Sensitivity Analysis

In this section, we use the PRCC (partial rank correlation coefficient) to evaluate the impact of model parameters on the dynamics of the model (1). PRCC provides a global sensitivity analysis for nonlinear but monotone relationships between inputs and outputs (Marino et al. 2008). Recall that $R_0 = \max\{R_{0,MM}, R_{0,fm}R_{0,mf} + R_{0,fM}R_{0,Mf}/(1 - R_{0,MM})\}$ and $R_{0,f} = R_{0,fm}R_{0,mf} + R_{0,fM}R_{0,Mf}/(1 - R_{0,MM})$ for $R_{0,MM} < 1$. From Sect. 4.2, we know that $R_0 < 1$ is needed to eliminate the disease. We want to ensure that $R_{0,MM} < 1$ and then $R_{0,f} < 1$. Thus, we are most concerned with the parameters that have greatest impact on $R_{0,MM}$ as well as $R_{0,f}$ for $R_{0,MM} < 1$. We also care about which parameters have great impact on the prevalence. Therefore, in our sensitivity analysis, the inputs are parameters and the outputs

are $R_{0,MM}$, $R_{0,f}$ (when $R_{0,MM} < 1$), the prevalence in each subgroup and the total population. The reason we do not choose R_0 as an output is the monotonicity requirement for PRCC. This is also another reason for our requirement $R_{0,MM} < 1$ in the sensitivity analysis of $R_{0,f}$. In the inputs, there is a special parameter called dummy. It does not appear in the model so it won't affect the outputs. The PRCC value for this dummy parameter should be zero in the ideal case. However, there always exists some error, for instance from aliasing and interference effect. Consequently, we introduce this dummy parameter to quantify these artifacts. Parameters with sensitivity index less than or equal to that of the dummy parameter should be considered not significantly different from zero.

In all the sensitivity analyses except for $R_{0,f}$, we choose the vaccination proportion $\phi_f = \phi_m = \phi_M = 0.5$ as baseline values and [0.01, 0.99] as their ranges. For $R_{0,f}$, we choose $\phi_f = \phi_m = 0.5$, $\phi_M = 0.92$ as baseline values and [0.01, 0.99], [0.01, 0.99], [0.88, 0.99] as the range for ϕ_f, ϕ_m and ϕ_M, respectively. A larger value of ϕ_M is used for the sensitivity test of $R_{0,f}$ because of the requirement $R_{0,MM} < 1$. The sample size is 10,000 for Fig. 4a, b and 5000 for Fig. 4c–f. The parameters with a larger PRCC index (absolute value greater than 0.5) have more significant influence on the output (Taylor 1990). The negative or positive sign of the PRCC value indicates that the parameter is inversely or positively correlated with the outputs. From Fig. 4, we see that the most significant parameters affecting $R_{0,MM}$ are $\phi_M = -0.9992$, $\delta_M = -0.5312$, $\tau = -0.528$, $\beta_{MM} = 0.8543$ and $c_{MM} = 0.7685$; for $R_{0,f}$ the parameters are $\phi_f = -0.9194$, $\phi_m = -0.9194$, $\beta_{mf} = 0.6609$ and $\beta_{fm} = 0.5179$; for I_f/N_f the parameters are $\phi_f = -0.8923$, $\phi_m = -0.8683$, $\tau = -0.5878$, $\beta_{mf} = 0.8049$, $c_{fm} = 0.6218$ and $c_{mf} = 0.5088$; for I_m/N_m the parameters are $\phi_m = -0.681$, $\phi_f = -0.6216$ and $\beta_{mf} = 0.5121$; for I_M/N_M the parameters are $\phi_M = -0.9612$, $\tau = -0.8122$, $\mu_M = -0.5415$, $\beta_{MM} = 0.8258$ and $c_{MM} = 0.7348$; for the total prevalence $(I_f + I_m + I_M)/N$ the parameters are $\phi_m = -0.7848$, $\phi_f = -0.7273$, $\tau = -0.5413$ and $\beta_{mf} = 0.6315$. From these sensitivity analyses, we find that the proportion of vaccination always has the greatest impact on the basic reproduction number and the disease prevalence.

5.3 The Influence of Vaccination on Prevalence

We investigate the influence of vaccination on the prevalence. If only heterosexual females are vaccinated, i.e., $\phi_m = \phi_M = 0$, Fig. 5 shows the prevalence in heterosexual females, heterosexual males, MSM and total population assuming $\phi_f = 0, 0.2, 0.4, 0.6, 0.8, 1$. When ϕ_f increases, all the prevalences decline but with different speeds. The prevalences in heterosexual females and males fall rapidly and go to zero as ϕ_f increases to 1. The prevalence in the total population also decreases quickly but converges to a positive constant. However, the prevalence in MSM only slightly goes down. We obtain similar results when only vaccinating heterosexual males (Fig. 6).

If we only vaccinate MSM, the change is quite significant. From Fig. 7a, b we see that the prevalence in heterosexual females and males are almost the same no matter how many vaccines are given to MSM. The prevalences in MSM and total population

decrease as ϕ_M increases (Fig. 7c, d). The extent of the decline for MSM is much larger than that for the total population.

We further consider several extreme situations of vaccinating different groups. When vaccinating all heterosexual males and MSM but none of heterosexual females (i.e., $\phi_m = \phi_M = 1$ and $\phi_f = 0$), Fig. 8a shows that all the prevalences go to zero. The same situation occurs when $\phi_f = \phi_M = 1$ and $\phi_m = 0$ (Fig. 8b). However, when vaccinating all heterosexual females and males ($\phi_f = \phi_m = 1$), no vaccination ($\phi_M = 0$, Fig. 8c) or low vaccination proportion ($\phi_M = 0.3$, Fig. 8d) in MSM results in an endemic disease in MSM as well as in the total population. This prevalence is due to the transmission within MSM. When $R_{0,MM} > 1$, the transmission within MSM can always make the disease endemic. Thus, to eliminate the infection, the vaccination priority should be given to MSM.

5.4 Best Vaccination Strategy

The basic reproduction number $R_{0,MM} < 1$ is necessary for disease elimination. Using our parameter values, the vaccination proportion for MSM, i.e., ϕ_M needs to be larger than a threshold value $\widehat{\phi}_M = 0.7672$ for $R_{0,MM} < 1$. We consider the case when the total number of HPV vaccine shots v is fixed. A critical question arises: what is the best way to distribute them among heterosexual females, males and MSM? Recall that $\overline{R}_0$ is the average basic reproduction number, which represents the average number of secondary cases generated by one infectious individual in an entirely susceptible population. We want to minimize $\overline{R}_0$ subject to the following conditions

$$\phi_f \Lambda_f + \phi_m \Lambda_m + \phi_M \Lambda_M = v \ (v \text{ is a constant}),\ 0 \le \phi_f \le 1,\ 0 \le \phi_m \le 1,\ \widehat{\phi}_M \le \phi_M \le 1.$$

The best distribution strategy, given different values of v, is given in Table 2. It can be seen that the best strategy to reduce $\overline{R}_0$ is to vaccinate MSM firstly as many as possible, then heterosexual females, lastly heterosexual males.

It follows from $\phi_f \Lambda_f + \phi_m \Lambda_m + \phi_M \Lambda_M = v$ that $\phi_m = (v - \phi_f \Lambda_f - \phi_M \Lambda_M)/\Lambda_m$. Thus, we can view $\overline{R}_0(\phi_f, \phi_m, \phi_M)$ as a function of ϕ_f and ϕ_M with $\phi_M > \widehat{\phi}_M$. Using $v = 80{,}000$ as an example, we plot $\overline{R}_0$ in terms of ϕ_f and ϕ_M (Fig. 9a). It can be seen that $min\overline{R}_0 = 0.5116$, which is obtained at $\phi_f = 0.75$ and $\phi_M = 1$. This is consistent with the result in Table 2. From Fig. 9a we also find that the value of $\overline{R}_0$ at the point $\phi_f = 0, \phi_M = 1$ is 0.5117, which is very close to the $min\overline{R}_0$. This indicates that after the vaccination of all MSM, giving all the vaccines to only heterosexual females or males will result in a very similar $\overline{R}_0$. Interestingly, if vaccines are distributed to both genders, then we will get a larger $\overline{R}_0$. The simulation shows that the evener the distribution, the larger the value of $\overline{R}_0$. In fact, from Fig. 9a, we have the same observation for any fixed ϕ_M. This is further confirmed in another example in which $v = 100{,}000$ (Fig. 9b).

An evener vaccine distribution to both genders leads to a larger average basic reproduction number, which should also result in a higher prevalence. We compare the prevalence in the total population in Fig. 10. In the upper panel, we let $\phi_M = 0.8$

and in the lower panel ϕ_M is 0.9. Giving all vaccines to only heterosexual females or males results in very close prevalence in the total population (giving all of them to only females is slightly better). However, distributing vaccines to both genders equally leads to higher prevalence (Fig. 10a, b. Similar scenario occurs for $\phi_M = 0.9$ although a larger ϕ_M decreases the prevalence (Fig. 10c, d).

Plotting $min\overline{R}_0$ in terms of v from Table 2, we find that the decreasing speed of $min\overline{R}_0$ becomes slower as the vaccine availability v increases (Fig. 11a). Figure 11b shows the prevalence in total population with fixed vaccine amount applying the best vaccine distribution strategy, namely, first vaccinate MSM as many as possible, then vaccinate heterosexual females as many as possible, finally give the rest of the vaccines to heterosexual males. When the amount of vaccine increases from 0 to 40,000, from 40,000 to 80,000, from 80,000 to 120,000, and from 120,000 to 160,000, the prevalence declines to a different degree. The range of decline in the first case is the largest, while in the last case the decline is the smallest. This indicates that the efficacy of using the same amount of vaccine is different. Vaccination becomes less effective in reducing HPV prevalence as more vaccines are given. Thus, it is more effective to allocate vaccines to a region with lower vaccination coverage.

6 Discussion

In this paper, we developed a dynamic model in the heterosexually active population combined with sexually active MSM to evaluate the epidemiological impact of HPV vaccination. The model is different from many other HPV infection models that usually only include heterosexual population. The standard incidence form used in our model is also distinct from other papers. We explained our choice in Remark 1 and gave a reasonable biological interpretation. Mathematical analyses of the model were carried out. We introduced basic reproduction numbers $R_{0,f}$, $R_{0,m}$ and $R_{0,M}$ for heterosexual females, heterosexual males and MSM, respectively. The average basic reproduction number $\overline{R}_0$ was also defined and is given by $\overline{R}_0 = (R_{0,f}+R_{0,m}+R_{0,M})/3$. Besides, we derived the threshold R_0 and investigated the relationship with other basic reproduction numbers $R_{0,f}$, $R_{0,m}$ and $R_{0,M}$. Unlike papers that define only one basic reproduction number, usually derived by finding the threshold for the disease-free equilibrium to be locally asymptotically stable or by using the next generation method, here we defined basic reproduction numbers according to different transmission routes. There are five basic transmission routes, namely, from heterosexual female to heterosexual male and vice versa, from heterosexual female to MSM and vice versa, and transmission within MSM (denoted by $R_{0,fm}$, $R_{0,mf}$, $R_{0,fM}$, $R_{0,Mf}$ and $R_{0,MM}$, respectively). Based on these five basic transmission routes, we derived the completed transmission routes from heterosexual females to heterosexual females, heterosexual males to heterosexual males, and MSM to MSM. They are used to calculate the three basic reproduction numbers $R_{0,f}$, $R_{0,m}$ and $R_{0,M}$. Because the basic reproduction number represents the number of secondary cases generated by one infectious individual in an entirely susceptible population during the whole infectious period and there are three infectious classes in our model (I_f, I_m and I_M), defining three basic reproduction numbers helped us better investigate the transmission. From Sects. 3 and 4, the threshold parameter R_0

has close relationship with the basic reproduction numbers. We also showed R_0 as a threshold for the stability of disease-free equilibrium and the existence of the endemic equilibrium.

Combining the sensitivity analyses and numerical investigations, we have the following conclusions on the influence of vaccination on the disease prevalence. (1) Heterosexual females and males can obtain great benefit from vaccinating either gender, but almost no benefit from vaccinating MSM; (2) MSM only get minor benefit from vaccinating heterosexual females or males; (3) A certain coverage of MSM vaccination is necessary for eliminating the infection in the total population. Because heterosexual females mainly have sex with heterosexual males and vice versa, and MSM that only account for a small proportion in the total population mainly have sex with MSM, the above results are reasonable and consistent with our analytical results in Sects. 3 and 4. HPV vaccine has been introduced in some countries for years. Most of these countries only vaccinated girls at the beginning. Even today many countries still only offer HPV vaccine to females. Several papers showed that the prevalence of HPV infection had declined greatly in both females and males even in countries with girls-only policy. However, MSM did not benefit from the herd protection provided by the vaccination of girls (Drolet et al. 2015; Sauvageau and Dufour-Turbis 2016). These are consistent with our modeling results.

Given a fixed amount of vaccine, we obtain the following conclusions on vaccine distribution. (1) The best distribution strategy is to vaccinate MSM firstly as many as possible, then heterosexual females, lastly heterosexual males; (2) For a fixed vaccination coverage of MSM (ϕ_M), giving the remaining vaccines to only heterosexual females or males as many as possible leads to a similar prevalence in the total population. This prevalence is lower than that when distributing the vaccines to both genders. The evener the distribution, the higher the prevalence in the total population; (3) Vaccination becomes less effective in reducing HPV prevalence as more vaccines are administered. It is more effective to allocate vaccines to a region with lower vaccination coverage. Because the probability of HPV transmission is higher for MSM and MSM can spread the infection within their own group, it is reasonable to give the vaccination priority to them, particularly when the objective of vaccination is to eliminate the infection in the entire population. The result that an evener distribution between males and females leads to a worse vaccination outcome can be explained using a simple example. Suppose that after vaccinating all MSM there are 100 HPV vaccines left for 200 heterosexual people (100 females and 100 males). The HPV vaccine is assumed to be perfect (i.e., provide 100% protection). If we give the 100 HPV vaccines to 100 heterosexual females or males, then nobody will have the risk of getting infected. This is clearly better than if we distribute the 100 vaccines evenly to the two heterosexual populations.

Model results show that the vaccination priority should be given to MSM and that vaccinating either heterosexual females or males with high coverage is better than vaccinating both genders. In those countries that have achieved high coverage of HPV vaccination in females, the most effective way is to vaccinate MSM exclusively. However, such a strategy is not easy to implement in practice for a few reasons. For example, the sexual orientation of some young boys is still unreliable. Some people also think that it is not ethical, fair or socially responsible to have a public health policy

that forces men to rely on herd immunity, which may take a long time to achieve. Therefore, some studies suggest that boys should also be vaccinated (Sauvageau and Dufour-Turbis 2016; Stanley 2012; Fairley et al. 2017). On the other hand, due to the shortage of HPV vaccine worldwide, the WHO called for countries to suspend vaccination of boys in 2019 (Arie 2019). This is supported by studies showing that increasing coverage in girls was more effective than including boys in the vaccination program (Kim et al. 2007; Basu et al. 2008). Another reason supporting the girls-only vaccination policy is that vaccinating girls can largely and directly reduce the incidence of HPV-related cancers in women, such as cervical cancer.

In the paper, we used the standard incidence and assumed homogeneous mixing in the models. This may not capture the diverse patterns of interactions underlying HPV transmission. The heterogeneity can come from age, sex, spatial and social structures, and behavior changes (Bansal et al. 2007). Individual-based models may be developed to take these heterogeneities into account. However, it will bring challenges to model tractability. Even under the assumption of homogeneous mixing, our model is still complicated. It is hard to get an explicit expression for the basic reproduction number using the next generation method. We derived a threshold parameter R_0 from the disease-free equilibrium (DFE) and showed that the DFE is locally and globally asymptotically stable when $R_0 < 1$. We further obtained three basic reproduction numbers ($R_{0,f}$, $R_{0,m}$ and $R_{0,M}$) for heterosexual females, heterosexual males and MSM, respectively, according to the transmission routes. Because of the multiple groups and multiple transmission routes, it is challenging to define the basic reproduction number for the whole model from biology. This motivated us to define an average basic reproduction number $\bar{R}_0$, which represents the average number of secondary infections induced by one infected individual (female, male, or MSM). Assigning a larger coefficient on a certain group, e.g., women that usually have a heavier HPV-associated cancer burden, can put more weight on the relative contribution from that group. However, because of the lack of quantitative comparison of these three groups, we simply took the arithmetic average of the basic reproduction numbers of the three groups. This average explicitly includes the contributions from all the three groups, as compared with R_0 that only involves MSM and females. The vaccine distribution results obtained by minimizing $\bar{R}_0$ or the disease prevalence in the total population agree with each other, which supports the minimization of the average basic reproduction number as a criterion when developing the best vaccine distribution strategy.

For many virus infections, recovery can provide protection against future infection. However, for HPV the results are mixed on whether naturally acquired HPV antibodies can protect against subsequent infection. We adopted the SIS modeling framework in view of a number of studies showing no protection in females, males and MSM (Ranjeva et al. 2017; Trottier et al. 2010; Moscicki et al. 2012; Beachler et al. 2018). In a systematic review and meta-analysis that searched the MEDLINE and EMBASE databases for studies up to year 2016 examining natural HPV immunity, it was found that HPV antibodies acquired through natural infection provide modest protection against subsequent cervical HPV infection in female subjects (Beachler et al. 2016). However, the protection in male subjects is not significant. If the susceptible–infectious–recovered (SIR) or SIRS model is used, the basic reproduction number for each population obtained as we did in this paper remains the same as that using the SIS

model. Therefore, the average basic reproduction number $\bar{R}_0$ remains unchanged. Our conclusions on the vaccine distribution strategy, obtained by minimizing $\bar{R}_0$, would not be affected by the choice of these models. Lastly, all the conclusions in this paper are drawn based on HPV infection rather than cancer burden. Whether the vaccination guidelines informed by this study are affected when the objective is to reduce HPV-associated cancer incidence remains to be further investigated.

In summary, we used a mathematical model including heterosexual population and MSM to evaluate the epidemiological influence of HPV vaccination. Vaccine distribution strategies might be different according to the objective of vaccination programs. Our modeling results may provide some quantitative information helping policymakers formulate guidelines for vaccine distribution to reduce HPV prevalence in a region on the basis of the vaccine availability and existing vaccination coverage among populations.

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Appendix A: Proof of the Well-Posedness of System (1)

For reference, we introduce a theorem by Thieme (2018). Let $\Re_+^n = [0, +\infty)^n$ be the cone of nonnegative vector in $\Re^n$. Let $F : \Re_+^{n+1} \to \Re^n$

$$F(t, x) = (F_1(t, x), \cdots, F_n(t, x)), \quad x = (x_1, \cdots, x_n),$$

be locally Lipschitz and $F_j(t, x) \geq 0$ when $t \geq 0$, $x \in \Re_+^n$, $x_j = 0$. For every $x^0 \in \Re_+^n$, there exists a unique solution of $x' = F(t, x)$ and $x(0) = x^0$, which is defined on some interval $[0, b)$ where $b > 0$. If $b < \infty$, then

$$\limsup_{t \nearrow b} \sum_{j=1}^{n} x_j(t) = \infty.$$

We use this theorem to prove that system (1) is well-posed. First, we show that the region

$$D = \{(S_f, V_f, I_f, S_m, V_m, I_m, S_M, V_M, I_M) \in \Re_+^9 : S_k + V_k + I_k \leq \Lambda_k/\mu_k, k = f, m, M\}$$

is positively invariant and attracts all solutions of system (1). From $N_k' = \Lambda_k - \mu_k N_k$, $k = f, m, M$, we have

$$N_k(t) = \frac{\Lambda_k}{\mu_k} + \left[N_k(0) - \frac{\Lambda_k}{\mu_k} \right] e^{-\mu_k t}.$$

Therefore, we have $N_k(t) \leq \Lambda_k/\mu_k$ for any $t \geq 0$ if $N_k(0) \leq \Lambda_k/\mu_k$. This shows that D is positively invariant. Furthermore, if $N_k(0) > \Lambda_k/\mu_k$, then $N_k(t)$ approaches

Λ_k/μ_k asymptotically. This shows that the region D attracts all solutions in $\Re^9_+$. Therefore, D is epidemiologically well-posed.

Next, we use Thieme's theorem to prove that for any initial value in D, there exists a unique solution of system (1) with values in D for $t \in [0, +\infty)$. It follows from $\lim_{t\to\infty} N_k(t) = N_k^* = \Lambda_k/\mu_k$ that there exists $T > 0$ such that $N_k(t) > N_k^*/2$ for all $t > T$. By shifting, we can assume for $t \geq 0$, $N_k^*/2 < N_k(t) \leq N_k^*$. Let $x = (S_f, V_f, I_f, S_m, V_m, I_m, S_M, V_M, I_M) \in \Re^9_+$ and $F(x) = (F_1(x), F_2(x), F_3(x), F_4(x), F_5(x), F_6(x), F_7(x), F_8(x), F_9(x))$, where

$$
\begin{aligned}
F_1(x) &= (1-\phi_f)\Lambda_f - \lambda_f S_f + \delta_f I_f - \mu_f S_f,\\
F_2(x) &= \phi_f \Lambda_f - (1-\tau)\lambda_f V_f - \mu_f V_f,\\
F_3(x) &= \lambda_f S_f + (1-\tau)\lambda_f V_f - (\delta_f + \mu_f) I_f,\\
F_4(x) &= (1-\phi_m)\Lambda_m - \lambda_m S_m + \delta_m I_m - \mu_m S_m,\\
F_5(x) &= \phi_m \Lambda_m - (1-\tau)\lambda_m V_m - \mu_m V_m,\\
F_6(x) &= \lambda_m S_m + (1-\tau)\lambda_m V_m - (\delta_m + \mu_m) I_m,\\
F_7(x) &= (1-\phi_M)\Lambda_M - \lambda_M S_M + \delta_M I_M - \mu_M S_M,\\
F_8(x) &= \phi_M \Lambda_M - (1-\tau)\lambda_M V_M - \mu_M V_M,\\
F_9(x) &= \lambda_M S_M + (1-\tau)\lambda_M V_M - (\delta_M + \mu_M) I_M.
\end{aligned}
$$

For any $x, \overline{x} \in D$,

$$
\begin{aligned}
|F_1(x) - F_1(\overline{x})| &= |-\lambda_f(S_f - \overline{S}_f) - (\lambda_f - \overline{\lambda}_f)\overline{S}_f\\
&\quad + \delta_f(I_f - \overline{I}_f) - \mu_f(S_f - \overline{S}_f)|\\
&\leq K_1|S_f - \overline{S}_f| + \frac{c_{mf}\beta_{mf}\overline{S}_f}{N_f\overline{N}_f}|I_m\overline{N}_f - \overline{I}_m N_f|\\
&\quad + \frac{c_{Mf}\beta_{Mf}\overline{S}_f}{N_f\overline{N}_f}|I_M\overline{N}_f - \overline{I}_M N_f| + \mu_f|S_f - \overline{S}_f| + \delta_f|I_f - \overline{I}_f|\\
&\leq K_1|S_f - \overline{S}_f| + \mu_f|S_f - \overline{S}_f| + \delta_f|I_f - \overline{I}_f|\\
&\quad + \frac{c_{mf}\beta_{mf}\overline{S}_f}{N_f\overline{N}_f}(|I_m - \overline{I}_m|\overline{N}_f + \overline{I}_m|N_f - \overline{N}_f|)\\
&\quad + \frac{c_{Mf}\beta_{Mf}\overline{S}_f}{N_f\overline{N}_f}(|I_M - \overline{I}_M|\overline{N}_f + \overline{I}_M|N_f - \overline{N}_f|)\\
&\leq K_1|S_f - \overline{S}_f| + \mu_f|S_f - \overline{S}_f| + \delta_f|I_f - \overline{I}_f| + K_1|N_f - \overline{N}_f|\\
&\quad + c_{mf}\beta_{mf}|I_m - \overline{I}_m| + c_{Mf}\beta_{Mf}|I_M - \overline{I}_M|\\
&\leq (2K_1 + \mu_f + \delta_f)(|S_f - \overline{S}_f| + |I_f - \overline{I}_f| + |V_f - \overline{V}_f|)\\
&\quad + c_{mf}\beta_{mf}|I_m - \overline{I}_m| + c_{Mf}\beta_{Mf}|I_M - \overline{I}_M|\\
&\leq K_2(|S_f - \overline{S}_f| + |I_f - \overline{I}_f| + |V_f - \overline{V}_f|\\
&\quad + |I_m - \overline{I}_m| + |I_M - \overline{I}_M|),
\end{aligned}
$$

where

$$K_1 = \frac{2(c_{mf}\beta_{mf}N_m^* + c_{Mf}\beta_{Mf}N_M^*)}{N_f^*},$$
$$K_2 = \max\{2K_1 + \mu_f + \delta_f, c_{mf}\beta_{mf}, c_{Mf}\beta_{Mf}\}.$$

By similar arguments, we can show that the other components of $F(x)$ are locally Lipschitz in x. It's easy to check that $||F(x) - F(\overline{x})|| \leq M||x - \overline{x}||$ for some $M > 0$. Thus, $F(x)$ is locally Lipschitz.

If $S_f = 0$, then $F_1(x) = (1 - \phi_f)\Lambda_f + \delta_f I_f \geq 0$ whenever $t \geq 0$, $x \in \Re_+^9$. Similarly, we have $F_k(x) \geq 0$ whenever $t \geq 0$, $x \in \Re_+^9$, $k = 2, \cdots, 9$. Therefore, by Thieme's Theorem, for every $x^0 \in D$, there exists a unique solution of $x' = F(x)$ and $x(0) = x^0$, with values in D. The solution is defined on some interval $[0, b)$, $b > 0$. Because $\limsup_{t \nearrow b} \sum_{j=1}^{n} x_j(t) = N_f^* + N_m^* + N_M^* < \infty$, again by Thieme's Theorem, we have $b = \infty$. Thus, our model is both epidemiologically and mathematically well posed.

Appendix B: Proof of Proposition 1

Assume the contrary. Then for every $\varepsilon > 0$, $\limsup_{t\to\infty} I_M(t) < \frac{\varepsilon}{2}$. Thus, there exists $T_1(\varepsilon) > 0$ such that $I_M(t) < \varepsilon$ for all $t > T_1(\varepsilon)$. Because $\lim_{t\to\infty} N_M(t) = \frac{\Lambda_M}{\mu_M}$, there exists $T_2 > 0$ such that $N_M(t) > \frac{\Lambda_M}{2\mu_M}$ for all $t > T_2$. In particular, for

$$\varepsilon_0 = \frac{[c_{MM}\beta_{MM} - (\delta_M + \mu_M)]\Lambda_M}{4\mu_M c_{MM}\beta_{MM}} > 0$$

and $t > T = \max\{T_1(\varepsilon_0), T_2\}$, we have

$$\begin{aligned}
I_M'(t) &= \frac{c_{MM}\beta_{MM}I_M + c_{fM}\beta_{fM}I_f}{N_M}S_M - (\delta_M + \mu_M)I_M \\
&\geq \frac{c_{MM}\beta_{MM}I_M}{N_M}S_M - (\delta_M + \mu_M)I_M \\
&= \left[\frac{c_{MM}\beta_{MM}}{N_M}(N_M - I_M) - (\delta_M + \mu_M)\right]I_M \\
&> \left[c_{MM}\beta_{MM} - (\delta_M + \mu_M) - c_{MM}\beta_{MM}\frac{2\mu_M\varepsilon_0}{\Lambda_M}\right]I_M \\
&= \frac{1}{2}(\delta_M + \mu_M)(R_{0,MM} - 1)I_M.
\end{aligned}$$

Thus, $I_M(t) \geq I_M(0)e^{\frac{1}{2}(\delta_M+\mu_M)(R_{0,MM}-1)t}$. Because $R_{0,MM} > 1$, we conclude that for $I_M(0) > 0$ $\lim_{t\to\infty} I_M(t) = +\infty$. This contradicts the assumption. Thus, if $R_{0,MM} > 1$, I_M is uniformly weakly endemic.

Appendix C: Proof of Proposition 3

If $R_{0,MM} < 1$, then $R_{0,f} = R_{0,fm}R_{0,mf} + R_{0,fM}\sum_{n=0}^{\infty} R_{0,MM}^n R_{0,Mf} = R_{0,fm}R_{0,mf} + \frac{R_{0,fM}R_{0,Mf}}{1-R_{0,MM}}$. From $R_{0,f} < 1$, we have $R_{0,fm}R_{0,mf} < 1$ and $\frac{R_{0,fM}R_{0,Mf}}{1-R_{0,MM}} < 1$. Thus,

$$\begin{aligned} R_{0,m} &= R_{0,mf}\left(1 + R_{0,fM}\sum_{n=0}^{\infty} R_{0,MM}^n R_{0,Mf}\right)R_{0,fm} \\ &= R_{0,fm}R_{0,mf} + R_{0,fm}R_{0,mf}\frac{R_{0,fM}R_{0,Mf}}{1-R_{0,MM}} \\ &\leq R_{0,fm}R_{0,mf} + \frac{R_{0,fM}R_{0,Mf}}{1-R_{0,MM}} \\ &= R_{0,f} < 1. \end{aligned}$$

We also have

$$\begin{aligned} R_{0,M} - 1 &= R_{0,MM} + R_{0,Mf}(1 + R_{0,fm}R_{0,mf})R_{0,fM} - 1 \\ &= (R_{0,MM}-1)\left(1 - \frac{R_{0,fM}R_{0,Mf}}{1-R_{0,MM}} - \frac{R_{0,fM}R_{0,Mf}}{1-R_{0,MM}}R_{0,fm}R_{0,mf}\right). \end{aligned}$$

From $R_{0,f} < 1$ and $\frac{R_{0,fM}R_{0,Mf}}{1-R_{0,MM}} < 1$, we know

$$\begin{aligned} &\frac{R_{0,fM}R_{0,Mf}}{1-R_{0,MM}} + \frac{R_{0,fM}R_{0,Mf}}{1-R_{0,MM}}R_{0,fm}R_{0,mf} < \frac{R_{0,fM}R_{0,Mf}}{1-R_{0,MM}} \\ &\quad + R_{0,fm}R_{0,mf} = R_{0,f} < 1. \end{aligned}$$

It follows from $R_{0,MM} < 1$ that $R_{0,M} - 1 < 0$, i.e., $R_{0,M} < 1$.

Appendix D: Proof of Theorem 2

Define the following Lyapunov function

$$L = \left(S_f - S_f^0 - S_f^0 \ln \frac{S_f}{S_f^0} + I_f\right) + R_{0,mf}\left(S_m - S_m^0 - S_m^0 \ln \frac{S_m}{S_m^0} + I_m\right) + \frac{R_{0,Mf}}{1 - R_{0,MM}}\left(S_M - S_M^0 - S_M^0 \ln \frac{S_M}{S_M^0} + I_M\right).$$

It's clear that when $R_0 < 1$, L is radially unbounded and positive definite in the entire space D. The derivative of L along the trajectories of system (2) yields

$$\begin{aligned}
\dot{L} =& \left[(1 - \frac{S_f^0}{S_f})S_f' + I_f'\right] + R_{0,mf}\left[(1 - \frac{S_m^0}{S_m})S_m' + I_m'\right] + \frac{R_{0,Mf}}{1 - R_{0,MM}}\left[(1 - \frac{S_M^0}{S_M})S_M' + I_M'\right] \\
=& \left(1 - \frac{S_f^0}{S_f}\right)(\Lambda_f - \lambda_f S_f + \delta_f I_f - \mu_f S_f) + [\lambda_f S_f - (\delta_f + \mu_f) I_f] \\
&+ R_{0,mf}\left\{\left(1 - \frac{S_m^0}{S_m}\right)(\Lambda_m - \lambda_m S_m + \delta_m I_m - \mu_m S_m) + [\lambda_m S_m - (\delta_m + \mu_m) I_m]\right\} \\
&+ \frac{R_{0,Mf}}{1 - R_{0,MM}}\left\{\left(1 - \frac{S_M^0}{S_M}\right)(\Lambda_M - \lambda_M S_M + \delta_M I_M - \mu_M S_M) + [\lambda_M S_M - (\delta_M + \mu_M) I_M]\right\}.
\end{aligned}$$

Using the equilibrium conditions $\Lambda_k = \mu_k S_k^0$, $N_k = S_k^0$, $\frac{S_k^0}{S_k} \geq 1$, $k = f, m, M$, and collecting terms, we obtain

$$\begin{aligned}
\dot{L} =& \left[\left(1 - \frac{S_f^0}{S_f}\right)\mu_f(S_f^0 - S_f) + S_f^0\lambda_f - \left(\frac{S_f^0}{S_f}\delta_f + \mu_f\right) I_f\right] \\
&+ R_{0,mf}\left[\left(1 - \frac{S_m^0}{S_m}\right)\mu_m(S_m^0 - S_m) + S_m^0\lambda_m - \left(\frac{S_m^0}{S_m}\delta_m + \mu_m\right) I_m\right] \\
&+ \frac{R_{0,Mf}}{1 - R_{0,MM}}\left[\left(1 - \frac{S_M^0}{S_M}\right)\mu_M(S_M^0 - S_M) + S_M^0\lambda_M - \left(\frac{S_M^0}{S_M}\delta_M + \mu_M\right) I_M\right] \\
\leq& -\frac{\mu_f}{S_f}(S_f^0 - S_f)^2 - R_{0,mf}\frac{\mu_m}{S_m}(S_m^0 - S_m)^2 - \frac{R_{0,Mf}}{1 - R_{0,MM}}\frac{\mu_M}{S_M}(S_M^0 - S_M)^2 \\
&+ [c_{mf}\beta_{mf} I_m + c_{Mf}\beta_{Mf} I_M - (\delta_f + \mu_f) I_f] \\
&+ R_{0,mf}[c_{fm}\beta_{fm} I_f - (\delta_m + \mu_m) I_m] \\
&+ \frac{R_{0,Mf}}{1 - R_{0,MM}}[c_{MM}\beta_{MM} I_M + c_{fM}\beta_{fM} I_f - (\delta_M + \mu_M) I_M] \\
\leq& -\frac{\mu_f}{S_f}(S_f^0 - S_f)^2 - R_{0,mf}\frac{\mu_m}{S_m}(S_m^0 - S_m)^2 - \frac{R_{0,Mf}}{1 - R_{0,MM}}\frac{\mu_M}{S_M}(S_M^0 - S_M)^2 \\
&+ (\delta_f + \mu_f)\left(R_{0,fm}R_{0,mf} + \frac{R_{0,fM}R_{0,Mf}}{1 - R_{0,MM}} - 1\right) I_f \leq 0.
\end{aligned}$$

$\dot{L}$ is 0 only at DFE. Therefore, the DFE E_0 is globally asymptotically stable when $R_0 \leq 1$.

Appendix E: Proof of Proposition 7

For reference, we introduce a theorem by Castillo-Chavez and Song (2004) [also in Martcheva (2015)]. Consider the following general system of ODEs with a parameter ϕ:

$$\frac{dx}{dt} = f(x, \phi), \quad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n, \quad f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}), \tag{3}$$

where $x = 0$ is an equilibrium point of the system, i.e., $f(0, \phi) \equiv 0$ for all ϕ. We assume that

$A1$ $\mathscr{A} = D_x f(0, 0) = (\frac{\partial f_i}{\partial x_j}(0, 0))$ is the linearized matrix of the system around the equilibrium 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of $\mathscr{A}$, and other eigenvalues have negative real parts.

$A2$ The matrix $\mathscr{A}$ has a nonnegative right eigenvector w and a left eigenvector v each corresponding to the zero eigenvalue.

Let f_k be the kth component of f, $a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0, 0)$ and $b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0, 0)$. The local dynamics of the system around 0 are completely determined by the signs of a and b:

(i) $a > 0, b > 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable and there exists a positive unstable positive equilibrium; when $0 < \phi \ll 1$, 0 is locally asymptotically stable and there exists a positive unstable equilibrium;

(ii) $a < 0, < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium;

(iii) $a > 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is unstable and a positive unstable equilibrium appears;

(iv) $a < 0, b > 0$. When $\phi < 0$ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly, a negative unstable equilibrium becomes positive and locally asymptotically stable.

We notice the following when using the above theorem.

(1) The equilibrium 0 is the DFE in our model. The parameter ϕ is one of the parameters in the reproduction number and the critical value of ϕ is the value of the parameter that makes the reproduction number equal to one.

(2) Since the DFE has positive entries, the right eigenvector w doesn't need to be nonnegative. The components of the right eigenvector w that correspond to positive entries in the DFE could be negative. However, the components that correspond to zero entries in the DFE should be nonnegative.

Now we use this theorem to prove Proposition 7. Choose β_{fm} as the bifurcation parameter and let β_{fm}^* be the critical value such that $R_0(\phi_f, \phi_m, \phi_M) = 1$. Thus, $R_{0,MM}(\phi_M) < 1$ and β_{fm}^* satisfies $R_{0,fm}(\phi_m) R_{0,mf}(\phi_f) + R_{0,fM}(\phi_M) \frac{1}{1 - R_{0,MM}(\phi_M)} R_{0,Mf}(\phi_f) = 1$.

Reordering variables as $x = (I_f, I_m, I_M, S_f, V_f, S_m, V_m, S_M, V_m)^T$, the Jacobian matrix of system (1) evaluated at the $\overline{E}_0$ and β^*_{fm} is $\mathscr{A} = \begin{pmatrix} J_{11} & 0 \\ J_{21} & J_{22} \end{pmatrix}$, where

$$J_{11} = \begin{pmatrix} -(\delta_f + \mu_f) & c_{mf}\beta_{mf}[(1-\phi_f) + (1-\tau)\phi_f] & c_{Mf}\beta_{Mf}[(1-\phi_f) + (1-\tau)\phi_f] \\ c_{fm}\beta^*_{fm}[(1-\phi_m) + (1-\tau)\phi_m] & -(\delta_m + \mu_m) & 0 \\ c_{fM}\beta_{fM}[(1-\phi_M) + (1-\tau)\phi_M] & 0 & -(\delta_M + \mu_M) + c_{MM}\beta_{MM}[(1-\phi_M) + (1-\tau)\phi_M] \end{pmatrix},$$

$$J_{21} = \begin{pmatrix} \delta_f & -c_{mf}\beta_{mf}(1-\phi_f) & -c_{Mf}\beta_{Mf}(1-\phi_f) \\ 0 & -c_{mf}\beta_{mf}(1-\tau)\phi_f & -c_{Mf}\beta_{Mf}(1-\tau)\phi_f \\ -c_{fm}\beta^*_{fm}(1-\phi_m) & \delta_m & 0 \\ -c_{fm}\beta^*_{fm}(1-\tau)\phi_m & 0 & 0 \\ -c_{fM}\beta_{fM}(1-\phi_M) & 0 & \delta_M - c_{MM}\beta_{MM}(1-\phi_M) \\ -c_{fM}\beta_{fM}(1-\tau)\phi_M & 0 & -c_{MM}\beta_{MM}(1-\tau)\phi_M \end{pmatrix},$$

and

$$J_{22} = \begin{pmatrix} -\mu_f & 0 & 0 & 0 & 0 & 0 \\ 0 & -\mu_f & 0 & 0 & 0 & 0 \\ 0 & 0 & -\mu_m & 0 & 0 & 0 \\ 0 & 0 & 0 & -\mu_m & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu_M & 0 \\ 0 & 0 & 0 & 0 & 0 & -\mu_M \end{pmatrix}.$$

It's easy to check that zero is a simple eigenvalue of $\mathscr{A}$ and the other eigenvalues have negative real parts. Thus, condition $A1$ is satisfied. Moreover, it can be shown that $\mathscr{A}$ has a right eigenvector (corresponding to the zero eigenvalue), given by $w = (w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9)^T$, where

$$\begin{aligned}
w_1 &= 1, \quad w_2 = \frac{\delta_f + \mu_f}{\delta_m + \mu_m} R_{0,fm}(\phi_m)|_{\beta_{fm}=\beta^*_{fm}} =: p > 0, \\
w_3 &= \frac{\delta_f + \mu_f}{\delta_M + \mu_M} \frac{R_{0,fM}(\phi_M)}{1 - R_{0,MM}(\phi_M)} =: q > 0, \\
w_4 &= -\frac{1}{\mu_f}[c_{mf}\beta_{mf}(1-\phi_f)p + c_{Mf}\beta_{Mf}(1-\phi_f)q - \delta_f], \\
w_5 &= -\frac{1}{\mu_f}[c_{mf}\beta_{mf}(1-\tau)\phi_f p + c_{Mf}\beta_{Mf}(1-\tau)\phi_f q], \\
w_6 &= -\frac{1}{\mu_m}[c_{fm}\beta^*_{fm}(1-\phi_m) - \delta_m p], \\
w_7 &= -\frac{1}{\mu_m} c_{fm}\beta^*_{fm}(1-\tau)\phi_m, \\
w_8 &= -\frac{1}{\mu_M}\{c_{fM}\beta_{fM}(1-\phi_M)p + [c_{MM}\beta_{MM}(1-\phi_M) - \delta_M]q\},
\end{aligned}$$

$$w_9 = -\frac{1}{\mu_f}[c_{fM}\beta_{fM}(1-\tau)\phi_M + c_{MM}\beta_{MM}(1-\tau)\phi_M q].$$

Besides, $\mathscr{A}$ also has a left eigenvector (corresponding to the zero eigenvalue), given by $v = (v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)^T$, where

$$\begin{aligned} &v_1 = 1, \quad v_2 = R_{0,mf}(\phi_f), \quad v_3 = \frac{R_{0,Mf}(\phi_f)}{1 - R_{0,MM}(\phi_M)}, \\ &v_4 = v_5 = v_6 = v_7 = v_8 = v_9 = 0. \end{aligned}$$

We denote the right-hand side functions of system (1) as f_i, $i = 1, \cdots, 9$. Because the last six components of v are zeros, we only need the derivatives of f_1, f_2 and f_3. At the DFE and $\beta_{fm} = \beta^*_{fm}$, the associated nonzero secondary partial derivatives are

$$\begin{aligned} &\frac{\partial^2 f_1}{\partial I_f \partial I_m} = -\frac{c_{mf}\beta_{mf}\mu_f}{\Lambda_f}, \quad \frac{\partial^2 f_1}{\partial I_f \partial I_M} = -\frac{c_{Mf}\beta_{Mf}\mu_f}{\Lambda_f}, \\ &\frac{\partial^2 f_2}{\partial I_f \partial I_m} = -\frac{c_{fm}\beta^*_{fm}\mu_m}{\Lambda_m}, \quad \frac{\partial^2 f_3}{\partial I_f \partial I_M} = -\frac{(c_{MM}\beta_{MM} + c_{fM}\beta_{fM})\mu_M}{\Lambda_M}, \\ &\frac{\partial^2 f_3}{\partial I_m \partial I_M} = -\frac{c_{MM}\beta_{MM}\mu_M}{\Lambda_M}, \quad \frac{\partial^2 f_3}{\partial I_M^2} = -\frac{2c_{MM}\beta_{MM}\mu_M}{\Lambda_M}, \\ &\frac{\partial^2 f_3}{\partial I_M \partial S_f} = \frac{\partial^2 f_3}{\partial I_M \partial V_f} = \frac{\partial^2 f_3}{\partial I_M \partial S_m} = \frac{\partial^2 f_3}{\partial I_M \partial V_m} = \frac{\partial^2 f_3}{\partial I_M \partial S_M} = \frac{\partial^2 f_3}{\partial I_M \partial V_M} = -\frac{c_{MM}\beta_{MM}\mu_M}{\Lambda_M}, \\ &\frac{\partial^2 f_2}{\partial I_f \partial \beta_{fm}} = c_{fm}. \end{aligned}$$

Therefore, $b = v_2 w_1 \dfrac{\partial^2 f_2}{\partial I_f \partial \beta_{fm}} = R_{0,mf}(\phi_f) c_{fm} > 0$ and

$$\begin{aligned} a =& 2v_1 w_1 w_2 \frac{\partial^2 f_1}{\partial I_f \partial I_m} + 2v_1 w_1 w_3 \frac{\partial^2 f_1}{\partial I_f \partial I_M} + 2v_2 w_1 w_2 \frac{\partial^2 f_2}{\partial I_f \partial I_m} \\ &+ 2v_3 w_1 w_3 \frac{\partial^2 f_3}{\partial I_f \partial I_M} + 2v_3 w_2 w_3 \frac{\partial^2 f_3}{\partial I_m \partial I_M} + v_3 w_3^2 \frac{\partial^2 f_3}{\partial I_M^2} + 2v_3 w_3 w_4 \frac{\partial^2 f_3}{\partial I_M \partial S_f} \\ &+ 2v_3 w_3 w_5 \frac{\partial^2 f_3}{\partial I_M \partial V_f} + 2v_3 w_3 w_6 \frac{\partial^2 f_3}{\partial I_M \partial S_m} + 2v_3 w_3 w_7 \frac{\partial^2 f_3}{\partial I_M \partial V_m} \\ &+ 2v_3 w_3 w_8 \frac{\partial^2 f_3}{\partial I_M \partial S_M} + 2v_3 w_3 w_9 \frac{\partial^2 f_3}{\partial I_M \partial V_M} \\ =& 2p\left(-\frac{c_{mf}\beta_{mf}\mu_f}{\Lambda_f}\right) + 2q\left(-\frac{c_{Mf}\beta_{Mf}\mu_f}{\Lambda_f}\right) + 2R_{0,mf}(\phi_f)p\left(-\frac{c_{fm}\beta^*_{fm}\mu_m}{\Lambda_m}\right) \\ &+ 2\frac{R_{0,Mf}(\phi_f)}{1 - R_{0,MM}(\phi_M)} q\left\{\left[-\frac{(c_{MM}\beta_{MM} + c_{fM}\beta_{fM})\mu_M}{\Lambda_M}\right]\right. \\ &\left. + p\left(-\frac{c_{MM}\beta_{MM}\mu_M}{\Lambda_M}\right) + q\left(-\frac{c_{MM}\beta_{MM}\mu_M}{\Lambda_M}\right)\right\} \end{aligned}$$

$$
\begin{aligned}
&+2\frac{R_{0,Mf}(\phi_f)}{1-R_{0,MM}(\phi_M)}q\left(-\frac{c_{MM}\beta_{MM}\mu_M}{\Lambda_M}\right)(w_4+w_5+w_6+w_7+w_8+w_9)\\
=&-2p\frac{c_{mf}\beta_{mf}\mu_f}{\Lambda_f}-2q\frac{c_{Mf}\beta_{Mf}\mu_f}{\Lambda_f}-2R_{0,mf}(\phi_f)p\frac{c_{fm}\beta^*_{fm}\mu_m}{\Lambda_m}\\
&-2\frac{R_{0,Mf}(\phi_f)}{1-R_{0,MM}(\phi_M)}q\frac{\mu_M}{\Lambda_M}[c_{fM}\beta_{fM}+c_{MM}\beta_{MM}(1+p+q)]\\
&+2\frac{R_{0,Mf}(\phi_f)}{1-R_{0,MM}(\phi_M)}q\frac{c_{MM}\beta_{MM}\mu_M}{\Lambda_M}(1+p+q)\\
=&-2p\frac{c_{mf}\beta_{mf}\mu_f}{\Lambda_f}-2q\frac{c_{Mf}\beta_{Mf}\mu_f}{\Lambda_f}-2R_{0,mf}(\phi_f)p\frac{c_{fm}\beta^*_{fm}\mu_m}{\Lambda_m}\\
&-2\frac{R_{0,Mf}(\phi_f)}{1-R_{0,MM}(\phi_M)}q\frac{\mu_M}{\Lambda_M}c_{fM}\beta_{fM}<0.
\end{aligned}
$$

According to the theorem by Castillo-Chavez and Song (2004), system (1) only has forward bifurcation.

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