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Research Paper

The effect of public health awareness and behaviors on the transmission dynamics of syphilis in Northwest China, 2006–2018, based on a multiple-stages mathematical model

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ABSTRACT

Syphilis, a sexually transmitted infectious disease caused by the bacterium treponema pallidum, has re-emerged as a global public health issue with an estimated 12 million people infected each year. Understanding the impacts of health awareness and behaviors on transmission dynamics of syphilis can help to establish optimal control strategy in different regions. In this paper, we develop a multiple-stage SIRS epidemic model taking into account the public health awareness and behaviors of syphilis. First, the basic reproduction number $\mathcal{R}_0$ is obtained, which determines the global dynamics behaviors of the model. We derive the necessary conditions for implementing optimal control and the corresponding optimal solution for mitigation syphilis by using Pontryagin's Maximum Principle. Based on the data of syphilis in Ningxia from 2006 to 2018, the parameterizations and model calibration are carried out. The fitting results are in good agreement with the data. Moreover, sensitivity analysis shows that the public awareness induced protective behaviors C_e, compliance of condom-induced preventability ε and treatment for the primary syphilis m_1 play an important role in mitigating the risk of syphilis outbreaks. These results can help us gain insights into the epidemiology of syphilis and provide guidance for the public health authorities to implement health education programs.
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1. Introduction

Syphilis is a sexually transmitted infection caused by the bacterium treponema pallidum (CDC, 2021). In 2015, about 45.4 million people were infected with syphilis, with 6 million new cases (GBD 2015). During 2015, it caused about 107,000 deaths, down from 202,000 in 1990 (Lozano, 2012). After decreasing dramatically with the availability of penicillin in the 1940s, rates of infection have increased since the turn of the millennium in many countries, often in combination with human immunodeficiency virus (HIV) (GBD , 2015). This is believed to be partly due to increased promiscuity, prostitution, decreasing use

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of condoms, and unsafe sexual practices among men who have sex with men (Gao et al., 2009). Generally, syphilis is transmitted by sexual contact or during pregnancy from a mother to her baby. Because spirochete is able to pass through intact mucous membranes or compromised skin, it can be transmitted by kissing near a lesion, as well as oral, vaginal, and anal sex (Syphilis-act Sheet(D, 2019; Stamm, 2010). Approximately 30%–60% of those exposed to primary or secondary syphilis will get the disease. Its infectivity is exemplified by the fact that an individual inoculated with only 57 organisms has a 50% chance of being infected (Eccleston et al., 2008).

Syphilis has been known as "the great imitator" as it may cause symptoms similar to many other diseases (Syphilis-act Sheet(D, 2019; Kent & Romanelli, 2008). The infection progresses through multiple stages when left untreated, including primary, secondary, latent, and tertiary stages. Infectious individuals can be in one of these four different stages, and the signs and symptoms vary depending on which stage they present (Kent & Romanelli, 2008). The primary stage classically presents with a single chancre (a firm, painless, non-itchy skin ulceration which usually has 1 cm–2 cm in diameter) though there may be multiple sores. In secondary syphilis, a diffuse rash occurs, which frequently involves the palms of the hands and soles of the feet. There may also be sores in the mouth or vagina. The latent syphilis can last for years with few or no symptoms. In tertiary syphilis, there are gummas (soft, non-cancerous growths), neurological problems, or heart symptoms. More details about these four stages are summarized in the following:

- Primary syphilis, usually lasting between 3 and 6 weeks, is typically acquired by direct sexual contact with another person of infectious lesions (Kent & Romanelli, 2008). Approximately 3–90 days after the initial exposure (average 21 days) a skin lesion, called a chancre, appears at the point of contact. This is classically (40% of the time) a single, firm, painless, non-itchy skin ulceration with a clean base and sharp borders approximately 0.3–3.0 cm in size (Eccleston et al., 2008).
- Secondary syphilis occurs approximately four to ten weeks after the primary infection (Kent & Romanelli, 2008). While secondary disease is known for the many different ways it can manifest, symptoms most commonly involve the skin, mucous membranes, and lymph nodes (Syphilis-act Sheet(D, 2019). There may be a symmetrical, reddish-pink, non-itchy rash on the trunk and extremities, including the palms and soles.
- Latent syphilis is defined as having serologic proof of infection without symptoms of disease (Kent & Romanelli, 2008). It is further described as either early (usually lasting over 10 weeks, and less than 1 year after secondary syphilis) or late (more than 1 year after secondary syphilis) in the United States (Syphilis-act Sheet(D, 2019). The United Kingdom uses a cut-off of two years for early and late latent syphilis. Early latent syphilis may have a relapse of symptoms in 25% of cases. Late latent syphilis is asymptomatic, and not as contagious as early latent syphilis (Aadland et al., 2013).
- Tertiary syphilis may occur approximately 3–15 years after the initial infection, and may be divided into three different forms: gummatous syphilis (15%), late neurosyphilis (6.5%), and cardiovascular syphilis (10%) (Syphilis-act Sheet(D, 2019). Without treatment, a third of infected people develop tertiary disease. People with tertiary syphilis are not infectious (Garnett et al., 1997).

Dynamical models have provided a deeper understanding of the transmission mechanism of syphilis in a population (Iboi & Okuonghae, 2016; Okuonghae et al., 2019). Garnett et al. formulated and analyzed a mathematical model in which they considered the basic stages of the disease and assumed that infected individuals acquire temporary immunity only after recovery from the latent and tertiary infections (Garnett et al., 1997). Grassly et al. fitted real-life data to an SIRS (susceptible-infected-recovered-susceptible) syphilis model using data for 68 US cities for the period 1941–2002 (Grassly et al., 2005). Milner and Zhao developed a mathematical model which assumed that secondary and later syphilis infections confer partial immunity, and considered inoculation along with behavioural patterns as possible tools for controlling syphilis (Milner & Zhao, 2010). Iboi and Okuonghae (Iboi & Okuonghae, 2016) rigorously analyzed a mathematical model for syphilis transmission that includes the early and late latent stages of syphilis infection, reversions of early latent syphilis to the primary and secondary stages as well as the three potential outcomes emanating from the late latent stage of infection. Saad-Roy et al. (Saad-Roy et al., 2016) developed a deterministic model for syphilis transmission in an MSM (men who have sex with men) population, they calculated the control reproduction number, and determined the variation and robustness of the control reproduction number based on numerical methods. Echigoya et al. (Echigoya et al., 2020) estimated the incidence and diagnosis rate in Japan using a mathematical model that captures the time course of infection, and they found that the diagnosis and reporting rate did not vary greatly over time. By using of spectrum sexually transmitted infections model, Korenromp et al. (Korenromp et al., 2018) estimated national-level trends in the prevalence of probable active syphilis in adult women to inform program planning, target-setting, and progress evaluation in STI control, and suggested that increased investment in national syphilis surveillance and control efforts are needed to reach a 90% reduction in the incidence of syphilis between 2018 and 2030 of WHO.

The public awareness play an important role in public health prevention strategies. The implementation of these control strategies depends on the publics behaviors (Greenhalgh et al., 2015; Yan et al., 2016). Thus, the raising public health

awareness may be related to the transmissibility of syphilis by changing the contact rate. The Baidu index recently was selected as a proxy to measure the public awareness with respect to the syphilis (Zhao et al., 2019, 2020). As shown in Fig. 2, the public awareness of syphilis in Ningxia suddenly switched from a low level to a high level during 2013–2014, which implies that the public awareness of syphilis increased significantly from 2013. In fact, the prevalence of syphilis kept increasing before 2013, leading to more and more susceptible population paying attention to the health education of syphilis. Thus, the raising public awareness may reduce the contact rate between susceptible and infected subpopulations by changing the public health behaviors.

How to quantitatively measure the effect of public awareness on the transmission of syphilis in Northwest China is one of the meaningful issues. Understanding the impacts of health awareness and behaviors on the transmission dynamics of syphilis can help to establish the optimal control strategies in different regions. The purpose of this study is to explore the role of public awareness in syphilis transmission and assess the optimal control strategies by mathematical modelling method. The rest of this paper is organized as follows: in the next Section 2, we formulate the syphilis transmission model, study the existence and stability of equilibria, calculate the basic reproduction ratio $\mathcal{R}_0$ and prove the global stability of the equilibria. In Section 3, the necessary conditions for implementing the optimal control strategies are derived. Then in Section 4, model calibration, sensitivity analysis and assessing the control strategy are carried out. Finally, a brief conclusion and discussion of this paper is given.

2. Materials and methods

2.1. Data collection

The spatial distribution of syphilis cases of Ningxia in Northwestern China from 2006 to 2018 were obtained from the National Notifiable Disease Surveillance System (NNDSS) (see Fig. 1). As shown in Fig. 1, between 2006 and 2018, a total of 28,509 syphilis cases were reported. The number of syphilis cases experiences a very rapid growth from 2006 to 2013, and then declines slowly from 3565 in 2013 to 3254 in 2015, but tends to grow again in 2016. We have collected the syphilis cases of different stages in Ningxia, as displayed in Fig. 3. Latent syphilis infection accounts for a large percentage of the total syphilis cases, while primary and secondary syphilis are also the important components.

2.2. Model formulation

In this subsection, we introduce a deterministic model to character the effect of public awareness on the transmission of syphilis. Let $N(t)$ be the total sexually-active population in Ningxia, which can be divided into the six sub-populations labeled S, I_p, I_s, L, I_t and R. Let $S(t)$ denote the number of individuals who are susceptible to syphilis at time t. $I_p(t)$, $I_s(t)$, $L(t)$ and $I_t(t)$

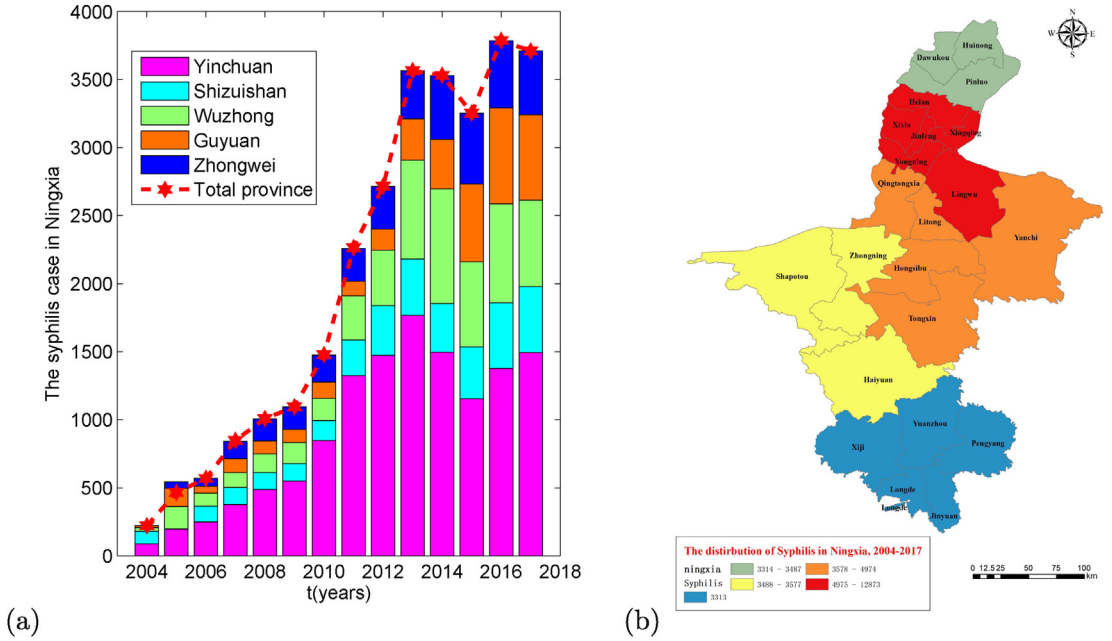

Fig. 1. The spatial distribution of syphilis cases in Ningxia, China from 2006 to 2018.

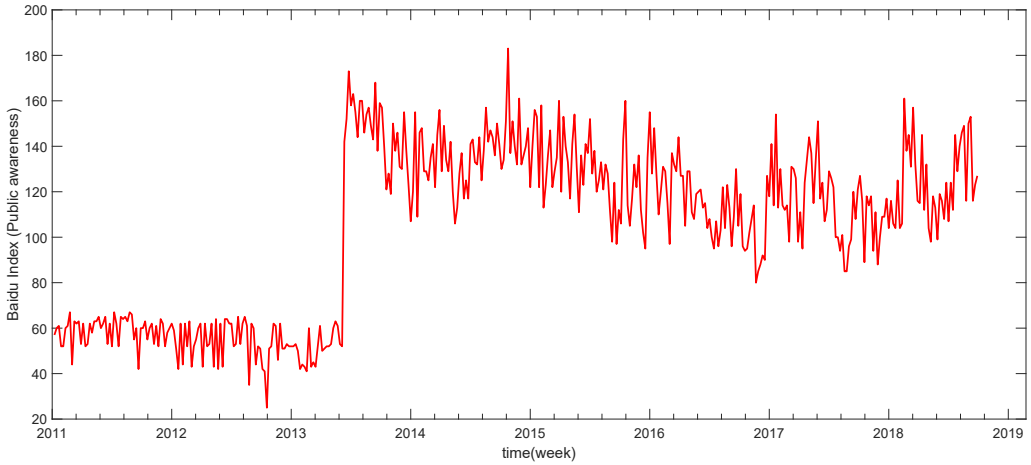

Fig. 2. The weekly Baidu index with respect to the public awareness of syphilis from 2010 to 2018.

represent the number of individuals who are in the primary, the secondary, the latent and the tertiary syphilis stages, respectively. $R(t)$ is the number of recovered individuals at time t.

(i) Due the asymptomatic or mild-symptom for the primary and secondary stage syphilis (Garnett et al., 1997), we assume that the main source of infection is the primary or secondary syphilis patients.

(ii) Considering the sustaining increased public awareness of syphilis in Ningxia as shown in Fig. 2, a switch point of public awareness occurs in 2013. Just as Bagnoli et al. (Bagnoli et al., 2007) pointed out that a disease that manifests itself in a visible way induces modifications in the social network: lower frequency of contacts, higher level of personal hygiene, prevention measures (masks), etc. In fact, individuals will strengthen the public health awareness and then change health behaviors once they perceive the risk of a disease. Motivated by these ideas, we use the Baidu index (BDI) with respect to syphilis to reflect the public health awareness (information about the incidence of syphilis) (Zhao et al., 2019, 2020), and assume that the information about the incidence of syphilis translates into a lower infection probability. Thus, we propose the stepwise protective behaviors rate c_e depending on BDI to describe the effects of public awareness on the transmission of syphilis in primary and secondary stages as follows:

$$c_e = \begin{cases} 1, & \text{if} \quad t \le 2013, \\ \dfrac{1}{1+\theta \exp\left[\dfrac{(BDI_{after2013} - BDI_{before2013})}{BDI_{before2013}}\right]}, & \text{if} \quad t > 2013, \end{cases}$$

where $BDI_{after2013}$ and $BDI_{before2013}$ are the mean of Baidu index with respect to the syphilis after 2013 and before 2013, respectively. $(BDI_{after2013} - BDI_{before2013})/BDI_{before2013}$ describes the growth rate of Baidu index with respect to the syphilis. Here, we assume that the protective behaviors depend on the change of public awareness, which can be measured by the data of Baidu index during the study period. Since the increased public awareness (BDI) may change the protective behaviors of people and then reduce the contact rate, C_e is a decreasing function of BDI.

(iii) The condom plays an important role in prevention of syphilis (Chen et al., 2007). We use ε to reflect the compliance of condom-induced preventability of syphilis, which is negatively associated with the probability of infected by contacting with primary or secondary syphilis infections.

(iv) We ignore the death due to the syphilis (Syphilis. https://baike.b).

According to the flowchart in Fig. 4, the multi-stage syphilis transmission model is given as follows:

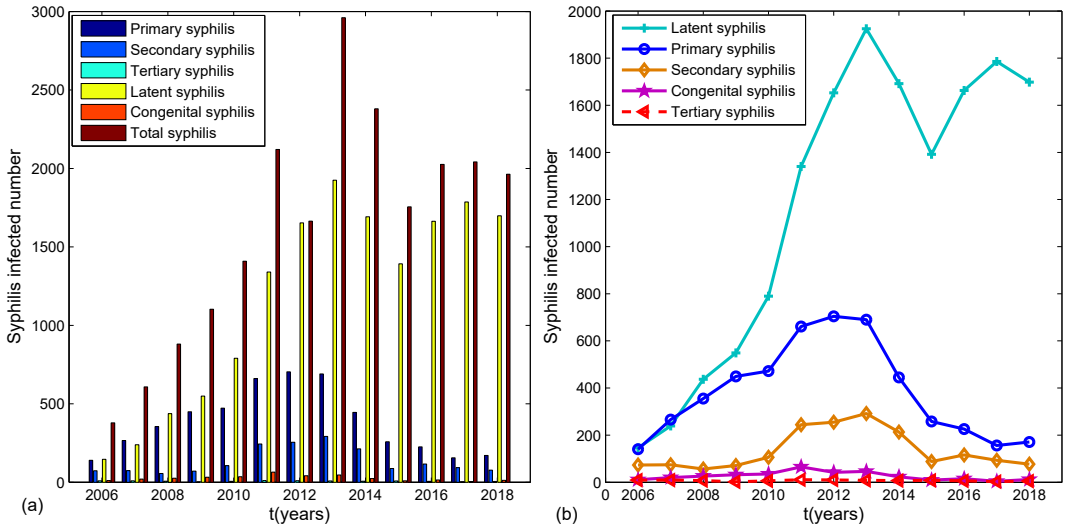

Fig. 3. The number of syphilis at different infection stages from 2006 to 2018 in Ningxia, China.

$$\begin{cases} \dfrac{dS(t)}{dt} = \Lambda - (1-\varepsilon)c_e\left[\beta_1 I_p(t) + \beta_2 I_s(t)\right]S(t) - \mu S(t) + \delta R(t), \\ \dfrac{dI_p(t)}{dt} = (1-\varepsilon)c_e\left[\beta_1 I_p(t) + \beta_2 I_s(t)\right]S(t) - (r_1 + m_1 + \mu)I_p(t), \\ \dfrac{dI_s(t)}{dt} = r_1 I_p(t) - (m_2 + r_2 + \mu)I_s(t), \\ \dfrac{dL(t)}{dt} = r_2 I_s(t) - (m_3 + r_3 + \mu)L(t), \\ \dfrac{dI_t(t)}{dt} = r_3 L(t) - (m_4 + \mu)I_t(t), \\ \dfrac{dR(t)}{dt} = m_1 I_p(t) + m_2 I_s(t) + m_3 L(t) + m_4 I_t(t) - (\delta + \mu)R(t), \end{cases} \tag{1}$$

with initial values

$$S(0) = S_0 \geq 0, I_p(0) = I_{p0} \geq 0, I_s(0) = I_{s0} \geq 0, L(0) = L_0 \geq 0, I_t(0) = I_{t0} \geq 0, R(0) = R_0 \geq 0. \tag{2}$$

All parameters are positive and the corresponding biological meanings are listed in Table 1.
Note that $N(t)$ is the total population size, and $N(t) = S(t) + I_p(t) + I_s(t) + L(t) + I_t(t) + R(t)$. Then, we have

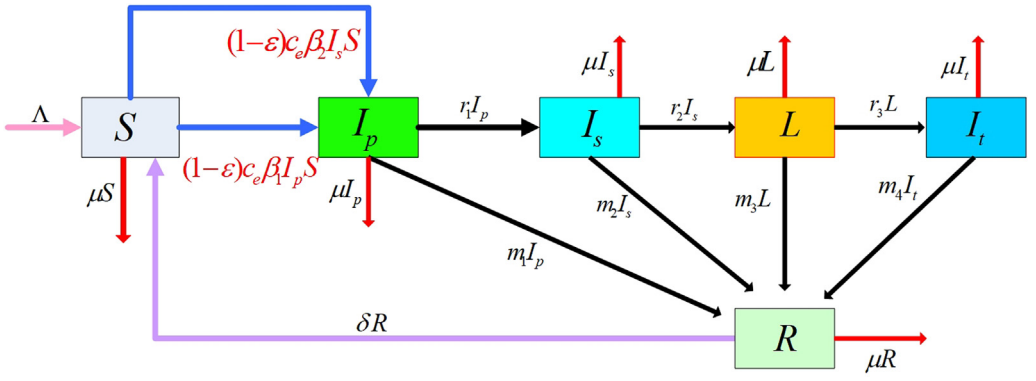

Fig. 4. The flow chart of syphilis transmission with multiple-stage infections.

Table 1
Biological meanings of the parameters in model (1).

Parameters	Biological meanings	Unit
Λ	Growth rate of the population	per year
μ	Nature death rate	per year
β_1	Probability of infected contact by primary syphilis	–
β_2	Probability of infected contact by secondary syphilis	–
ε	Efficiency of condom-induced preventability of syphilis	–
c_e	The protective behaviors rate	per year
r_1	Progression rate of primary syphilis becomes secondary syphilis	per year
r_2	Progression rate of secondary syphilis becomes latent syphilis	per year
r_3	Progression rate of latent syphilis becomes tertiary syphilis	per year
m_1	Treatment rate in primary syphilis stage	per year
m_2	Treatment rate in secondary syphilis stage	per year
m_3	Treatment rate in latent syphilis stage	per year
m_4	Treatment rate in tertiary syphilis stage	per year
δ	Relapse rate of recovered return to susceptible subpopulation	per year

$$\frac{dN(t)}{dt} = \Lambda - \mu N(t), \tag{3}$$

which implies that $\limsup_{t} \to\infty N\ (t\ ) \le \frac{\Lambda}{\mu}$. Furthermore, we can obtain the feasible region of model (1)

$$\Gamma = \left\{ \left(S, I_p, I_s, L, I_t, R \right) \in \mathbb{R}_+^6 0 \le S(t) + I_p(t) + I_s(t) + L(t) + I_t(t) + R(t) \le \frac{\Lambda}{\mu} \right\} \tag{4}$$

It is the positively invariant of model (1).

2 3. Model analysis

The basic reproduction number $\mathcal{R}_0$, one important threshold quantity to determine whether an epidemic will spread or die out, is defined as the expected number of secondary cases produced by one infected person during its infectious period in a completely susceptible population (Diekmann et al., 1990). Notice that $E^0 = (S^0, 0, 0, 0, 0, 0)$ is the disease-free equilibrium of model (1.1), where $S^0 = \frac{\Lambda}{\mu}$. The disease states are I_p, I_s, L and I_t. Following the next generation matrix methods in (van den Dreessche & Watmough, 2008), we can define that

$$\mathscr{F} = \begin{pmatrix} (1-\varepsilon)c_e(\beta_1 I_p + \beta_2 I_s)S \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad \text{and} \quad \mathscr{V} = \begin{pmatrix} (r_1 + m_1 + \mu)I_p \\ -r_1 I_p + (m_2 + r_2 + \mu)I_s \\ -r_2 I_s + (m_3 + r_3 + \mu)L \\ -r_3 L + (m_4 + \mu)I_t \end{pmatrix}$$

Then

$$F = \begin{pmatrix} (1-\varepsilon)c_e\beta_1 S^0 & (1-\varepsilon)c_e\beta_2 S^0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

and

$$V = \begin{pmatrix} r_1 + m_1 + \mu & 0 & 0 & 0 \\ -r_1 & m_2 + r_2 + \mu & 0 & 0 \\ 0 & -r_2 & m_3 + r_3 + \mu & 0 \\ 0 & 0 & -r_3 & m_4 + \mu \end{pmatrix}$$

Then, we can calculate that

$$FV^{-1} = \begin{pmatrix} \frac{(1-\varepsilon)c_e\beta_1\Lambda}{\mu(r_1+m_1+\mu)} + \frac{(1-\varepsilon)c_e\beta_2 r_1\Lambda}{\mu(r_1+m_1+\mu)(m_2+r_2+\mu)} & \frac{(1-\varepsilon)c_e\beta_2\Lambda}{\mu(m_2+r_2+\mu)} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

The basic reproduction number of model (1) is the largest eigenvalue of the matrix FV^{-1}, that is

$$\mathcal{R}_0 = \rho(FV^{-1}) = \frac{(1-\varepsilon)c_e\beta_1\Lambda}{\mu(r_1+m_1+\mu)} + \frac{(1-\varepsilon)c_e\beta_2 r_1\Lambda}{\mu(r_1+m_1+\mu)(m_2+r_2+\mu)} = \mathcal{R}_{01} + \mathcal{R}_{02}. \tag{5}$$

Remark 2.1. Notice that $\mathcal{R}_{01}$ and $\mathcal{R}_{02}$ are the expected number of new infections caused by the primary and secondary syphilis infected population, respectively. $r_1 + m_1 + \mu$ is the average duration of infection at the first stage, and $r_2 + m_2 + \mu$ is the average duration of infection at the secondary stage. The endemic equilibrium $E^* = (S^*, I_p^*, I_s^*, L^*, I_t^*, R^*)$ of model (1) is determined by the following equations for a special case ($\delta = 0$):

$$\begin{cases} \Lambda - \mu S^* - (1-\varepsilon)c_e\left(\beta_1 I_p^* + \beta_2 I_s^*\right)S^* = 0, \\ (1-\varepsilon)c_e(\beta_1 I_p^* + \beta_2 I_s^*)S^* - k_1 I_p^* = 0, \\ r_1 I_p^* - k_2 I_s^* = 0, \\ r_2 I_s^* - k_3 L^* = 0, \\ r_3 L^* - k_4 I_t^* = 0, \\ m_1 I_p^* + m_2 I_s^* + m_3 L^* + m_4 I_t^* - \mu R^* = 0, \end{cases} \tag{6}$$

where $k_1 = r_1 + m_1 + \mu$, $k_2 = m_2 + r_2 + \mu$, $k_3 = m_3 + r_3 + \mu$, $k_4 = m_4 + \mu$.

By a simple calculation from (6), we have that if $\mathcal{R}_0 > 1$, there exists only one positive endemic equilibrium E^* which satisfies

$$S^* = \frac{k_1 k_2}{(1-\varepsilon)c_e(\beta_1 k_2 + \beta_2 r_1)}, \qquad I_p^* = \frac{k_2}{r_1} I_s^*, \qquad L^* = \frac{r_2}{k_3} I_s^*, \qquad I_t^* = \frac{r_2 r_3}{k_3 k_4} I_s^*,$$

$$R^* = \frac{1}{\mu}\left(\frac{m_1 k_2}{r_1} + m_2 + m_3\frac{r_2}{k_3} + m_4\frac{r_2 r_3}{k_3 k_4}\right) I_s^*,$$

and

$$I_s^* = \frac{r_1(1-\varepsilon)c_e(\beta_1 k_2 + \beta_2 r_1)}{\mu k_1^2 k_2^2}(\mathcal{R}_0 - 1).$$

We also give the following global stability of the disease-free equilibrium and endemic equilibrium for model (1). The proofs are deferred in Appendix.

Theorem 2.1. *The disease-free equilibrium E^0 is globally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

Theorem 2.2. *If $\mathcal{R}_0 > 1$ and $\delta = 0$, model (1) has only one endemic equilibrium E^*, which is globally asymptotically stable.*

3. Optimal control analysis

In this section, we extend model (1) by including two time-dependent control variables, which correspond to two control strategies, respectively. First, we use Pontryagin's Maximum Principle (Pontryagin et al., 1962) to derive the necessary conditions for the existence of an optimal control.

In model (1), we consider two control strategies. The control of using public health education and promotion program to change the protective behaviors, such as increasing the compliance of condom use or avoiding effective contact with high-risk groups, is denoted by a factor of $1 - u_1(t)$. The control variable $u_2(t)$ represents the treatment of syphilis in the primary or secondary stage. Then the optimal control model is give by

$$\begin{cases} \dfrac{dS(t)}{dt} = \Lambda - (1-u_1(t))(1-\varepsilon)c_e\big(\beta_1 I_p(t) + \beta_2 I_s(t)\big)S(t) - \mu S(t) + \delta R(t), \\ \dfrac{dI_p(t)}{dt} = (1-u_1(t))(1-\varepsilon)c_e\big[\beta_1 I_p(t) + \beta_2 I_s(t)\big]S(t) - (r_1 + (1+u_2(t))m_1 + \mu)I_p(t), \\ \dfrac{dI_s(t)}{dt} = r_1 I_p(t) - ((1+u_2(t))m_2 + r_2 + \mu)I_s(t), \\ \dfrac{dL(t)}{dt} = r_2 I_s(t) - (m_3 + r_3 + \mu)L(t), \\ \dfrac{dI_t(t)}{dt} = r_3 L(t) - (m_4 + \mu)I_t(t), \\ \dfrac{dR(t)}{dt} = (1+u_2(t))m_1 I_p(t) + (1+u_2(t))m_2 I_s(t) + m_3 L(t) + m_4 I_t(t) - (\delta + \mu)R(t). \end{cases} \tag{7}$$

For a nonnegative initial condition, the control function $u(t) = (u_1(t), u_2(t))$ belongs to the control set U defined by

$$U = \Big\{(u_1, u_2) : u_i \text{ is Lebsegue measurable},\ 0 \le u_i(t) \le 1, t \in \Big[0, t_f\Big], i = 1, 2\Big\}, \tag{8}$$

where t_f is the control period. System (7) has nonnegative bounded solutions. Then the optimal control problem corresponds to minimizing the objective function

$$J = \int_0^{t_f} \Big[A_1 I_p + A_2 I_s + A_3 L + A_4 I_t + \frac{1}{2}\Big(\xi_1 u_1^2 + \xi_2 u_2^2\Big)\Big]dt, \tag{9}$$

where A_i, $i = 1, 2, 3, 4$ represent the weights for the numbers of primary, secondary, latent and tertiary syphilis infection population, respectively. The values of ξ_1 and ξ_2 are measures of the benefit and cost associated with the control variables u_1 and u_2, respectively.

Theorem 3.1. *There exists* $u^* = (u_1^*, u_2^*) \in U$ *such that*

$$J(u_1^*, u_2^*) = \min_U J(u_1, u_2),$$

subjecting to the control model (7) with the initial conditions.

Proof. The existence of an optimal control can be verified by applying the results in Lukes (1982). It is easy to check that both the state variables and control variables are non-negative. The control set U is closed and convex by its definition, and the integrand of function (9), i.e., $A_1 I_p + A_2 I_s + A_3 L + A_4 I_t + \frac{1}{2}(\xi_1 u_1^2 + \xi_2 u_2^2)$, is also convex on U. The control system (7) is bounded which determines the compactness of the existence of the optimal control. Thus, there exists a constant $\kappa > 1$, and positive values υ_1 and υ_2, such that

$$A_1 I_p + A_2 I_S + A_3 L + A_4 I_t + \frac{1}{2}\Big(\xi_1 u_1^2 + \xi_2 u_2^2\Big) \ge \upsilon_1(|u_1|^2 + |u_2|^2)^{\frac{\kappa}{2}} - \upsilon_2.$$

This completes the existence of an optimal control.

Next, to determine the characterization of the optimal control, we consider the optimal control problem (7)–(9) to find the Lagrangian function and Hamiltonian function according to the Pontrygain's Maximum Principle. The Lagrangian function is

$$L(S, I_p, I_s, L, I_t, R, u) = A_1 I_p(t) + A_2 I_s(t) + A_3 L(t) + A_4 I_t(t) + \frac{1}{2}\Big(\xi_1 u_1^2 + \xi_2 u_2^2\Big),$$

and the Hamiltonian function is

$$
\begin{aligned}
H(S, I_p, I_s, L, I_t, R, u_1, u_2, \lambda) = {} & A_1 I_p(t) + A_2 I_s(t) + A_3 L(t) + A_4 I_t(t) + \tfrac{1}{2}\left(\xi_1 u_1^2 + \xi_2 u_2^2\right) \\
& + \lambda_1(t)\left[\Lambda - (1-u_1(t))(1-\varepsilon)c_e\left(\beta_1 I_p(t) + \beta_2 I_s(t)\right)S(t) - \mu S(t) + \delta R(t)\right] \\
& + \lambda_2(t)\left[(1-u_1(t))(1-\varepsilon)c_e\left(\beta_1 I_p(t) + \beta_2 I_s(t)\right)S(t) - (r_1 + (1+u_2(t))m_1 + \mu)I_p(t)\right] \\
& + \lambda_3(t)\left[r_1 I_p(t) - ((1+u_2(t))m_2 + r_2 + \mu)I_s(t)\right] \\
& + \lambda_4(t)[r_2 I_s(t) - (m_3 + r_3 + \mu)L(t)] + \lambda_5(t)[r_3 L(t) - (m_4 + \mu)I_t(t) \\
& + \lambda_6(t)\left[(1+u_2(t))m_1 I_p(t) + (1+u_2(t))m_2 I_s(t) + m_3 L(t) + m_4 I_t(t) - (\delta + \mu)R(t)\right],
\end{aligned}
\tag{10}
$$

where $\lambda_i(t)$, $i = 1, 2, \ldots, 6$ are adjoint variables.

Theorem 3.2. *Let S, I_p, I_s, L, I_t and R be the state solutions for model (1). Given an optimal control* $(u_1{}^*, u_2{}^*)$, *there exist adjoint variables*, $\lambda_i(t)$, $i = 1, 2, \ldots, 6$ *satisfying*

$$
\begin{cases}
\dfrac{d\lambda_1(t)}{dt} = \lambda_1\left[\mu + (1-u_1)(1-\varepsilon)c_e\left(\beta_1 I_p(t) + \beta_2 I_s(t)\right) - \Lambda\right] - \lambda_2\left[(1-u_1)(1-\varepsilon)c_e\left(\beta_1 I_p(t) + \beta_2 I_s(t)\right)\right], \\
\dfrac{d\lambda_2(t)}{dt} = [r_1 + (1+u_2)m_1 + \mu]\lambda_2 - \lambda_3 r_1 - \lambda_6(1+u_2)m_1 + (1-u_1)(1-\varepsilon)c_e\beta_1(\lambda_1 + \lambda_2)S - A_1, \\
\dfrac{d\lambda_3(t)}{dt} = (1-u_1)(1-\varepsilon)c_e\beta_2(\lambda_1 + \lambda_2)S - A_2 - [(1+u_2)m_2 + r_2 + \mu]\lambda_3 - r_2\lambda_4 - (1+u_2)m_2\lambda_6, \\
\dfrac{d\lambda_4(t)}{dt} = (m_2 + r_3 + \mu)\lambda_4 + r_3\lambda_5 + m_3\lambda_2 - A_3, \\
\dfrac{d\lambda_5(t)}{dt} = (m_4 + \mu)\lambda_5 - m_4\lambda_6 - A_4, \\
\dfrac{d\lambda_6(t)}{dt} = (\delta + \mu)\lambda_6 - \lambda_1\delta.
\end{cases}
$$

The terminal (boundary) condition are $\lambda_i(t_f) = 0$, $i = 1, 2, \ldots, 6$. *Furthermore, the optimal control* $u_1{}^*, u_2{}^*$ *are represented by*

$$
u_1^*(t) = \min\{\max\{u_1^c, 0\}, 1\}, u_2^*(t) = \min\{\max\{u_2^c, 0\}, 1\}, \tag{11}
$$

with

$$
u_1^c = \frac{(\lambda_2 - \lambda_1)(1-\varepsilon)c_e\left(\beta_1 I_p(t) + \beta_2 I_s(t)\right)S}{\xi_1}, u_2^c = \frac{(\lambda_2 - \lambda_6)m_1 I_p + (\lambda_3 - \lambda_6)m_2 I_s}{\xi_2}.
$$

Thus, we have

$$
u_i^* = \begin{cases} 0, & \text{if } u_i^c \le 0, \\ u_i^c, & \text{if } 0 < u_i^c < 1, \\ 1, & \text{if } u_i^c \ge 0, \end{cases}
$$

for $i = 1, 2$.

Proof. According to Pontryagin's maximum principle, the adjoint system can be obtained by

$$
\frac{d\lambda_i(t)}{dt} = -\frac{\partial H}{\partial x},
$$

where $x = S$, I_p, I_s, L, I_t and R. The terminal (boundary) condition are $\lambda_i(t_f) = 0$, $i = 1, 2, \ldots, 6$.

To derive the characterization of the optimal control in (11), we solve the equations on the interior of the control set U,

$$
\frac{\partial H}{\partial u_1} = 0 \quad \text{and} \quad \frac{\partial H}{\partial u_2} = 0.
$$

Substituting the terminal (boundary) condition for the control, the proof is completed.

Table 2
Parameter values in model (1).

Parameters	Unit	Baseline Value	Range	Source
Λ	person year^{-1}	6.098×10^{4}		Estimated
μ	year^{-1}	6.592×10^{-2}	(0.0141,0.0748)	Calculated (Ningxia data. http://nxda, 2021)
β_1	Dimensionless	1.237×10^{-6}	$(0.9330, 1.3029) \times 10^{-6}$	Estimated
β_2	Dimensionless	2.798×10^{-6}	$(1.1706, 8.2888) \times 10^{-6}$	Estimated
ε	Dimensionless	0.8	(0.5,1)	Garnett et al. (1997)
c_e	year^{-1}	4.6886	(3.3303,4.9928)	Estimated
r_1	year^{-1}	2.4624×10^{-4}		Garnett et al. (1997)
r_2	year^{-1}	1.3909	(1,2)	Garnett et al. (1997)
r_3	year^{-1}	9	(5.4,13.5)	Garnett et al. (1997)
m_1	year^{-1}	0.8967	(0,1)	Chen et al. (2007)
m_2	year^{-1}	0.8071	(0,1)	(Syphilis.)
m_3	year^{-1}	0.9626	(0,1)	(Syphilis.)
m_4	year^{-1}	0.0451	(0,1)	(Syphilis.)
δ	year^{-1}	1.6590×10^{-6}	(0,1)	Calculated (CDC, 2021)

4. Model calibration and sensitivity analysis

4.1. Model calibration from 2006 to 2018

According to existing literature, we can estimate the parameters whose values are listed in Table 2. The detailed estimation process of the parameter values are as follows:

(a) From the statistic results of Ningxia population statistic yearbook during 2006–2018, we can obtain the natural death rate of the whole population. The mean and the 95% confidence interval of the natural death rates are $\mu = 4.72 \times 10^{-3}$, 95%CI($4.59 \times 10^{-3}$, 4.83×10^{-3}).
(b) The initial data of model (1) are $S_0 = 2208245 \times 63\% = 1391194$,$I_{p0} = 73$,$I_{S0} = 140$,$L_0 = 146$,$I_{t0} = 9$,$R_0 = 0$ according to the real monitoring data at the beginning time of our study period.
(c) Using of the parameters listed in Table 2 and model (1), we simulated the infectious number of syphilis from 2006 to 2018. The parameters Λ, β_1, β_2 and C_e are obtained by the nonlinear Least-square method with the help of MATLAB tool *fminsearch*.

Fig. 5 shows the fitted result of model (1) and the syphilis infected data ($I = I_p + I_s + L + I_t$) from 2006 to 2018 in Ningxia. We observed that the actual infectious number of syphilis in Ningxia almost fall in the 95% CI of the simulation trajectories. Although some of the data are beyond or above the confidence level, our simulation results are in good agreement with the actual data in general.

4.2. Sensitivity analysis

Uncertainty and sensitivity analysis are necessary to explore the behavior of many complex models, since the structural complexity of models are coupled with a high degree of uncertainty in estimating the values of many input parameters (Blower & Dowlatabadi, 1994). In this section, we perform sensitivity analysis to quantify the impacts of each parameter in model (1) by using Latin Hypercube Sampling (LHS) and partial rank correlation coefficient (PRCC).

LHS is a stratified sampling technique which allows for an coefficient analysis of multiple parameters across uncertainty ranges simultaneously (Marino et al., 2008; Sanchez & Blower, 1997). With the simulated parameter values and the data of syphilis from 2006 to 2018 in Ningxia, we can obtain the numerical distribution of the basic reproduction number $\mathcal{R}_0$ (see Fig. 6 for more details), whose estimate is $\mathcal{R}_0 = 1.2344$ and the 95% confidence interval is (0.6735, 1.7952).

For the sensitivity analysis of $\mathcal{R}_0$, we can calculate partial rank correlation coefficient (PRCC), which reflects the correlations between parameters and $\mathcal{R}_0$. The PRCC of the estimated parameters with respect to $\mathcal{R}_0$ are listed in Table 3. It follows from Table 3 that there exists a positive correlation between C_e, Λ, β_1, β_2 and $\mathcal{R}_0$, and a negative correlation between μ, ε, m_1,

Table 3
PRCC of the estimated parameters with respect to $\mathcal{R}_0$.

Parameters	PRCC	p-value	Parameters	PRCC	p-value
c_e	0.1786	<0.001	ε	−0.5720	<0.001
Λ	0.0917	0.0039	m_1	−0.1828	<0.001
β_1	0.0738	0.0202	m_2	−0.0873	0.0178
β_2	0.06	0.0589	r_1	−0.0487	0.1255
r_2	0.0362	0.255	μ	−0.0933	<0.001

m_2, r_1, r_2, and $\mathcal{R}_0$. These results suggest that the public awareness C_e, health behaviors compliance ε and treatment m_1 play the most important role to mitigate the risk of syphilis in Ningxia. Thus, the syphilis can be effectively mitigated by using the following control strategies:

- Continue to carry out public health education programmes and improve the compliance of healthy behaviors (i.e., increase public awareness C_e and health behaviors compliance ε).
- Carry out standardized treatment as early as possible for patients at the primary syphilis, which can increase the effects of treatment (i.e. increase m_1).

4.3. Assessment of control strategies

In this subsection, we further investigate the impacts of various control strategies on reducing the spread of syphilis in Ningxia. Based on the validated parameters listed in Table 2, we carry out the following numerical simulations to explore the migration strategies on the total infected number ($I = I_p + I_s + L + I_t$) and infection risk ($\mathcal{R}_0$), respectively.

In Fig. 7, we study the effect of public awareness induced protective behaviors of syphilis C_e, the compliance of condom-induced preventability of syphilis ε, and treatment of the primary syphilis m_1, on the dynamics of total number of infectious with syphilis. Fig. 7 (a) shows that the infectious number of syphilis is decreasing when the protective behaviors effective rate C_e decreases from baseline value to its 70%. Fig. 7 (b) illustrates that with the compliance rate of condom-induced preventability of syphilis ε increasing from baseline value to 130%, the infected number of syphilis is decreasing significantly. Fig. 7 (c) indicates that increasing the treatment rate for the primary stage syphilis m_1, fewer susceptible population will be infected by syphilis.

In Fig. 8, we explore the joint effects of C_e, ε and m_1 on the infection risk $\mathcal{R}_0$. As shown in Fig. 8 (a), the infection risk decreases with the increase in m_1 and ε. In Fig. 8(b), the risk of syphilis decreases when increasing m_1 and decreasing C_e. Fig. 8 (c) shows that decreasing C_e and increasing ε simultaneously, the risk of syphilis infection is significantly reduced.

Based on above analysis, we can draw the conclusion that the joint control strategies of C_e, ε and m_1 can significantly reduce the risk of syphilis infection below unit.

5. Conclusion

In face of health threat posed by increasing syphilis worldwide, WHO have publicized plans to eliminate syphilis actively and set syphilis reduction targets for 2030 (World Health Organization, 2021). Public health awareness and behaviors play an important role in the prevention and control of sexually transmitted disease. In this paper, we develop a multiple-stage SIRS epidemic model considering the public health awareness and behaviors of syphilis. The basic reproduction number $\mathcal{R}_0$ of the model is calculated. We also proved that if $\mathcal{R}_0 < 1$, the disease-free equilibrium E^0 is globally asymptotically stable, then syphilis epidemic could be controlled. But if $\mathcal{R}_0 > 1$ and $\delta = 0$, the model admits a unique endemic equilibrium E^*, which is

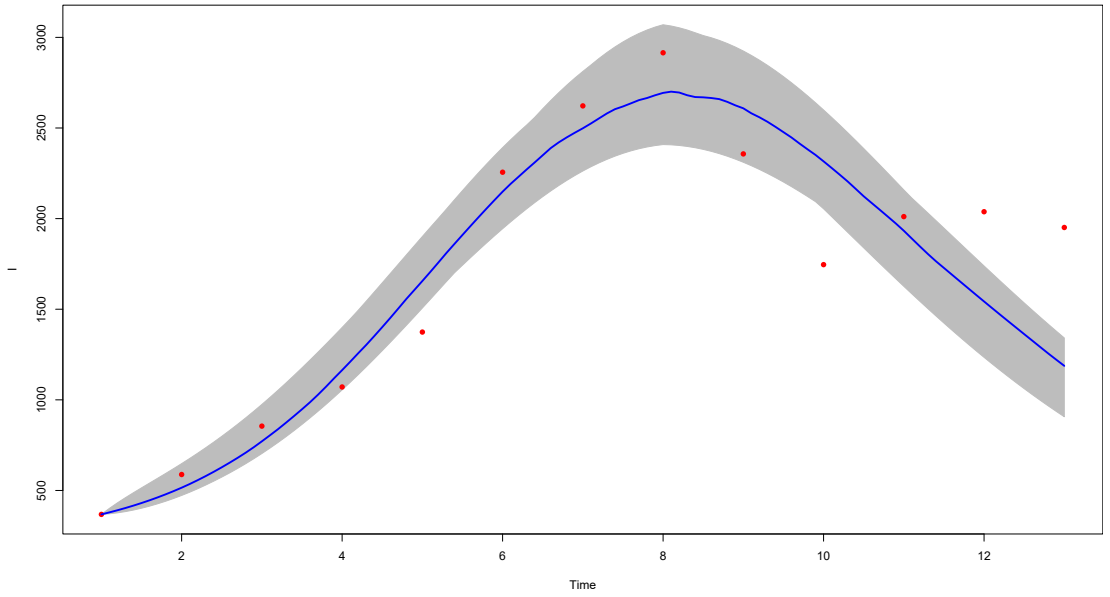

Fig. 5. The fitted result of model (1) with the syphilis infected data (total infected number $I = I_p + I_s + L + I_t$) from 2006 to 2018 in Ningxia.

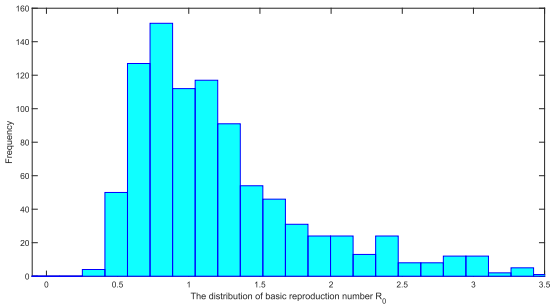

Fig. 6. The numerical distribution of the basic reproduction number $\mathcal{R}_0$.

globally asymptotically stable. Moreover, we derive the necessary conditions for implementing optimal control and the corresponding optimal solution for mitigation syphilis by using Pontryagin's Maximum Principle.

Based on the data of syphilis in Ningxia from 2006 to 2018, the parameterizations and model calibration are carried out. The numerical solution of model (1) is in close agreement with the data (as shown in Fig. 5). The basic reproduction number of syphilis is estimated to be approximately $R_0 = 1.2344$ with a 95% confidence interval $(0.6735, 1.7952)$. The sensitivity analysis (PRCC) of parameters with respect to $\mathcal{R}_0$ shows that the public awareness induced protective behaviors C_e, compliance of condom-induced preventability ε and treatment for the primary syphilis m_1 play a critical role in mitigating the syphilis outbreaks. We then explore the impact of various control strategies on reducing the infected number of syphilis, that is, decreasing C_e, increasing ε, and increasing m_1, respectively. Since the singular implementation of any one strategy discussed above may be not sufficient to effectively control syphilis at the population-level (as shown in Fig. 7), the joint control strategy is more effective to reduce the infectious number of syphilis at a more attainable level. These results can help us understand the epidemiology of syphilis and provide guidance for the public health authorities to implement health education programs. More precisely,

(i) Decreasing the public awareness induced protective behaviors C_e is helpful for the prevention and control of syphilis. The increasing public awareness leads to more protective behaviors of syphilis being carried out, which reduces the contact rate between susceptible and infectious individuals (Rahman & Rahman, 2007). Generally, public health education programs play a tremendous role in limiting the spread of infectious disease (Gallagher & Updegraff, 2012; Yan et al., 2016), by changing the behaviors of susceptibles (Greenhalgh et al., 2015; Zhao et al., 2018).

(ii) In the past years, much work has been done to investigate the effects of using condom on the dynamics of sexually-transmitted diseases (Gutierrez et al., 2010). For example, Zhou pointed out that chlamydia and gonorrhea are twice as likely to be infected as syphilis if condoms are not used (Zhou et al., 2012). Gutierrez et al. (Gutierrez et al., 2010) showed a positive relationship between general increase in condom use and its effect on the sero-prevalence of STDs. Thus, increasing the compliance of condom-induced preventability ε is beneficial in controlling syphilis by reducing the probability of infection in susceptible subpopulation.

(iii) Since there is no safe and effective vaccine against syphilis currently, syphilis control relies heavily on early diagnosis and treatment of syphilis in the primary stage. The early syphilis infection can be treated by penicillin G benzathine (Stamm, 2010; Yang et al., 2010). As a result, increasing the treatment for the primary stage m_1 can favor the control of infection risk of syphilis. This reinforces results of our endemic model, that is, early treatment is important to control syphilis. Thus, reliable diagnostic tests to detect syphilis in its primary stage is crucial to disease control.

This study also has several limitations: First, there are some new developed approaches to reduce the syphilis epidemic in different regions recently. For example, Juher et al. (Juher et al., 2017) designed a new notification strategies (partner notification (PN) system), indicating that notifying the community about the infection state of few central nodes can potentially contribute to reducing the number of cases. Whereas we only consider two kinds of control strategies (public health awareness induced protective behaviors and treatment of syphilis in the primary or secondary stage) in this study. More intervention strategies, such as notification strategies, etc, are included in model (1) may be more practical. Second, unfortunately, some of the data are beyond or above the confidence level in Fig. 5, there are some reasons may be responsible to this. With the development of economy, the incidence of syphilis in Yinchuan increased rapidly. Center for Disease Control and Prevention of Yinchuan carried out standardized diagnosis, treatment and accuracy verification of syphilis in basic public health services after 2013, which increases the report rate of syphilis patients. Thus, the change of report rate may be responsible to the slight rebound of infected number of syphilis from 2015 to 2017. Considering a syphilis model with time-dependent report rate may be more realistic. This is also a limitation. Third, development of a syphilis vaccine would be a potential promising step towards control. Champredon et al. (Champredon et al., 2016) used a mathematical model to explore the potential impact of rolling out a hypothetical syphilis vaccine on morbidity from both syphilis and HIV and compare it to the impact of expanded screen and treat programmes using existing treatments, they suggested that an efficacious vaccine

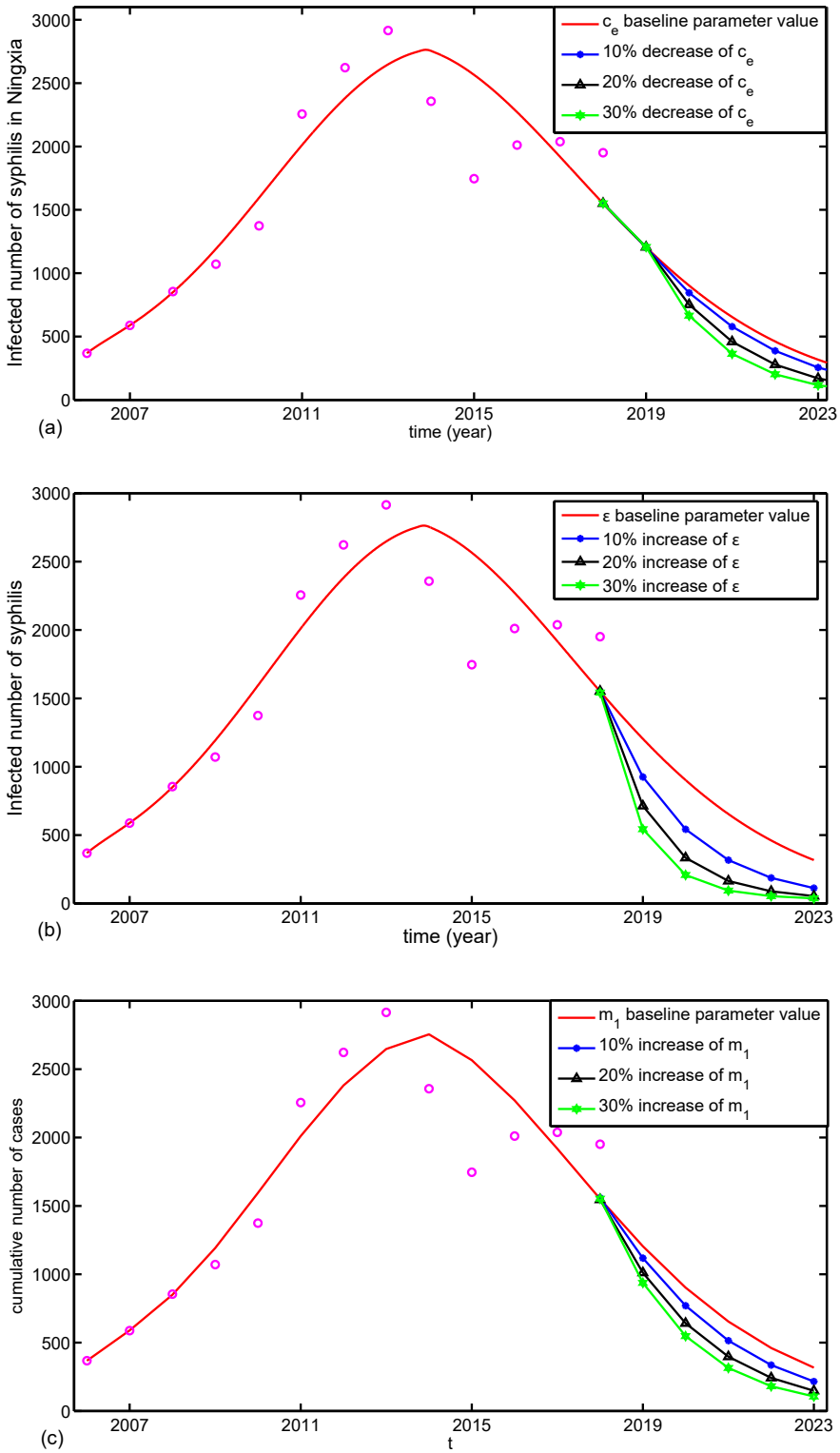

Fig. 7. Sensitivity of the solutions of model (1) with respect to parameters C_e, ε and m_2. The infectious number of syphilis (a) under migration strategy of decreasing C_e from 1 to 0.7; (b) under migration strategy of increasing ε from 1 to 1.3; and (c) under migration strategy of increasing m_1 from 1 to 1.3, respectively.

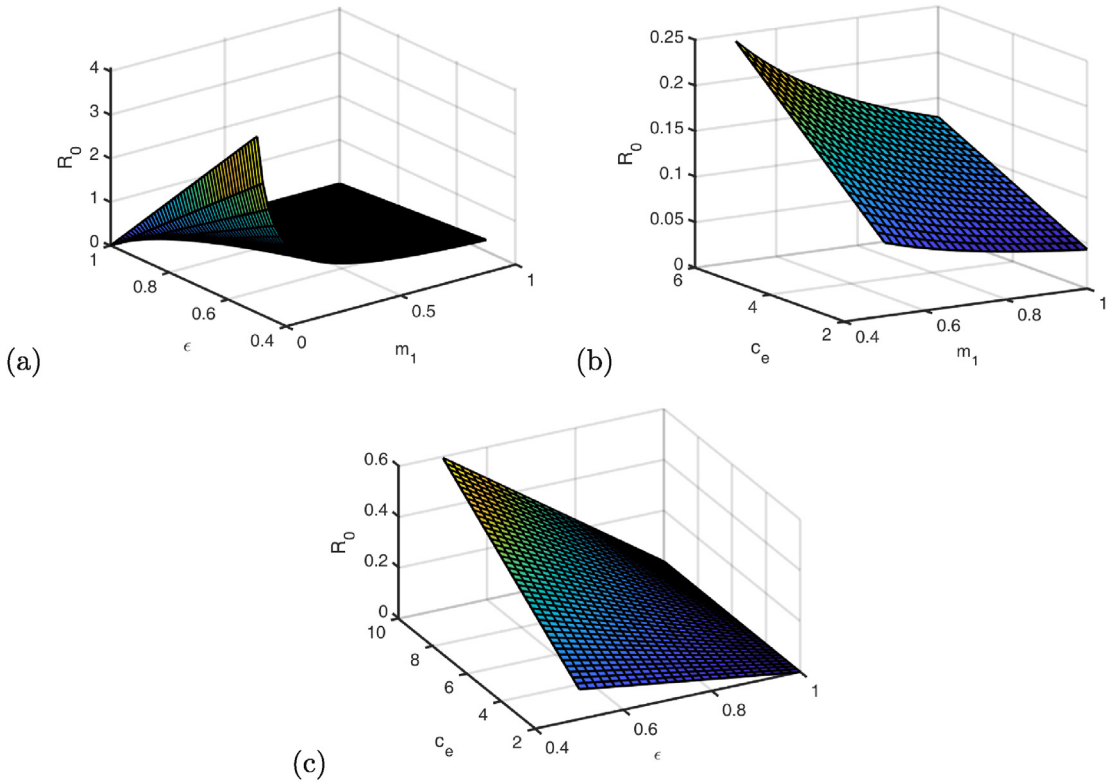

Fig. 8. The effects of ε, m_1 and C_e on the infection risk ($\mathcal{R}_0$). (a) $\mathcal{R}_0$ with respect to ε and m_1, (b) $\mathcal{R}_0$ with respect to m_1 and C_e, (b) $\mathcal{R}_0$ with respect to ε and C_e.

has the potential to sharply reduce syphilis prevalence under a wide range of scenarios. We ignore the syphilis vaccine in model (1) due to vaccine is not yet available for syphilis, whereas it is worth to consider this issue in future.

Declaration of competing interest

The authors declare that there is no conflict of interests regarding the publication of this paper. All authors read and agree to submit this manuscript to your journal.

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Appendix

Proof of Theorem 2.1. The Jacobian matrix $\mathcal{J}_0$ at the disease-free equilibrium is

$$\mathcal{J}_0 = \begin{pmatrix} -\mu & -(1-\varepsilon)c_e\beta_1 S^0 & -(1-\varepsilon)c_e\beta_2 S^0 & 0 & 0 & 0 \\ 0 & (1-\varepsilon)c_e\beta_1 S^0 - k_1 & (1-\varepsilon)c_e\beta_2 S^0 & 0 & 0 & 0 \\ 0 & r_1 & \beta_2 S^0 - k_2 & 0 & 0 & 0 \\ 0 & 0 & -k_2 & -k_3 & 0 & 0 \\ 0 & 0 & 0 & r_3 & -k_4 & 0 \\ 0 & m_1 & m_2 & m_3 & m_4 & -(\delta+\mu) \end{pmatrix} \tag{11}$$

where $k_i = m_i + r_i + \mu$ for $i = 1, 2, 3$, and $k_4 = m_4 + \mu$. The eigenvalues of the Jacobian matrix are

$$\lambda = -\mu, \lambda = -(m_3 + r_3 + \mu), \lambda = -(m_4 + \mu), \lambda = -(\delta + \mu),$$

and the roots λ_1 and λ_2 of the following equation:

$$\lambda^2 + \left[k_1 + k_2 - \frac{\Lambda(1-\varepsilon)c_e\beta_1}{\mu}\right]\lambda + k_1k_2(1-\mathcal{R}_0) = 0.$$

It follows from Vieta's formulas that if $\mathcal{R}_0 < 1$ then

$$\begin{aligned}\lambda_1 + \lambda_2 &= \frac{1}{2}\left[\frac{\Lambda(1-\varepsilon)c_e\beta_1}{\mu} - k_1 - k_2\right] < 0,\\ \lambda_1\lambda_2 &= k_1k_2(1-R_0) > 0,\end{aligned}$$

If and only if $\mathcal{R}_0 < 1$, all eigenvalues of the Jacobian matrix $\mathcal{J}_0$ have negative real parts. Thus, the disease-free equilibrium E^0 is locally asymptotically stable if $\mathcal{R}_0 < 1$.

Define a Lyapunov function V_1:

$$V_1 = \alpha_1 I_p + \alpha_2 I_s,$$

where

$$\alpha_1 = \frac{1}{k_1} + \frac{\beta_2 r_1}{\beta_1 k_1 k_2}, \alpha_2 = \frac{\beta_2}{\beta_1 k_2}.$$

Differentiating V_1 along solution of model (1) results in

$$\begin{aligned}\frac{dV_1}{dt} &= \alpha_1\frac{dI_p}{dt} + \alpha_2\frac{dI_s}{dt} = \alpha_1(1-\varepsilon)c_e\left[\beta_1 I_p S + \beta_2 I_s S - k_1 I_p\right] + \alpha_2\left(r_1 I_p - k_2 I_s\right)\\ &= \left[\alpha_1(1-\varepsilon)c_e\beta_1 S + \alpha_2 r_1 - \alpha_1 k_1\right]I_p + \left[\alpha_1(1-\varepsilon)c_e\beta_2 S - \alpha_2 k_2\right]I_s\\ &\le \left[\alpha_1(1-\varepsilon)c_e\beta_1 S^0 + \alpha_2 r_1 - \alpha_1 k_1\right]I_p + \left[\alpha_1(1-\varepsilon)c_e\beta_2 S^0 - \alpha_2 k_2\right]I_s\\ &= \left[\frac{(1-\varepsilon)c_e\beta_1 S^0}{k_1} + \frac{r_1(1-\varepsilon)c_e\beta_2 S^0}{k_1 k_2} - 1\right]I_p + \frac{\beta_2}{\beta_1}\left[\frac{(1-\varepsilon)c_e\beta_1 k_2 S^0}{k_1 k_2} + \frac{r_1(1-\varepsilon)c_e\beta_2 S^0}{k_1 k_2} - 1\right]I_s\\ &= \left[\frac{(1-\varepsilon)c_e\Lambda(\beta_1 k_2 + r_1\beta_2)}{\mu k_1 k_2} - 1\right]I_p + \frac{\beta_2}{\beta_1}\left[\frac{(1-\varepsilon)c_e\Lambda(\beta_1 k_2 + r_1\beta_2)}{\mu k_1 k_2} - 1\right]I_s\\ &= (\mathcal{R}_0 - 1)I_p + \frac{\beta_2}{\beta_1}(\mathcal{R}_0 - 1)I_s.\end{aligned} \tag{12}$$

It is easy to see that if $\mathcal{R}_0 \le 1$ then $\frac{dV_1}{dt} \le 0$. $\frac{dV_1}{dt} = 0$ if and only if $I_p(t) = I_s(t) = 0$. Thus, as $t \to \infty$, we have

$$(I_p(t), I_s(t), L(t), I_t(t), R(t)) \to (0, 0, 0, 0, 0).$$

Substituting $I_p(t) = I_s(t) = L(t) = I_t(t) = R(t) = 0$ into model (1) gives $S(t) \to \frac{\Lambda}{\mu}$ as $t \to \infty$. Therefore, according to the LaSalle's invariance principle (LaSalle & Lefschetz, 1976), the proof is completed.

Proof of Theorem 2.2. The Jacobian matrix $\mathcal{J}_1$ at the endemic equilibrium is

$$\mathcal{J}_1 = \begin{pmatrix} -(1-\varepsilon)c_e\left(\beta_1 I_p^* + \beta_2 I_s^*\right) - \mu & -(1-\varepsilon)c_e\beta_1 S^* & -(1-\varepsilon)c_e\beta_2 S^* & 0 & 0 & 0\\ (1-\varepsilon)c_e\left(\beta_1 I_p^* + \beta_2 I_s^*\right) & (1-\varepsilon)c_e\beta_1 S^* - k_1 & (1-\varepsilon)c_e\beta_2 S^* & 0 & 0 & 0\\ 0 & r_1 & -k_2 & 0 & 0 & 0\\ 0 & 0 & r_2 & -k_3 & 0 & 0\\ 0 & 0 & 0 & r_3 & -k_4 & 0\\ 0 & m_1 & m_2 & m_3 & m_4 & -\mu \end{pmatrix} \tag{13}$$

Let $\mathcal{J}_{11} = (\ -(1-\varepsilon)c_e\left(\beta_1 I_p{}^* + \beta_2 I_s{}^*\right) - \mu - (1-\varepsilon)c_e\beta_1 S^* - (1-\varepsilon)c_e\beta_2 S^*\ (1-\varepsilon)c_e\left(\beta_1 I_p{}^* + \beta_2 I_s{}^*\right)\ (1-\varepsilon)c_e\beta_1 S^* - k_1\ (1-\varepsilon)c_e\beta_2 S^*\ 0 r_1\ -k_2\ )$. We obtain the characteristic equation:

$$|xI-\mathcal{J}_{11}| = (x+\mu)\Big(x^2+(k_1+k_2-(1-\varepsilon)c_e\beta_1S^*)x+k_1k_2-(1-\varepsilon)c_ek_2\beta_1S^*-(1-\varepsilon)c_er_1\beta_2S^*\Big) + (1-\varepsilon)c_e\Big(\beta_1I_p^*+\beta_2I_s^*\Big)(x+k_1)(x+k_2) \quad = x^3+a_2x^2+a_1x+a_0,$$

where

$$a_0 = k_1k_2(1-\varepsilon)c_e\Big(\beta_1I_p^*+\beta_2I_s^*\Big),$$
$$a_1 = (1-\varepsilon)c_e\Big(\beta_1I_p^*+\beta_2I_s^*\Big)(k_1+k_2)+\mu\Big(k_2+\frac{(1-\varepsilon)c_e\beta_2r_1S^*}{k_2}\Big),$$
$$a_2 = \mu+k_2+\frac{(1-\varepsilon)c_e\beta_2r_1S^*}{k_2}+(1-\varepsilon)c_e\Big(\beta_1I_p^*+\beta_2I_s^*\Big).$$

Besides, it is easy to check that $a_1 > k_1\Big((1-\varepsilon)c_e(\beta_1I_p^*+\beta_2I_s^*)\Big) > 0$, $a_2 > k_2 > 0$ and

$$a_1a_2 > k_1k_2(1-\varepsilon)c_e\Big(\beta_1I_p^*+\beta_2I_s^*\Big) = a_0.$$

Noticing that $a_0 = \frac{k_1k_2}{\mu S^*}2(\mathcal{R}_0-1)$, the Routh-Hurwitz criterion implies that the endemic equilibrium E^* is locally asymptotically stable if $a_0 > 0$, which is equivalent to $\mathcal{R}_0 > 1$.

Next, we define a Lyapunov function V_2:

$$\begin{aligned} V_2 &= \Big(S-S^*-S^*ln\tfrac{S}{S^*}\Big)+\Big(I_p-I_p^*-I_p^*ln\tfrac{I_p}{I_p^*}\Big)+\gamma_1\Big(I_s-I_s^*-I_s^*ln\tfrac{I_s}{I_s^*}\Big) \\ &= V_{21}+V_{22}, \end{aligned} \tag{14}$$

with $\gamma_1 = (1-\varepsilon)c_e\beta_2I_s^*S^*\frac{1}{r_1I_p^*}$.

$$\frac{dV_{21}}{dt} = \Big(1-\frac{S^*}{S}\Big)\frac{dS}{dt}+\Big(1-\frac{I_p^*}{I_p}\Big)\frac{dI_p}{dt} = \Big(1-\frac{S^*}{S}\Big)\Big(\mu S^*+(1-\varepsilon)c_e\Big(\beta_1I_p^*+\beta_2I_s^*\Big)S^*-(1-\varepsilon)c_e[\beta_1I_p+\beta_2I_s]S-\mu S\Big)$$
$$+\Big(1-\frac{I_p^*}{I_p}\Big)\big((1-\varepsilon)c_e[\beta_1I_p+\beta_2I_s]S-k_1I_p\big) = -\mu\frac{(S-S^*)^2}{S}+(1-\varepsilon)c_e\Big(\beta_1I_p^*+\beta_2I_s^*\Big)S^*-(1-\varepsilon)c_e[\beta_1I_p+\beta_2I_s]S$$
$$-(1-\varepsilon)c_e\Big(\beta_1I_p^*+\beta_2I_s^*\Big)\frac{S^{*2}}{S}+(1-\varepsilon)c_e[\beta_1I_p+\beta_2I_s]S^*+(1-\varepsilon)c_e[\beta_1I_p+\beta_2I_s]S$$
$$-k_1I_p-(1-\varepsilon)c_e[\beta_1I_p+\beta_2I_s]\frac{SI_p^*}{I_p}+k_1I_p^* = -\mu\frac{(S-S^*)^2}{S}+(1-\varepsilon)c_e\Big(\beta_1I_p^*+\beta_2I_s^*\Big)S^*-(1-\varepsilon)c_e\Big(\beta_1I_p^*+\beta_2I_s^*\Big)\frac{S^{*2}}{S}$$
$$+(1-\varepsilon)c_e[\beta_1I_p+\beta_2I_s]S^*-k_1I_p^*\frac{I_p}{I_p^*}-(1-\varepsilon)c_e[\beta_1I_p+\beta_2I_s]\frac{SI_p^*}{I_p}+k_1I_p^* = -\mu\frac{(S-S^*)^2}{S}+(1-\varepsilon)c_e\beta_1I_p^*S^*\Big(2-\frac{S^*}{S}-\frac{S}{S^*}\Big)$$
$$+(1-\varepsilon)c_e\beta_2I_s^*S^*\Big(2-\frac{S^*}{S}+\frac{I_s}{I_s^*}-\frac{I_p}{I_p^*}-\frac{I_sI_p^*S}{I_s^*I_pS^*}\Big) \leqslant -\mu\frac{(S-S^*)^2}{S}+(1-\varepsilon)c_e\beta_1I_p^*S^*\Big(2-\frac{S^*}{S}-\frac{S}{S^*}\Big)$$
$$+(1-\varepsilon)c_e\beta_2I_s^*S^*\Big(\frac{I_s}{I_s^*}-ln\Big(\frac{I_s}{I_s^*}\Big)-\frac{I_p}{I_p^*}+ln\Big(\frac{I_p}{I_p^*}\Big)\Big),$$

and

$$\frac{dV_{22}}{dt} = \Big(1-\frac{I_s^*}{I_s}\Big)\frac{dI_s}{dt} = \Big(1-\frac{I_s^*}{I_s}\Big)(r_1I_p-k_2I_s)$$
$$= r_1I_p-k_2I_s-r_1\frac{I_pI_s^*}{I_s}+k_2I_s^*$$
$$= r_1I_p^*\Big(1+\frac{I_p}{I_p^*}-\frac{I_s}{I_s^*}-\frac{I_pI_s^*}{I_p^*I_s}\Big)$$
$$\leqslant r_1I_p^*\Big(\tfrac{I_p}{I_p^*}-ln\Big(\tfrac{I_p}{I_p^*}\Big)-\tfrac{I_s}{I_s^*}+ln\Big(\tfrac{I_s}{I_s^*}\Big)\Big)$$

Thus, we have

$$\frac{dV_2}{dt} = \frac{dV_{21}}{dt} + \frac{(1-\varepsilon)c_e\beta_2 I_s^* S^*}{r_1 I_p^*}\frac{dV_{22}}{dt} \leqslant -\mu\frac{(S-S^*)^2}{S} + (1-\varepsilon)c_e\beta_1 I_p^* S^*\left(2 - \frac{S^*}{S} - \frac{S}{S^*}\right) \leqslant 0.$$

It is clear that $\frac{dV_2}{dt} = 0$ if and only if $\mathcal{R}_0 = 1$. □

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