Mathematical Biosciences and Engineering

http://www.aimspress.com/journal/MBE

Mathematical Biosciences and Engineering, 16(1): 397–420.
DOI: 10.3934/mbe.2019019
Received: 04 April 2018
Accepted: 04 September 2018
Published: 13 December 2018

Research article

Dynamics of an age-structured heroin transmission model with vaccination and treatment

Xi-Chao Duan[1,*], **Xue-Zhi Li**[2,*] **and Maia Martcheva**[3]

[1] College of Science, University of Shanghai for Science and Technology, Shanghai 200093, China, School of Mathematical Sciences, Tongji University, Shanghai 200092, China

[2] College of Mathematics and Information Science, Henan Normal University, Xinxiang 453007, China

[3] Department of Mathematics, University of Florida, 358 Little Hall, PO Box 118105, Gainesville, FL 32611–8105, United States

* **Correspondence:** Email: xcduan82@126.com, xzli66@126.com.

Abstract: Based on the development of heroin vaccine, in this paper, we propose an age structured heroin transmission model with treatment and vaccination. The model allows the drug reuse rate of the individuals in treatment to depend on a treatment-age and the vaccine waning rate of the vaccinated to depend on a vaccination age. Meanwhile, the model allows that the heroin vaccine provides an imperfect protection (i.e., the vaccinated individuals can also become drug addicted). We derive the basic reproduction number which dependents on vaccination. The basic reproduction number completely determines the persistence and extinction of heroin spread, i.e., if the basic reproduction number is less than one the drug-free steady state is globally asymptotically stable (i.e., the heroin spread dies out), if the basic reproduction number is larger than one, there exists an unique positive steady state and it is locally and globally stable in some special cases. Finally, some numerical simulations are carried out to illustrate the stability of the positive steady state.

Keywords: heroin transmission model; age of vaccination; basic reproduction number; drug-free steady state; drug spread steady state

1. Introduction

Heroin is a highly abused opioid and incurs a significant detriment to society worldwide. Heroin usually appears as a white or brown powder or as a black sticky substance, known as “black tar heroin” [1], and its most frequent routes of delivery were intravenous injection (25%) and inhalation [12]. It crosses the blood-brain barrier within 15–20 seconds, rapidly achieving a high level syndrome in

the brain and the central nervous system which causes both the 'rush' experienced by users and the toxicity [25]. Heroin users are at high risk for addiction. It is estimated that about 23% of individuals who use heroin become dependent on it.

More recently, a heroin conjugate vaccine attracted much attentions. It was developed through comprehensive evaluation of hapten structure, carrier protein, adjuvant and dosing, which can generate a significant and sustained antidrug IgG titers in each subject and it is effective in rhesus monkeys [3]. Also, it is found that immunization of mice with an optimized heroin-tetanus toxoid (TT) conjugate can reduce heroin potency by $> 15\%$ and the vaccine effects proved to be durable and persisting for over eight months. Although it is unknown what will happen if the heroin vaccine is used in clinical setting, the heroin vaccine brings much hope for the defence against and control of heroin abuse.

In fact, the spread of heroin habituation and addiction can be well modeled by epidemic type models as "transmission" occurs in the form of peer pressure where established users recruit susceptible individuals into trying and using the drug [4, 9, 16], that is, mathematical modelling is a means to provide a general insight for how classes of drug takers behave, and as such, could hopefully becomes a useful device to aid specialist teams in devising treatment strategies. Modeling heroin addiction and spread in epidemic fashion is not new [21]. Recently, Fang *et al.* [10] proposed a age-structured heroin transmission model and proved its global dynamics behaviors. Usually, the population is divided into three classes, namely the number of susceptibles, $S(t)$, the number of drug users not in treatment, $U_1(t)$ and the number of drug users in treatment, $U_2(t)$, respectively. Naturally, we wonder how the heroin vaccine effects the heroin transmission process.

The study of vaccination has been the subject of intense theoretical analysis [2,7,8,14,17–20,27,29]. Based on the study of classical epidemic models, Kribs-Zaleta and Velasco-Hernández [17] added a compartment V into an SIS model and studied the vaccination of disease such as pertussis and tuberculosis; Kribs-Zaleta and Martcheva [18] studied the effects of a vaccination campaign upon spread of a non-fatal disease which features both acute and chronic infective stages, as well as variable infectivity and recovery rates in the chronic stage. Interestingly, Xiao and Tang [29] developed a simple SIV epidemic model including susceptible, infected and imperfectly vaccinated classes, with a nonlinear incidence rate and there would be backward bifurcations; Arino et al. [2] also showed that, if vaccines are imperfect, i.e., vaccinated individuals can be infected, there could be backward bifurcations.

To study the role of the heroin vaccine in the control of heroin abuse, adding a compartment $V(t)$ into a heroin transmission model is necessary. To our best knowledge, there is no related work in this field by now. Hopefully, mathematical modeling can provide a new insight into the interaction mechanism between the vaccinated, the susceptibles, the drug users and the individuals in treatment.

Motivated by the development of the heroin vaccine, in this paper, we present an age structured heroin transmission SU_1U_2V model which incorporates a drug reuse rate $\alpha(a)$ dependant on treat-age (i.e., the time since the host has been in treatment) and a vaccine waning rate dependant on vaccination age (i.e., the time since the host has been vaccinated). We also assume the susceptible population is vaccinated at a constant rate ψ, the vaccinated individuals can be infected at reduced rate $\sigma\beta$ with $0 \leq \sigma \leq 1$. Obviously, $\sigma = 0$ means the vaccine is completely effective in preventing infection, while

$\sigma = 1$ means that the vaccine is utterly ineffective. As a result, the system is as follows:

$$\begin{cases} \dfrac{dS}{dt} = \Lambda - (\mu + \psi)S(t) - \beta S(t)U_1(t) + \displaystyle\int_0^\infty \alpha(a)V(a,t)da, \\ \dfrac{dU_1}{dt} = \beta S(t)U_1(t) + \sigma\beta U_1(t)\displaystyle\int_0^\infty V(a,t)da + \int_0^\infty p(\theta)U_2(\theta,t)d\theta \\ \qquad\qquad -(\mu + \delta_1 + \gamma)U_1(t), \\ \dfrac{\partial U_2(\theta,t)}{\partial\theta} + \dfrac{\partial U_2(\theta,t)}{\partial t} = -(\mu + \delta_2 + p(\theta))U_2(\theta,t), \\ \dfrac{\partial V(a,t)}{\partial a} + \dfrac{\partial V(a,t)}{\partial t} = -(\mu + \alpha(a) + \sigma\beta U_1(t))V(a,t) \end{cases} \tag{1}$$

for $t > 0$, with the initial and boundary conditions:

$$\begin{cases} U_2(0,t) = \gamma U_1(t), \quad V(0,t) = \psi S(t), \\ S(0) = S_0,\ U_1(0) = U_{10},\ U_2(\theta,0) = U_{20}(\theta),\ V(a,0) = V_0(a), \end{cases} \tag{2}$$

where $U_{20}(\theta), V_0(a) \in L^1_+(0,\infty)$.

In system (1)–(2), θ is the treat-age, that is the time that has elapsed since a drug user is in treatment; $U_2(\theta,t)$ is the density of drug users in treatment with age θ at time t; $S(t)$ is the density of the susceptibles at time t; $U_1(t)$ is the density of drug users not in treatment, initial and relapsed drug users. The positive constant Λ is the recruitment of susceptible, μ the natural death rate of the general population, β is the force of drug use per contact with the susceptible per unit time, $\sigma\beta$ is the force of drug use per contact with the vaccinated individuals per unit time, γ is the rate of drug users who enter treatment, δ_1 a removal rate that includes drug-related deaths of users not in treatment and a spontaneous recovery rate, individuals not in treatment who stop using drugs but are no longer susceptible, δ_2 a removal rate that includes the drug-related deaths of users in treatment and a rate of successful "cure" that corresponds to recovery to a drug free life and immunity to drug addiction for the duration of the modelling time period. The function $p(\theta)$ is the probability of a drug user in treatment with the treatment-age θ relapsing to the untreated users.

Throughout the paper, we make the following assumptions: (A1) there is a positive number of drug users not in treatment, i.e., $U_{10} > 0$; (A2) the initial conditions $U_{20}(\theta)$ and $V_0(a)$ are uniformly bounded respectively for $\theta, a \in (0, +\infty)$; (A3) the maps $\theta \to p(\theta)$ and $a \to \alpha(a)$ are almost everywhere bounded and belong to $L^\infty_+((0,+\infty),\mathbb{R}) \setminus \{0_{L^\infty}\}$.

The paper is organized as follows. In the next section, we present some preliminary results of system (1)–(2). In Section 3, we prove the local and global stability of the drug-free steady state of system (1). In Section 4, we present the existence and the stability results of the drug spread steady state of system (1) when the basic reproduction number is larger than one. Finally, in Section 5, a brief discussion and some numerical examples are presented.

2. Preliminary results

In this section, we give some basic results prepared for the further study of system (1).

For the sake of convenience, we let

$$\Phi_1(\theta) = e^{-\int_0^\theta (\mu+\delta_2+p(\tau))d\tau}, \quad \int_0^\infty \Phi_1(\theta)d\theta = \phi_1,$$

$$\begin{aligned}
\Phi(\theta) &= \gamma p(\theta) e^{-\int_0^\theta (\mu+\delta_2+p(\tau))d\tau}, \quad \int_0^\infty \Phi(\theta)d\theta = \phi, \\
k_1(a) &= e^{-\int_0^a (\mu+\alpha(\tau))d\tau}, \quad \int_0^\infty k_1(a)da = \mathscr{K}_1, \\
k(a) &= \alpha(a) e^{-\int_0^a (\mu+\alpha(\tau))d\tau}, \quad \int_0^\infty k(a)da = \mathscr{K}.
\end{aligned}$$

By simple calculations, we have that $\mathscr{K} = 1 - \mu\mathscr{K}_1$ and $\phi = \gamma - \gamma(\mu + \delta_2)\phi_1$.

Naturally, system (1)–(2) has a unique drug-free steady state $E^0(S^0, 0, 0, V^0(a))$ which satisfies that

$$\begin{cases}
0 = \Lambda - (\mu + \psi)S^0 + \displaystyle\int_0^\infty \alpha(a)V^0(a)da, \\
\dfrac{dV^0(a)}{da} = -(\mu + \alpha(a))V^0(a), \\
V^0(0) = \psi S^0.
\end{cases} \tag{3}$$

Solving the last two equations, we have that

$$V^0(a) = \psi S^0 e^{-\int_0^a (\mu+\alpha(\tau))d\tau} = \psi S^0 k_1(a). \tag{4}$$

Substituting Equation (4) into the first equation of (3), we have that

$$S^0 = \frac{\Lambda}{\mu + \psi(1 - \mathscr{K})} = \frac{\Lambda}{\mu(1 + \psi\mathscr{K}_1)}. \tag{5}$$

Thus, we have that

$$V^0(a) = \frac{\psi\Lambda}{\mu(1 + \psi\mathscr{K}_1)} k_1(a). \tag{6}$$

According to the definition of the basic reproduction number in existing literatures [5,6,28], we define the basic reproduction number $\mathcal{R}_0$ as:

$$\begin{aligned}
\mathcal{R}_0 &= \frac{\beta}{\mu + \delta_1 + \gamma - \phi}\left(S^0 + \sigma\int_0^\infty V^0(a)da\right) \\
&= \frac{\beta}{\mu + \delta_1 + \gamma(\mu + \delta_2)\phi_1} \cdot \frac{\Lambda}{\mu(1 + \psi\mathscr{K}_1)} \cdot (1 + \sigma\psi\mathscr{K}_1).
\end{aligned} \tag{7}$$

According to [24], any positive equilibrium $(S^*, U_1^*, U_2^*(\theta), V^*(a))$ of system (1), if it exists, must be a constant solution of the following equations

$$\begin{cases} 0 = \Lambda - \beta S^* U_1^* - (\mu + \psi) S^* + \int_0^\infty \alpha(a) V^*(a) da, \\ 0 = \beta S^* U_1^* + \sigma\beta U_1^* \int_0^\infty V^*(a) da - (\mu + \delta_1 + \gamma) U_1^* + \int_0^\infty p(\theta) U_2^*(\theta) d\theta, \\ \dfrac{dU_2^*(\theta)}{d\theta} = -(\mu + \delta_2 + p(\theta)) U_2^*(\theta), \\ U_2^*(0) = \gamma U_1^*, \\ \dfrac{dV^*(a)}{da} = -(\mu + \alpha(a) + \sigma\beta U_1^*) V^*(a), \\ V^*(0) = \psi S^*. \end{cases} \tag{8}$$

Let

$$\pi(a) = e^{-\int_0^a (\mu + \alpha(\tau) + \sigma\beta U_1^*) d\tau}, \quad \mathcal{K}_\pi = \int_0^\infty \pi(a) da. \tag{9}$$

By simple calculations, we have that

$$\int_0^\infty \psi\alpha(a)\pi(a) da = \psi - \psi(\mu + \sigma\beta U_1^*)\mathcal{K}_\pi. \tag{10}$$

From the third and the forth equation of (8), we have that

$$U_2^*(\theta) = \gamma U_1^* \Phi_1(\theta). \tag{11}$$

From the fifth and the sixth equation of (8), we have that

$$V^*(a) = \psi S^* \pi(a). \tag{12}$$

Substituting (11) and (12) into the second and the first equation of (8) respectively, we have that the following equations

$$\begin{cases} 0 = \Lambda - \beta S^* U_1^* + (\psi - \psi(\mu + \sigma\beta U_1^*)\mathcal{K}_\pi) S^* - (\mu + \psi) S^* \\ 0 = \beta S^* U_1^* + \sigma\beta U_1^* \mathcal{K}_\pi \psi S^* - (\mu + \delta_1 + \gamma) U_1^* + \phi U_1^*. \end{cases} \tag{13}$$

It follows from the first equation of (13), we have that

$$S^* = \frac{\Lambda}{\beta U_1^* + \psi(\mu + \sigma\beta U_1^*)\mathcal{K}_\pi + \mu}. \tag{14}$$

Substituting (14) into the second equation of (13) and eliminating U_1^*, we have that

$$1 = \frac{\beta\Lambda(1 + \sigma\psi\mathcal{K}_\pi)}{(\beta U_1^* + \psi(\mu + \sigma\beta U_1^*)\mathcal{K}_\pi + \mu)(\mu + \delta_1 + \gamma - \phi)}. \tag{15}$$

Define a function $\mathcal{F}(U_1^*)$ to be the right hand side of Equation (15). Obviously, $\mathcal{F}(0) = \mathcal{R}_0$. It follows from (9) we have that $\mathcal{F}(U_1^*)$ is a decreasing function of U_1^* and $\mathcal{F}(U_1^*) \to 0$ as $U_1^* \to \infty$. Thus, there exists an unique positive root of Equation (15) only if $\mathcal{R}_0 > 1$.

Summarizing the above discussion, we have the following result.

Theorem 2.1. *System* (1) *always has a drug-free steady state* E^0*, besides that, it has an unique drug spread steady state* E^* *only if* $\mathcal{R}_0 > 1$.

Now, by setting

$$N(t) = S(t) + U_1(t) + \int_0^\infty U_2(\theta, t)d\theta + \int_0^\infty V(a, t)da,$$

we deduce from (1) that $N(t)$ satisfies the following ordinary differential equation:

$$N'(t) = \Lambda - \mu N(t) - \delta_1 U_1(t) + \delta_2 \int_0^\infty U_2(\theta, t)d\theta \leq \Lambda - \mu N(t), \tag{16}$$

and therefore $\limsup_{t\to\infty} N(t) \leq \frac{\Lambda}{\mu}$. Denote

$$\Omega = \Big\{(S, U_1, U_2, V) \in \mathbb{R}_+ \times \mathbb{R}_+ \times L^1_+(0,\infty) \times L^1_+(0,\infty) : \\ S + U_1 + \int_0^\infty U_2(\theta, \cdot)d\theta + \int_0^\infty V(a, \cdot)da \leq \frac{\Lambda}{\mu}\Big\}$$

Then Ω is the maximum positively invariant set of system (1) that attracts all positive solutions of of (1). Therefore, we restrict our attention to solutions of (1) with initial conditions in Ω.

In the following, we use the approach introduced by Thieme [26]. Consider

$$\begin{aligned}
\mathcal{X} &= \mathbb{R} \times \mathbb{R} \times \mathbb{R} \times L^1((0,\infty), \mathbb{R}) \times \mathbb{R} \times L^1((0,\infty), \mathbb{R}),\\
\mathcal{X}_0 &= \mathbb{R} \times \mathbb{R} \times \{0\} \times L^1((0,\infty), \mathbb{R}) \times \{0\} \times L^1((0,\infty), \mathbb{R}),\\
\mathcal{X}_+ &= \mathbb{R}_+ \times \mathbb{R}_+ \times \mathbb{R}_+ \times L^1_+((0,\infty), \mathbb{R}) \times \mathbb{R}_+ \times L^1_+((0,\infty), \mathbb{R})
\end{aligned}$$

and

$$\mathcal{X}_{0+} = \mathcal{X}_0 \cap \mathcal{X}_+.$$

Let the linear operator $A : Dom(A) \subset \mathcal{X} \to \mathcal{X}$ defined by

$$A\begin{pmatrix} S \\ U_1 \\ \begin{pmatrix} 0 \\ U_2 \end{pmatrix} \\ \begin{pmatrix} 0 \\ V \end{pmatrix} \end{pmatrix} = \begin{pmatrix} -(\mu+\psi)S \\ -(\mu+\delta_1+\gamma)U_1 \\ \begin{pmatrix} -U_2(0) \\ -U_2' - (\mu+\delta_2+p(\theta))U_2 \end{pmatrix} \\ \begin{pmatrix} -V(0) \\ -V' - (\alpha(a)+\mu)V \end{pmatrix} \end{pmatrix}$$

with

$$Dom(A) = \mathbb{R} \times \mathbb{R} \times \{0\} \times W^{1,1}((0,+\infty), \mathbb{R}) \times \{0\} \times W^{1,1}((0,+\infty), \mathbb{R}),$$

where $W^{1,1}$ is a Sobolev space. Then $\overline{Dom(A)} = \mathcal{X}_0$ is not dense in $\mathcal{X}$. We consider a nonlinear map

$\mathcal{F} : \overline{Dom(A)} \to \mathcal{X}$ which is defined by

$$\mathcal{F}(t) = \begin{pmatrix} \Lambda - \beta S(t)U_1(t) + \int_0^\infty \alpha(a)v(a,t)da \\ \beta S(t)U_1(t) + \sigma\beta U_1(t)\int_0^\infty V(a,t)da + \int_0^\infty p(\theta,t)U_2(\theta,t)d\theta \\ \begin{pmatrix} \psi S(t) \\ 0_{L^1} \end{pmatrix} \\ \begin{pmatrix} \gamma U_1(t) \\ (\sigma\beta U_1(t)V(a,t))_{L^1} \end{pmatrix} \end{pmatrix},$$

and let

$$u(t) = \left(S(t),\ U_1(t),\ \begin{pmatrix} 0 \\ U_2(\cdot,t) \end{pmatrix},\ \begin{pmatrix} 0 \\ V(\cdot,t) \end{pmatrix}\right)^T.$$

Then, we can reformulate system (2.3) as the following abstract Cauchy problem:

$$\frac{du(t)}{dt} = Au(t) + \mathcal{F}(t) \quad \text{for} \quad t \geq 0, \quad \text{with} \quad u(0) = x \in \mathcal{X}_{0+}. \tag{17}$$

By applying the results in Hale [11], Magal [22], and Magal and Thieme [23], we obtain the following theorem.

Theorem 2.2. *System* (1) *generates a unique continuous semiflow* $\{\mathcal{U}(t)\}_{t\geq 0}$ *on* $\mathcal{X}_{0+}$ *that is bounded dissipative and asymptotically smooth. Furthermore, the semiflow* $\{\mathcal{U}(t)\}_{t\geq 0}$ *has a global compact attractor* $\mathcal{A}$ *in* $\mathcal{X}_{0+}$*, which attracts the bounded sets of* $\mathcal{X}_{0+}$.

3. The stability of the drug-free steady state

In this section, by use of characteristic equation, we will prove the local and global stability of the drug-free steady state E^0.

For the sake of convenience, we give the following Laplace transforms of the corresponding functions

$$\begin{aligned} \widehat{\Phi}(\lambda) &= \int_0^\infty \Phi(\theta)e^{-\lambda\theta}d\theta,\ \ \widehat{\Phi}_1(\lambda) = \int_0^\infty \Phi_1(\theta)e^{-\lambda\theta}d\theta, \\ \widehat{\mathcal{K}}(\lambda) &= \int_0^\infty k(a)e^{-\lambda a}da,\ \ \widehat{\mathcal{K}_1}(\lambda) = \int_0^\infty k_1(a)e^{-\lambda a}da. \end{aligned} \tag{18}$$

By direct calculations, we have the following relationships

$$\widehat{\mathcal{K}}(\lambda) = 1 - (\lambda+\mu)\widehat{\mathcal{K}_1}(\lambda) \ \text{ and } \ \widehat{\Phi}(\lambda) = \gamma - \gamma(\lambda+\mu+\delta_2)\widehat{\Phi}_1(\lambda). \tag{19}$$

Theorem 3.1. *The drug-free steady state* E^0 *is locally asymptotically stable if* $\mathcal{R}_0 < 1$*, and unstable if* $\mathcal{R}_0 > 1$.

Proof. By linearization of system (1) at the drug-free steady state E^0, we can obtain the corresponding linearized system. We let

$$S(t) = \widetilde{S}(t) + S^0,\ U_1(t) = \widetilde{U}_1(t),\ U_2(\theta,t) = \widetilde{U}_2(\theta,t) \text{ and } V(a,t) = \widetilde{V}(a,t) + V^0(a).$$

By linearization of system (1) at the drug free steady state E^0, we obtain the following system

$$\begin{cases} \dfrac{d\widetilde{S}(t)}{dt} = -(\mu+\psi)\widetilde{S}(t) - \beta S^0 \widetilde{U}_1(t) + \displaystyle\int_0^\infty \alpha(a)\widetilde{V}(a,t)da, \\ \dfrac{d\widetilde{U}_1(t)}{dt} = \beta S^0 \widetilde{U}_1(t) + \sigma\beta \displaystyle\int_0^\infty V^0(a)da\widetilde{U}_1(t) + \int_0^\infty p(\theta)\widetilde{U}_2(\theta,t)d\theta \\ \qquad\qquad -(\mu+\delta_1+\gamma)\widetilde{U}_1(t), \\ \dfrac{\partial\widetilde{U}_2(\theta,t)}{\partial\theta} + \dfrac{\partial\widetilde{U}_2(\theta,t)}{\partial t} = -(\mu+\delta_2+p(\theta))\widetilde{U}_2(\theta,t), \\ \widetilde{U}_2(0,t) = \gamma\widetilde{U}_1(t), \\ \dfrac{\partial\widetilde{V}(a,t)}{\partial a} + \dfrac{\partial\widetilde{V}(a,t)}{\partial t} = -(\mu+\alpha(a))\widetilde{V}(a,t) - \sigma\beta V^0(a)\widetilde{U}_1(t), \\ \widetilde{V}(0,t) = \psi\widetilde{S}(t). \end{cases} \tag{20}$$

To analyze the asymptotic behaviors around E^0, we let

$$\widetilde{S}(t) = \overline{x}e^{\lambda t},\ \widetilde{U}_1(t) = \overline{y}e^{\lambda t},\ \widetilde{U}_2(\theta,t) = \overline{z}(\theta)e^{\lambda t},\ \text{and}\ \widetilde{V}(a,t) = \overline{w}(a)e^{\lambda t}$$

where $\overline{x}$, $\overline{y}$, $\overline{z}(\theta)$ and $\overline{w}(a)$ can be determined. Thus, we consider the following eigenvalue problem

$$\begin{cases} \lambda\overline{x} = -(\mu+\psi)\overline{x} - \beta S^0\overline{y}(t) + \displaystyle\int_0^\infty \alpha(a)\overline{w}(a)da, \\ \lambda\overline{y} = \beta S^0\overline{y} + \sigma\beta \displaystyle\int_0^\infty V^0(a)da\overline{y} - (\mu+\delta_1+\gamma)\overline{y} + \int_0^\infty p(\theta)\overline{z}(\theta)d\theta, \\ \dfrac{d\overline{z}(\theta)}{d\theta} = -(\lambda+\mu+\delta_2+p(\theta))\overline{z}(\theta), \\ \overline{z}(0) = \gamma\overline{y}, \\ \dfrac{d\overline{w}(a)}{da} = -(\lambda+\mu+\alpha(a))\overline{w}(a) - \sigma\beta V^0(a)\overline{y}, \\ \overline{w}(0) = \psi\overline{x}. \end{cases} \tag{21}$$

Solving the third equation of (21), we have

$$\overline{z}(\theta) = \overline{z}(0)e^{-\lambda\theta}\Phi_1(\theta) = \gamma\overline{y}e^{-\lambda\theta}\Phi_1(\theta). \tag{22}$$

Solving the fifth equation of (21), we have

$$\begin{aligned} \overline{w}(a) &= \overline{w}(0)e^{-\lambda a}k_1(a) - \sigma\beta\overline{y}\int_0^a e^{-\lambda(a-s)}\frac{k_1(a)}{k_1(s)}V^0(s)ds \\ &= \psi\overline{x}e^{-\lambda a}k_1(a) - \sigma\beta\psi S^0 k_1(a)\overline{y}\int_0^a e^{-\lambda(a-s)}ds \\ &= \psi\overline{x}e^{-\lambda a}k_1(a) - \sigma\beta\psi S^0 k_1(a)\overline{y}\frac{1}{\lambda}\left(1-e^{-\lambda a}\right). \end{aligned} \tag{23}$$

Substituting (23) and (22) into the first and the second equation of (21), we have the characteristic equation

$$\det(\Delta(\lambda)) = \begin{vmatrix} A_{11} & A_{12} \\ 0 & A_{22} \end{vmatrix} = 0, \tag{24}$$

where

$$\begin{aligned} A_{11} =& (\lambda+\mu)\left(1+\psi\widehat{\mathscr{K}_1}(\lambda)\right), \\ A_{12} =& \beta S^0\left(1+\frac{1}{\lambda}\sigma\psi(\widehat{\mathscr{K}}-\widehat{\mathscr{K}}(\lambda))\right), \\ A_{22} =& \lambda+(\mu+\delta_1+\gamma)-\widehat{\Phi}(\lambda)-\sigma\beta\psi S^0\mathscr{K}_1-\beta S^0. \end{aligned}$$

Then the roots of Equation (24) are determined by the following equations

$$(\lambda+\mu)\left(1+\psi\widehat{\mathscr{K}_1}(\lambda)\right)=0 \tag{25}$$

and

$$\lambda+(\mu+\delta_1+\gamma)-\widehat{\Phi}(\lambda)-\sigma\beta\psi S^0\mathscr{K}_1-\beta S^0=0. \tag{26}$$

Obviously, $\lambda=-\mu$ is the root of Equation (25). Then we need only to consider the root of Equation (26) which can be rewritten as

$$\lambda+\mu+\delta_1+\gamma(\lambda+\mu+\delta_2)\widehat{\Phi}_1(\lambda)=(\sigma\psi\mathscr{K}_1+1)\beta S^0. \tag{27}$$

We also have that

$$1=\frac{(\sigma\psi\mathscr{K}_1+1)\beta S^0}{\lambda+\mu+\delta_1+\gamma(\lambda+\mu+\delta_2)\widehat{\Phi}_1(\lambda)}. \tag{28}$$

Define a function $\mathcal{H}(\lambda)$ to be the right-hand side of Equation (28). It follows from the definition of the basic reproduction number $\mathcal{R}_0$ (see (7)), we have that $\mathcal{H}(0)=\mathcal{R}_0$. By direct computing, it is easy to show that $\mathcal{H}'(\lambda)<0$, that is, $\mathcal{H}(\lambda)$ is a decreasing function of λ with $\lim\limits_{t\to+\infty}\mathcal{H}(\lambda)=0$.

Assume that $\lambda=x+iy$ is a root of Equation (28). Then it follows from (28) that

$$x\geq 0\Rightarrow 1=|\mathcal{H}(\lambda)|\leq|\mathcal{H}(x)|\leq\mathcal{H}(0)=\mathcal{R}_0,\ \text{i.e.,}\ \mathcal{R}_0\geq 1.$$

Thus, we can have that $\Re(\lambda)$ is negative if $\mathcal{R}_0<1$, and therefore the steady state E^0 is locally asymptotically stable if $\mathcal{R}_0<1$ and it is unstable if $\mathcal{R}_0>1$. □

In the following, we will use the Fluctuation Lemma to establish the global stability of the drug-free steady state E^0. To this end, we first introduce the notation

$$g_\infty=\liminf_{t\to\infty}g(t)\ \text{ and }\ g^\infty=\limsup_{t\to\infty}g(t).$$

Then the Fluctuation Lemma is given as follows.

Lemma 3.2. *(Fluctuation Lemma [13]) Let $g:\mathbb{R}_+\to\mathbb{R}$ be a bounded and continuously differentiable function. Then there exist sequences $\{s_n\}$ and $\{t_n\}$ such that $s_n\to\infty$, $t_n\to\infty$, $g(s_n)\to g_\infty$, $g'(s_n)\to 0$, $g(t_n)\to g^\infty$ and $g'(t_n)\to 0$ as $n\to\infty$.*

Lemma 3.3. *[15] Suppose $f:\ \mathbb{R}_+ \to \mathbb{R}$ be a bounded function. Then*

$$\limsup_{t\to\infty}\int_0^t h(\theta)f(t-\theta)d\theta \le f^{\infty}\|h\|_1,$$

where $\|h\|_1 = \int_0^{\infty} h(s)ds$.

Using integration, $U_2(\theta,t)$ and $V(a,t)$ satisfy the following Volterra formulation:

$$U_2(\theta,t) = \begin{cases} \gamma U_1(t-\theta)\Phi_1(\theta), & \text{if } t \ge \theta, \\ U_2(\theta-t,0)\dfrac{\Phi_1(\theta)}{\Phi_1(\theta-t)}, & \text{if } \theta \ge t. \end{cases} \tag{29}$$

$$V(a,t) = \begin{cases} \psi S(t-a)e^{-\int_0^a(\mu+\alpha(\tau)+\sigma\beta U_1(t-\tau))d\tau}, & \text{if } t \ge a, \\ V(a-t,0)e^{-\int_0^t(\mu+\alpha(a-\tau)+\sigma\beta U_1(\tau))d\tau}, & \text{if } a \ge t. \end{cases} \tag{30}$$

Theorem 3.4. *If $\mathcal{R}_0 < 1$, then the drug-free steady state E^0 is the unique steady state of system* (1)*, and it is globally stable.*

Proof. Theorem 3.1 shows that the drug-free steady state E^0 of system (1)) is locally stable if $\mathcal{R}_0 < 1$. To use the Fluctuation Lemma, substituting the expressions of $V(a,t)$ and $U_2(\theta,t)$ into the first two equations of system (1), we have that

$$\begin{cases} \dfrac{dS}{dt} = \Lambda - \beta S(t)U_1(t) + \displaystyle\int_0^t \psi\alpha(a)e^{-\int_0^a(\mu+\alpha(\tau)+\sigma\beta U_1(t-\tau))d\tau}S(t-a)da \\ \qquad -(\mu+\psi)S(t) + F_V(t) \\ \dfrac{dU_1}{dt} = \beta S(t)U_1(t) + \sigma\beta U_1(t)\displaystyle\int_0^t \psi e^{-\int_0^a(\mu+\alpha(\tau)+\sigma\beta U_1(t-\tau))d\tau}S(t-a)da \\ \qquad -(\mu+\delta_1+\gamma)U_1(t) + \displaystyle\int_0^t \Phi(\theta)U_1(t-\theta)d\theta + F_U(t) + F_{UV}(t), \end{cases} \tag{31}$$

where

$$\begin{aligned} F_V(t) &= \int_t^{\infty} \psi\alpha(a)V(a-t,0)e^{-\int_0^t(\mu+\alpha(a-\tau)+\sigma\beta U_1(\tau))d\tau}da, \\ F_U(t) &= \int_t^{\infty} p(\theta)U_2(\theta-t,0)\frac{\Phi_1(\theta)}{\Phi_1(\theta-t)}d\theta, \\ F_{UV}(t) &= \sigma\beta U_1(t)\int_t^{\infty} V(a-t,0)e^{-\int_0^t(\mu+\alpha(a-\tau)+\sigma\beta U_1(\tau))d\tau}da \end{aligned}$$

with $\lim_{t\to\infty} F_V(t) = 0$, $\lim_{t\to\infty} F_U(t) = 0$ and $\lim_{t\to\infty} F_{UV}(t) = 0$.

Choose the sequences $t_n^1 \to \infty$ such that $S(t_n^1) \to S^{\infty}$ and $S'(t_n^1) \to 0$. Then $F_V(t) \to 0$ as $n \to \infty$. With the assistance of the Fluctuation Lemma, it follows from the first equation of (31) we have that

$$0 = \Lambda - \beta S^{\infty}U_1(t) - (\mu+\psi)S^{\infty} + S^{\infty}\psi\mathcal{K},$$

and

$$S^{\infty} \leq \frac{\Lambda}{\mu + \psi - \psi\mathcal{K}}.$$

Choose the sequences $t_n^2 \to \infty$ such that $U_1(t_n^2) \to U_1^{\infty}$ and $U_1'(t_n^2) \to 0$. Then $F_U(t) \to 0$ and $F_{UV}(t) \to 0$ as $n \to \infty$. With the assistance of the Fluctuation Lemma, it follows from the second equation of (31) we have that

$$\begin{aligned}
0 \leq & \beta S^{\infty} U_1^{\infty} + \sigma\beta\psi\mathcal{K}_1 S^{\infty} U_1^{\infty} - (\mu + \delta_1 + \gamma) U_1^{\infty} + \phi U_1^{\infty} \\
= & (\beta S^{\infty}(1 + \sigma\psi\mathcal{K}_1) - (\mu + \delta_1 + \gamma) + \phi)\, U_1^{\infty} \\
\leq & \left(\beta \frac{\Lambda(1 + \sigma\psi\mathcal{K}_1)}{\mu + \psi - \psi\mathcal{K}} - (\mu + \delta_1 + \gamma) + \phi\right) U_1^{\infty} \\
= & (\mu + \delta_1 + \gamma - \phi)(\mathcal{R}_0 - 1) U_1^{\infty}.
\end{aligned}$$

Thus we obtain that $U_1^{\infty} \to 0$ if $\mathcal{R}_0 < 1$. It then follows from (29) we have that $\lim_{t\to\infty} U_2(\theta, t) = 0$.

Choose the sequences $t_n^3 \to \infty$ such that $S(t_n^3) \to S_{\infty}$ and $S'(t_n^3) \to 0$. Note that $\lim_{n\to\infty} U_1(t_n^3) = 0$ and $\lim_{n\to\infty} F_V(t_n^3) = 0$. It then follows from the first equation of (31) we have that

$$0 = \Lambda - \beta S_{\infty} U_1^{\infty} - (\mu + \psi) S_{\infty} + \psi\mathcal{K} S_{\infty} = \Lambda - (\mu + \psi) S_{\infty} + \psi\mathcal{K} S_{\infty}.$$

It follows that

$$\frac{\Lambda}{\mu + \psi - \psi\mathcal{K}} = S_{\infty} \leq S^{\infty} \leq \frac{\Lambda}{\mu + \psi - \psi\mathcal{K}},$$

which implies that $\lim_{t\to\infty} S(t) = \frac{\Lambda}{\mu+\psi-\psi\mathcal{K}}$. It follows from (30) we have that

$$\lim_{t\to\infty} V(a, t) = \frac{\psi\Lambda}{\mu + \psi - \psi\mathcal{K}} k_1(a) = V^0(a).$$

Therefore, $(S, U_1, U_2, V) \to E^0$ in $\mathbb{R}_+ \times \mathbb{R}_+ \times L_+^1 \times L_+^1$ as $t \to \infty$. This completes the proof of Theorem 3.4. □

4. Stability of the drug spread steady state

This section aims to establish the stability of the drug spread steady state of system (1) in terms of the basic reproduction number $\mathcal{R}_0$.

By a similar discussion as Theorem 3.5 in [10], we have the uniform persistence result as following.

Theorem 4.1. *Suppose the heroin spread is initially present, i.e., $U_{10} > 0$. If $\mathcal{R}_0 > 1$, then the semiflow generated by system* (1) *is uniformly persistent, i.e., there exists $\varepsilon > 0$ which is independent of initial values such that*

$$\liminf_{t\to\infty} S(t) \geq \varepsilon,\ \liminf_{t\to\infty} U_1(t) \geq \varepsilon,\ \liminf_{t\to\infty} \|U_2(\cdot, t)\|_{L_+^1} \geq \varepsilon$$

and $\liminf_{t\to\infty} \|V(\cdot, t)\|_{L_+^1} \geq \varepsilon$.

For the sake of convenience, we let

$$\widehat{\mathscr{K}_\pi}(\lambda) := \int_0^\infty \pi(a)e^{-\lambda a}da, \text{ and } \widehat{\mathscr{K}_\alpha}(\lambda) = \int_0^\infty \alpha(a)\pi(a)e^{-\lambda a}da. \tag{32}$$

It then follows that

$$\widehat{\mathscr{K}_\alpha}(\lambda) = 1 - (\lambda + \mu + \sigma\beta U_1^*)\widehat{\mathscr{K}_\pi}(\lambda). \tag{33}$$

In the following, we try to study the stability of the drug spread steady state E^* (S^*, U_1^*, $U_2^*(\theta)$, $V^*(a)$) of system (1). We let

$$S(t) = \widetilde{S}(t) + S^*,\ U_1(t) = \widetilde{U}_1(t) + U_1^*,\ U_2(\theta,t) = \widetilde{U}_2(\theta,t) + U_2^*(\theta)$$

and $V(a,t) = \widetilde{V}(a,t) + V^*(a)$. By linearization of system (1) at the steady state E^*, we obtain the following system

$$\begin{cases} \dfrac{d\widetilde{S}(t)}{dt} = -(\mu+\psi)\widetilde{S}(t) - \beta U_1^*\widetilde{S}(t) - \beta S^*\widetilde{U}_1(t) + \displaystyle\int_0^\infty \alpha(a)\widetilde{V}(a,t)da, \\ \dfrac{d\widetilde{U}_1(t)}{dt} = \beta U_1^*\widetilde{S}(t) + \beta S^*\widetilde{U}_1(t) + \sigma\beta U_1^*\displaystyle\int_0^\infty \widetilde{V}(a,t)da + \sigma\beta\int_0^\infty V^*(a)da\widetilde{U}_1(t) \\ \qquad -(\mu+\delta_1+\gamma)\widetilde{U}_1(t) + \displaystyle\int_0^\infty p(\theta)\widetilde{U}_2(\theta,t)d\theta, \\ \dfrac{\partial\widetilde{U}_2(\theta,t)}{\partial\theta} + \dfrac{\partial\widetilde{U}_2(\theta,t)}{\partial t} = -(\mu+\delta_2+p(\theta))\widetilde{U}_2(\theta,t), \\ \widetilde{U}_2(0,t) = \gamma\widetilde{U}_1(t), \\ \dfrac{\partial\widetilde{V}(a,t)}{\partial a} + \dfrac{\partial\widetilde{V}(a,t)}{\partial t} = -(\mu+\alpha(a)+\sigma\beta U_1^*)\widetilde{V}(a,t) - \sigma\beta V^*(a)\widetilde{U}_1(t), \\ \widetilde{V}(0,t) = \psi\widetilde{S}(t). \end{cases} \tag{34}$$

To analyze the asymptotic behaviors around E^*, we let

$$\widetilde{S}(t) = \overline{x}e^{\lambda t},\ \widetilde{U}_1(t) = \overline{y}e^{\lambda t},\ \widetilde{U}_2(\theta,t) = \overline{z}(\theta)e^{\lambda t}, \text{ and } \widetilde{V}(a,t) = \overline{w}(a)e^{\lambda t}$$

where $\overline{x}$, $\overline{y}$, $\overline{z}(\theta)$ and $\overline{w}(a)$ can be determined. Then, we consider the following eigenvalue problem

$$\begin{cases} \lambda\overline{x} = -(\mu+\psi)\overline{x} - \beta U_1^*\overline{x} - \beta S^*\overline{y}(t) + \displaystyle\int_0^\infty \alpha(a)\overline{w}(a)da, \\ \lambda\overline{y} = \beta U_1^*\overline{x} + \beta S^*\overline{y} + \sigma\beta U_1^*\displaystyle\int_0^\infty \overline{w}(a)da + \int_0^\infty p(\theta)\overline{z}(\theta)d\theta \\ \qquad +\sigma\beta\displaystyle\int_0^\infty V^*(a)da\overline{y} - (\mu+\delta_1+\gamma)\overline{y}, \\ \dfrac{d\overline{z}(\theta)}{d\theta} = -(\lambda+\mu+\delta_2+p(\theta))\overline{z}(\theta), \\ \overline{z}(0) = \gamma\overline{y}, \\ \dfrac{d\overline{w}(a)}{da} = -(\lambda+\mu+\alpha(a)+\sigma\beta U_1^*)\overline{w}(a) - \sigma\beta V^*(a)\overline{y}, \\ \overline{w}(0) = \psi\overline{x}. \end{cases} \tag{35}$$

Solving the third equation of (35), we have

$$\overline{z}(\theta) = \overline{z}(0)e^{-\lambda\theta}\Phi_1(\theta) = \gamma\overline{y}e^{-\lambda\theta}\Phi_1(\theta). \tag{36}$$

Solving the fifth equation of (35), we have

$$\begin{aligned}\overline{w}(a) &= \overline{w}(0)e^{-\lambda a}\pi(a) - \sigma\beta\overline{y}\int_0^a e^{-\lambda(a-s)}\frac{\pi(a)}{\pi(s)}V^*(s)ds \\ &= \psi\overline{x}e^{-\lambda a}\pi(a) - \sigma\beta\overline{y}f(a,\lambda),\end{aligned} \tag{37}$$

where

$$\begin{aligned}f(a,\lambda) = &\int_0^a e^{-\lambda(a-s)}\frac{\pi(a)}{\pi(s)}V^*(s)ds = \psi S^*\pi(a)\int_0^a e^{-\lambda(a-s)}ds \\ =&\psi S^*\pi(a)\int_0^a e^{-\lambda s}ds = \psi S^*\pi(a)\frac{1}{\lambda}\left(1-e^{-\lambda a}\right).\end{aligned}$$

Substituting (37) into the first equation of (35), we have

$$\begin{aligned}\overline{x} &= -\frac{\overline{y}}{G_{11}}\left(\beta S^* + \sigma\beta\int_0^\infty \alpha(a)f(a,\lambda)da\right) \\ &= -\frac{\overline{y}}{G_{11}}\left[\beta S^* + \sigma\beta\psi S^*\frac{1}{\lambda}\int_0^\infty \alpha(a)\pi(a)\left(1-e^{-\lambda a}\right)da\right]\end{aligned} \tag{38}$$

where

$$G_{11} = \lambda + (\psi + \mu + \beta U_1^*) - \psi\widehat{\mathscr{K}_\alpha}(\lambda).$$

It follows from (33) we have that

$$G_{11} = (\lambda+\mu)\left(1+\psi\widehat{\mathscr{K}_\pi}(\lambda)\right) + \beta U_1^*\left(1+\sigma\psi\widehat{\mathscr{K}_\pi}(\lambda)\right).$$

Substituting (36) and (37) into the second equation of (35), by use of $\sigma\beta\psi S^*\mathscr{K}_\pi = (\mu+\delta_1+\gamma) - \beta S^* - \phi$ (i.e., the second equation of (13)), we have that

$$\left(\lambda + \phi - \Phi(\lambda) + \sigma^2\beta^2 U_1^*\int_0^\infty f(a,\lambda)da\right)\overline{y} = \left(\beta U_1^* + \sigma\psi\beta U_1^*\widehat{\mathscr{K}_\pi}(\lambda)\right)\overline{x}.$$

Substituting (38) into the above equation and dividing both sides by $\overline{y}$ leads to the characteristic equation

$$\begin{aligned}\lambda+ &\phi - \Phi(\lambda) + \sigma^2\beta^2\psi S^* U_1^*\frac{1}{\lambda}\int_0^\infty \pi(a)\left(1-e^{-\lambda a}\right)da \\ &= -\left(\beta U_1^* + \sigma\psi\beta U_1^*\widehat{\mathscr{K}_\pi}(\lambda)\right)\frac{1}{G_{11}} \\ &\quad\cdot\left[\beta S^* + \sigma\beta\psi S^*\frac{1}{\lambda}\int_0^\infty \alpha(a)\pi(a)\left(1-e^{-\lambda a}\right)da\right].\end{aligned} \tag{39}$$

It follows from Equation (39) we have that

$$\begin{aligned}
&G_{11}\left(\lambda+\phi-\widehat{\Phi}(\lambda)\right)\\
&+\beta^2 S^* U_1^*\left(1+\sigma\psi\widehat{\mathscr{K}_\pi}(\lambda)\right)^2+\frac{1}{\lambda}\sigma^2\beta^2\psi S^* U_1^* G_{11}\left(\mathscr{K}_\pi-\widehat{\mathscr{K}_\pi}(\lambda)\right)\\
&=\frac{1}{\lambda}\sigma\beta^2\psi S^* U_1^*\left(\mathscr{K}_\pi-\widehat{\mathscr{K}_\pi}(\lambda)\right)(\mu+\sigma\beta U_1^*)\left(1+\sigma\psi\widehat{\mathscr{K}_\pi}(\lambda)\right).
\end{aligned}\tag{40}$$

Due to the fact that the characteristic equation (39) is too complex, it is very difficult to determine the distribution of the eigenvalues. In the following, we will study the stability of the drug spread steady state E^* in three special cases of system (1) respectively.

Case (i) We assume that $\alpha(a)=0$, that is, the vaccine does not wane once the host is vaccinated. which is reasonable since the heroin does not change the toxic (pathogenic) substance. Mathematically, letting $\int_0^\infty V(a,t)da=V(t)$ in this case, we can rewrite system (1) as

$$\begin{cases}
\dfrac{dS}{dt}=\Lambda-(\mu+\psi)S(t)-\beta S(t)U_1(t),\\
\dfrac{dU_1}{dt}=\beta S(t)U_1(t)+\sigma\beta U_1(t)V(t)-(\mu+\delta_1+\gamma)U_1(t)+\displaystyle\int_0^\infty p(\theta)U_2(\theta,t)d\theta,\\
\dfrac{\partial U_2(\theta,t)}{\partial\theta}+\dfrac{\partial U_2(\theta,t)}{\partial t}=-(\mu+\delta_2+p(\theta))U_2(\theta,t),\\
\dfrac{dV(t)}{dt}=\psi S(t)-(\mu+\sigma\beta U_1(t))V(t),\\
U_2(0,t)=\gamma U_1(t),\\
S(0)=S_0,\ U_1(0)=U_{10},\ U_2(\theta,0)=U_{20}(\theta)\in L^1_+(0,\infty),\ V(0)=V_0.
\end{cases}\tag{41}$$

Then we have the following result.

Lemma 4.2. *If $\alpha(a)\equiv 0$, the drug spread steady state E^* of system* (41) *is locally asymptotically stable if it exists.*

Proof. Linearizing system (41) at its positive steady state $(S^*, U_1^*, U_2^*(\cdot), V^*)$, we have the following characteristic equation

$$\begin{vmatrix}
\lambda+\mu+\psi+\beta U_1^* & \beta S^* & 0\\
-\beta U_1^* & \lambda+\phi-\widehat{\Phi}(\lambda) & -\sigma\beta U_1^*\\
-\psi & \sigma\beta V^* & \lambda+\mu+\sigma\beta U_1^*
\end{vmatrix}=0.\tag{42}$$

By simple calculations, we have the following

$$B_1(\lambda)B_2(\lambda)(\lambda+\phi-\widehat{\Phi}(\lambda))+B_1(\lambda)\sigma^2\beta^2U_1^*V^*+B_2(\lambda)\beta^2U_1^*S^*+\sigma\psi\beta^2U_1^*S^*=0,\tag{43}$$

where

$$B_1(\lambda)=\lambda+\mu+\psi+\beta U_1^*,\quad B_2(\lambda)=\lambda+\mu+\sigma\beta U_1^*.$$

Obviously, if $\sigma\neq 0$, $\lambda=-(\mu+\psi+\beta U_1^*)$ and $\lambda=-(\mu+\sigma\beta U_1^*)$ are not the roots of Equation (43). Dividing both side of Equation (43) by $B_1(\lambda)B_2(\lambda)$ leads to

$$\lambda+\phi+Z=\widehat{\Phi}(\lambda),\tag{44}$$

where

$$Z = \frac{\sigma^2\beta^2 U_1^* V^*}{B_2(\lambda)} + \frac{\beta^2 U_1^* S^*}{B_1(\lambda)} + \frac{\sigma\psi\beta^2 U_1^* S^*}{B_1(\lambda)B_2(\lambda)}.$$

Now, assume that λ is a root of Equation (44) with $\Re(\lambda) \geq 0$. If we can prove the real part of Z is positive (see Appendix A for its detailed proof), then by using $|\widehat{\Phi}(\lambda)| \leq \phi$, we have

$$\phi \leq |\lambda + \phi| < |\lambda + \phi + Z| = |\widehat{\Phi}(\lambda)| \leq \phi$$

This contradiction implies that all roots of Equation (44) have negative real parts. Hence, the positive steady state $(S^*, U_1^*, U_2^*(\cdot), V^*)$ of system (41) is locally stable if it exists. □

Case (ii) We assume that $\sigma = 0$, i.e., the heroin vaccine can provide a prefect protection for the vaccinated individuals to avoid the heroin drug addiction. It then follows that $\pi(a) = k_1(a)$. Mathematically, in this case, system (1) can be rewritten as

$$\begin{cases} \dfrac{dS}{dt} = \Lambda - (\mu + \psi)S(t) - \beta S(t)U_1(t) + \displaystyle\int_0^\infty \alpha(a)V(a,t)da, \\ \dfrac{dU_1}{dt} = \beta S(t)U_1(t) - (\mu + \delta_1 + \gamma)U_1(t) + \displaystyle\int_0^\infty p(\theta)U_2(\theta,t)d\theta, \\ \dfrac{\partial U_2(\theta,t)}{\partial\theta} + \dfrac{\partial U_2(\theta,t)}{\partial t} = -(\mu + \delta_2 + p(\theta))U_2(\theta,t), \\ \dfrac{\partial V(a,t)}{\partial a} + \dfrac{\partial V(a,t)}{\partial t} = -(\mu + \alpha(a))V(a,t), \\ U_2(0,t) = \gamma U_1(t), \quad V(0,t) = \psi S(t), \\ S(0) = S_0,\ U_1(0) = U_{10},\ U_2(\theta,0) = U_{20}(\theta),\ V(a,0) = V_0(a). \end{cases} \tag{45}$$

Lemma 4.3. *If $\sigma = 0$, the drug spread steady state E^* of system* (45) *is globally asymptotically stable if it exists.*

Proof. It then follows from (18) and (19) we have that Equation (40) can be modified as

$$\left(\lambda + \mu + \psi + \beta U_1^* - \widehat{S}_\alpha(\lambda)\right)\left(\lambda + \phi - \widehat{\Phi}(\lambda)\right) + \beta^2 S^* U_1^* = 0. \tag{46}$$

Since $\lambda = 0$ is not the roots of Equation (46). Both sides of Equation (46) are divided by $\left(\lambda + \phi - \widehat{\Phi}(\lambda)\right)$, we obtain

$$\lambda + \mu + \psi + \beta U_1^* + Z_1 = \widehat{S}_\alpha(\lambda) \tag{47}$$

where

$$Z_1 = \frac{\beta^2 S^* U_1^*}{\lambda + \phi - \widehat{\Phi}(\lambda)}.$$

Assuming λ is a root of Equation (47), we can prove that $\Re(\lambda)$ (i.e., the real part of λ) is negative. Supposed $\Re(\lambda)$ is nonnegative, then the real part of Z is nonnegative (see Appendix B). It follows from (10) and (47) we have that

$$\psi < |\mu + \psi + \beta U_1^*| \leq |\lambda + \mu + \psi + \beta U_1^* + Z_1| = |\widehat{S}_\alpha(\lambda)| < \psi, \tag{48}$$

which is a contradiction. So, all roots of Equation (47) have negative real part, and therefore all roots of Equation (46) have negative real part and the drug spread steady state E^* of system (45) is locally asymptotically stable if it exists.

Based on the persistence results in Theorem 4.1 and the local stability results of E^* of system (45), we will use a suitable Lyapunov functional to prove the global stability of E^*.

Set $g(x) = x - 1 - \ln x$, for $x \in \mathbb{R}_+$. The function $g(x)$ has a global minimum at $x = 1$ with $g(1) = 0$. For our presentation here, we define

$$\varepsilon_1(\theta) = \int_\theta^\infty p(\tau) e^{-\int_\theta^\tau (\mu+\delta_2+p(s))ds} d\tau \text{ and } \varepsilon_2(a) = \int_a^\infty \alpha(\tau) V^*(\tau) d\tau. \tag{49}$$

Note that $\varepsilon_1(\theta)$, $\varepsilon_2(a) >$ for all $\theta > 0$ and $a > 0$ respectively. We can easily check that $\varepsilon_1(0) = \phi/\gamma$, $\varepsilon_2(0) = \int_0^\infty \alpha(a) V^*(a) da$ and

$$\frac{d\varepsilon_1(\theta)}{d\theta} = \varepsilon_1(\theta)(\mu + \delta_2 + p(\theta)) - p(\theta) \text{ and } \frac{d\varepsilon_2(a)}{da} = -\alpha(a) V^*(a). \tag{50}$$

Now, we define the following Lyapunov functional

$$W(t) = W_S(t) + W_{U_1}(t) + W_{U_2}(t) + W_V(t), \tag{51}$$

where

$$\begin{aligned} W_S(t) &= S^* g\left(\frac{S(t)}{S^*}\right), \\ W_{U_1}(t) &= U_1^* g\left(\frac{U_1(t)}{U_1^*}\right), \\ W_{U_2}(t) &= \int_0^\infty \varepsilon_1(\theta) U_2^*(\theta) g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right) d\theta, \\ W_V(t) &= \int_0^\infty \varepsilon_2(a) g\left(\frac{V(a,t)}{V^*(a)}\right) da, \end{aligned} \tag{52}$$

Then W is bounded. Then we calculate the time derivative of $W(t)$ along with the solutions of system (45). Following the results in the proof of Theorem 2.2 in [10] and the proof of Theorem 3.11 in [30], we have that

$$\begin{aligned} \frac{dW_S(t)}{dt} =& -(\mu+\psi) S^* \left(\frac{S^*}{S(t)} + \frac{S(t)}{S^*} - 2\right) + \beta S^* U_1^* \left(1 - \frac{S^*}{S(t)}\right)\left(1 - \frac{S(t)}{S^*}\frac{U_1(t)}{U_1^*}\right) \\ &+ \int_0^\infty \alpha(a) V^*(a) \left(\frac{V(a,t)}{V^*(a)} - \frac{V(a,t)}{V^*(a)}\frac{S^*}{S(t)} - 1 + \frac{S^*}{S(t)}\right) da, \\ \frac{dW_{U_1}(t)}{dt} =& \beta S(t) U_1(t) - \beta S^* U_1(t) - \beta S(t) U_1^* + \beta S^* U_1^* \\ &+ \int_0^\infty p(\theta) U_2^*(\theta) \left(\frac{U_2(\theta,t)}{U_2^*(\theta)} - \frac{U_1(t)}{U_1^*} - \frac{U_1^*}{U_1(t)}\frac{U_2(\theta,t)}{U_2^*(\theta)} + 1\right) d\theta, \\ \frac{dW_{U_2}(t)}{dt} =& -\varepsilon_1(\theta) U_2^*(\theta) g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)\Big|_{\theta=\infty} + \phi U_1^* g\left(\frac{U_1(t)}{U_1^*}\right) \end{aligned}$$

$$- \int_0^\infty p(\theta)U_2^*(\theta)g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)d\theta,$$

$$\begin{aligned}\frac{dW_V(t)}{dt} =& -\varepsilon_2(a)g\left(\frac{V(a,t)}{V^*(a)}\right)\Big|_{a=\infty} + \int_0^\infty \alpha(a)V^*(a)g\left(\frac{V(0,t)}{V^*(0)}\right)da \\ & - \int_0^\infty \alpha(a)V^*(a)g\left(\frac{V(a,t)}{V^*(a)}\right)da \\ =& + \int_0^\infty \alpha(a)V^*(a)\left(\frac{S(t)}{S^*} - \ln\frac{S^*}{S(t)} - \frac{V(a,t)}{V^*(a)} + \ln\frac{V(a,t)}{V^*(a)}\right)da \\ & - \varepsilon_2(a)g\left(\frac{V(a,t)}{V^*(a)}\right)\Big|_{a=\infty}.\end{aligned}$$

By adding $\frac{dW_S(t)}{dt}$ and $\frac{dW_V(t)}{dt}$ together, though some simple calculations, we have that

$$\begin{aligned}&\frac{dW_S(t)}{dt} + \frac{dW_V(t)}{dt} \\ =&\beta S^* U_1^*\left(1 - \frac{S^*}{S(t)}\right)\left(1 - \frac{S(t)}{S^*}\frac{U_1(t)}{U_1^*}\right) - (\mu+\psi)S^*\left(\frac{S^*}{S(t)} + \frac{S(t)}{S^*} - 2\right) \\ &+ \int_0^\infty \alpha(a)V^*(a)\left(\frac{S^*}{S(t)} + \frac{S(t)}{S^*} - 2\right)da - \int_0^\infty \alpha(a)V^*(a)g\left(\frac{V(a,t)}{V^*(a)}\frac{S^*}{S(t)}\right)da \\ &- \varepsilon_2(a)g\left(\frac{V(a,t)}{V^*(a)}\right)\Big|_{a=\infty} \\ =&\beta S^* U_1^*\left(1 - \frac{S^*}{S(t)}\right)\left(1 - \frac{S(t)}{S^*}\frac{U_1(t)}{U_1^*}\right) - \int_0^\infty \alpha(a)V^*(a)g\left(\frac{V(a,t)}{V^*(a)}\frac{S^*}{S(t)}\right)da \\ &- \varepsilon_2(a)g\left(\frac{V(a,t)}{V^*(a)}\right)\Big|_{a=\infty} + \left(\frac{S^*}{S(t)} + \frac{S(t)}{S^*} - 2\right)\left(\int_0^\infty \alpha(a)V^*(a)da - (\mu+\psi)S^*\right).\end{aligned}$$

Combining the above four compartments of the Lyapunov functionals, through some simple calculations, we obtain

$$\begin{aligned}\frac{dW(t)}{dt} =& -\Lambda\left(\frac{S^*}{S(t)} + \frac{S(t)}{S^*} - 2\right) - \varepsilon_1(\theta)U_2^*(\theta)g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)\Big|_{\theta=\infty} \\ & - \int_0^\infty p(\theta)U_2^*(\theta)g\left(\frac{U_1^*}{U_1(t)}\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)d\theta - \varepsilon_2(a)g\left(\frac{V(a,t)}{V^*(a)}\right)\Big|_{a=\infty} \le 0.\end{aligned}$$

Notice that equality holds only if $S(t) = S^*$, $U_1(t) = U_1^*$ and $U_2(\theta,t) = U_2^*(\theta)$. Thus we conclude that the largest positive invariant is the singleton $\{E^*\}$. By Lyapunov-LaSalle invariance principle, we conclude that the drug spread steady state E^* is globally asymptotically stable when it exists. □

Case (iii) We assume that $\sigma = 1$, i.e., the heroin vaccine is noneffective and cannot provide any protection from heroin drug addicted, the vaccination makes no sense. In this case, mathematically, the compartments S and V can be combined, system (1) can be rewritten as the system in [10] (see Appendix C for more details) and the drug spread steady state E^* is locally and globally stable.

5. Numerical simulation and discussion

In this paper, we have studied an age structured heroin transmission model with treatment and vaccination, in which the vaccination can only provide an imperfect protection and the vaccinated wanes the protection as vaccination age goes.

The basic reproduction number $\mathcal{R}_0$ of our system (1) has been found by the definition. When $\mathcal{R}_0 < 1$, system (1) has only the drug free steady state E^0 and it is globally asymptotically stable, which implies that the heroin drug will die out eventually. Meanwhile, from the expression of $\mathcal{R}_0$, we find that the vaccination, although it is imperfect, plays an important role in the control of heroin spread. When $\mathcal{R}_0 > 1$, system (1) has only the drug spread steady state E^* and it is uniformly persistent provided that the heroin spread is initially present. Due to the fact that the characteristic equation of system (1) at the drug spread steady state is very complex, it is difficult to discuss the distribution of its eigenvalues. From the biology angle, we have recast system (1) into three special cases and obtained the local and global stability of the drug spread steady state E^* if it exists (see Lemmas 4.2-4.3).

Recalling that the expression of $\mathcal{R}_0$ in (7), it follows from $0 \le \sigma \le 1$ we have that

$$\frac{\beta\Lambda}{\mu(\mu+\delta_1+\gamma(\mu+\delta_2)\phi_1)}\frac{1+\sigma\psi\mathcal{K}_1}{(1+\psi\mathcal{K}_1)} \le \frac{\beta\Lambda}{\mu(\mu+\delta_1+\gamma(\mu+\delta_2)\phi_1)}. \tag{53}$$

It implies that $\mathcal{R}_0(\psi) \le \mathcal{R}_0(0)$, i.e., the vaccination plays an important role in the basic reproduction number which can reduce the reproduction number, although the vaccine provides an imperfect protection. Thus, heroin vaccine will definitely benefit the people.

In the following, we will present some numerical simulations to study the dynamic behaviors of system (1) under the condition that the basic reproduction number is lager than one, i.e., $\mathcal{R}_0 > 1$. Before that, for simplicity, we take one month as the unit time. Note that the function $\theta \to p(\theta)$ and $a \to \alpha(a)$ are both almost everywhere bounded and belong to $L^\infty_+((0,+\infty),\mathbb{R}) \setminus \{0_{L^\infty}\}$. In this section we assume that the vaccine waning rate of the vaccinated individuals is

$$\alpha(a) = \begin{cases} 0.10(a-10)^2 e^{-0.35(a-10)}, & 10 < a \le 40; \\ 0.0025, & 40 < a < \overline{a}; \\ 0, & \text{otherwise}, \end{cases} \tag{54}$$

and the drug reuse rate of the individuals in treatment is

$$p(\theta) = 0.8(\theta+2)e^{-0.2(\theta+5)}, \tag{55}$$

for $\theta \in [0, \overline{\theta}]$, where $\overline{a}$, $\overline{\theta}$ are the maximum value of vaccination age and treat-age respectively. For simplify, we adopt that $\overline{a} = \overline{\theta} = 50$ (months).

To study the stability of the drug spread steady state of system (1), we adopt the other parameters in system (1) as follows

$$\Lambda = 10^3,\ \beta = 3.5\times10^{-7},\ \mu = 0.001, \delta_1 = 0.02,\ \delta_2 = 0.01,\ \psi = 0.1,\ \sigma = 0.85,\ \gamma = 4. \tag{56}$$

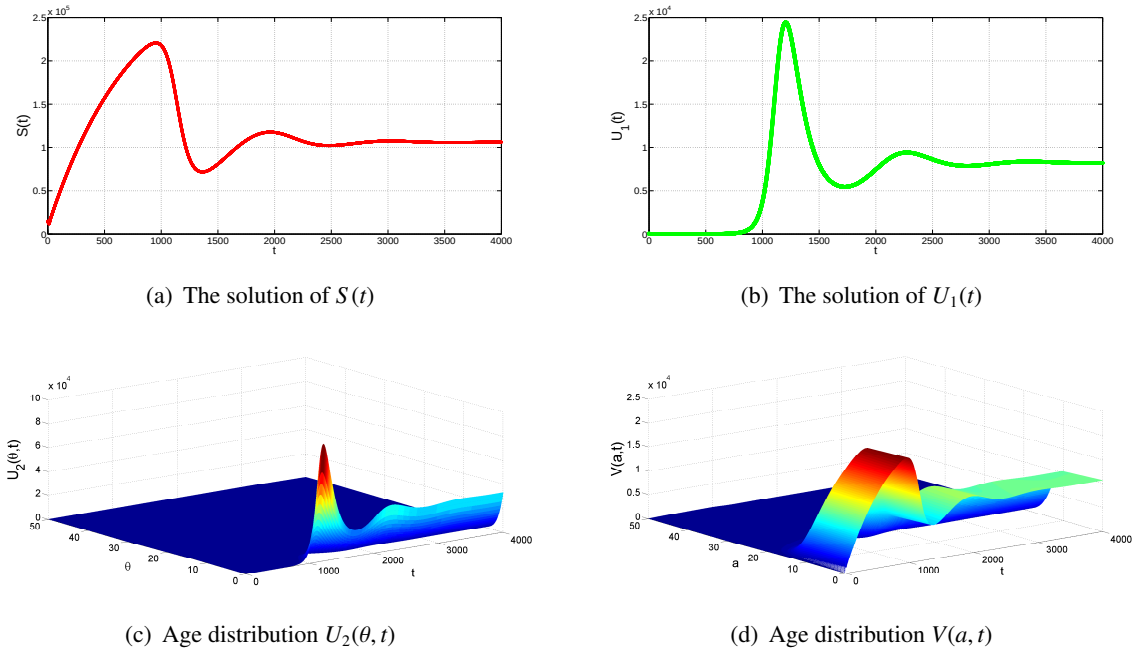
It follows from the expression of the basic reproduction number $\mathcal{R}_0$ that $\mathcal{R}_0 = 1.0117 > 1$. By use of the parameter values adopted in (54)-(56) and appropriate initial conditions, we will perform some

numerical simulations with the help of Matlab. The numerical simulations show that the drug spread steady state E^* is asymptotically stable if it exists (see Figure 1).

Furthermore, we want to illustrate that the stability of the drug spread steady state is not dependent on the initial conditions by numerical simulations. Let

$$\Lambda = 10^3,\ \beta = 7 \times 10^{-7},\ \mu = 0.001,\ \delta_1 = 0.02,\ \delta_2 = 0.01,\ \ \psi = 0.5,\ \sigma = 0.85,\ \gamma = 0.8. \tag{57}$$

We obtain that $\mathcal{R}_0 = 7.6102 > 1$ and simulate the solutions of system (1) under four pairs of initial values (see Figure 2). The numerical simulation results show that the stability of the drug spread steady state is not dependent on the initial conditions. In this case, we may conjecture that the drug spread steady state is globally asymptotically stable whenever it exists.



(a) The solution of $S(t)$

(b) The solution of $U_1(t)$

(c) Age distribution $U_2(\theta, t)$

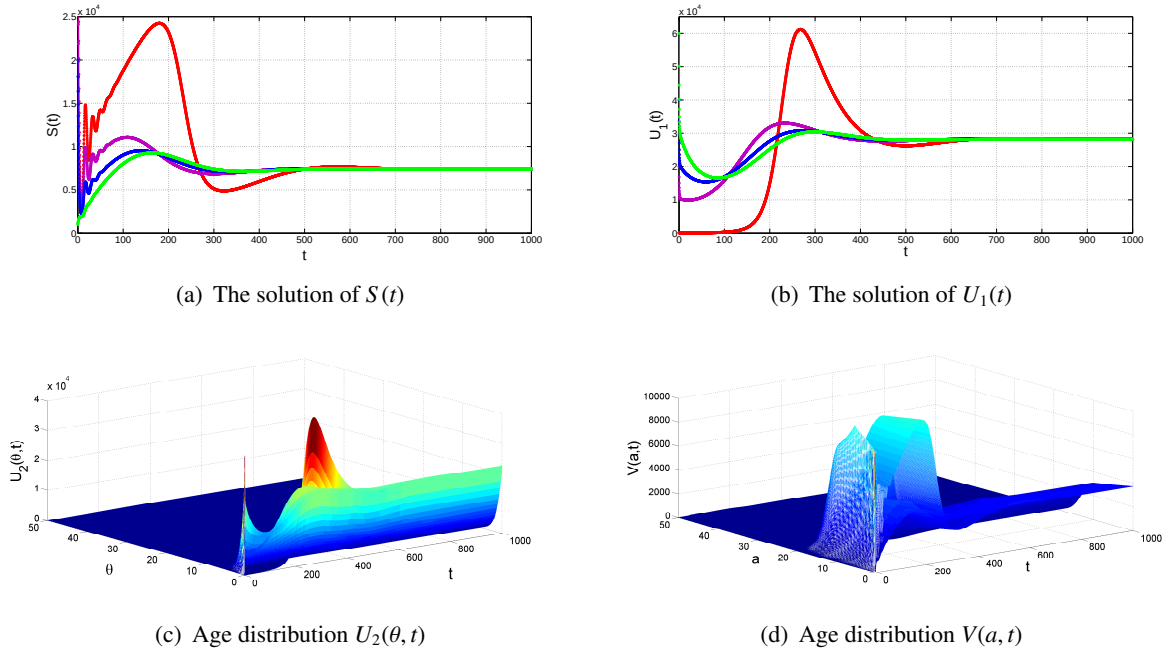
(d) Age distribution $V(a, t)$

Figure 1. If $\mathcal{R}_0 = 1.0117 > 1$, the drug spread steady state E^* of system (1) is asymptotically stable with initial conditions $S_0 = 15000$, $U_{10} = 100$, $U_{20}(0) = 10$, $U_{20}(\theta) = 0$ for $\theta \in (0, \overline{\theta}]$, $V_0(0) = 3000$, $V_0(a) = 0$ for $a \in [0, \overline{a}]$.

Appendix A.

In the course of the proof of Lemma 4.2, we let $\Re(\lambda) \geq 0$ and want to prove that $\Re(Z) > 0$, where

$$Z = \frac{\sigma^2\beta^2 U_1^* V^*}{B_2(\lambda)} + \frac{\beta^2 U_1^* S^*}{B_1(\lambda)} + \frac{\sigma\psi\beta^2 U_1^* S^*}{B_1(\lambda)B_2(\lambda)} \tag{A.1}.$$



(a) The solution of $S(t)$

(b) The solution of $U_1(t)$

(c) Age distribution $U_2(\theta, t)$

(d) Age distribution $V(a, t)$

Figure 2. If $\mathcal{R}_0 = 7.6102 > 1$, the solutions of system (1) approach the drug spread steady state E^* of system (1) with four different initial conditions.

To study the sign of $\Re(Z)$, we let $\lambda = x + iy$ with $x \geq 0$ which is assumed nonnegative in the proof of Lemma 4.2. Substituting $\lambda = x + iy$ into $(A.1)$, by some calculations, we can have that

$$\Re\left(\frac{\sigma^2\beta^2 U_1^* V^*}{B_2(\lambda)}\right) = \frac{(x + B_{22})\sigma^2\beta^2 U_1^* V^*}{(x + B_{22})^2 + y^2},$$
$$\Re\left(\frac{\beta^2 U_1^* S^*}{B_1(\lambda)}\right) = \frac{(x + B_{11})\beta^2 U_1^* S^*}{(x + B_{11})^2 + y^2},$$
$$\Re\left(\frac{\sigma\psi\beta^2 U_1^* S^*}{B_1(\lambda)B_2(\lambda)}\right) = \frac{[(x + B_{11})(x + B_{22}) - y^2]\sigma\psi\beta^2 U_1^* S^*}{[(x + B_{11})^2 + y^2][(x + B_{22})^2 + y^2]},$$

where

$$B_{11}(\lambda) = \mu + \psi + \beta U_1^*, \quad B_{22} = \mu + \sigma\beta U_1^*.$$

Summing the above three terms, we have that

$$\begin{aligned}\Re(Z) =& \Re\left(\frac{\sigma^2\beta^2 U_1^* V^*}{B_2(\lambda)}\right) + \Re\left(\frac{\beta^2 U_1^* S^*}{B_1(\lambda)}\right) + \Re\left(\frac{\sigma\psi\beta^2 U_1^* S^*}{B_1(\lambda)B_2(\lambda)}\right)\\ =& \frac{1}{C}\Big\{(x + B_{22})\sigma^2\beta^2 U_1^* V^*[(x + B_{11})^2 + y^2]\\ &+ (x + B_{11})\beta^2 U_1^* S^*[(x + B_{22})^2 + y^2]\\ &+ [(x + B_{11})(x + B_{22}) - y^2]\sigma\psi\beta^2 U_1^* S^*\Big\}\end{aligned}$$

$$=\frac{1}{C}\Big\{D_1 + D_2 y^2\Big\},$$

where

$$\begin{aligned}
C =&[(x + B_{11})^2 + y^2][(x + B_{22})^2 + y^2] > 0,\\
D_1 =&(x + B_{22})\sigma^2\beta^2 U_1^* V^*(x + B_{11})^2 + (x + B_{11})\beta^2 U_1^* S^*(x + B_{22})^2\\
&+ (x + B_{11})(x + B_{22})\sigma\psi\beta^2 U_1^* S^* > 0,\\
D_2 =&(x + B_{22})\sigma^2\beta^2 U_1^* V^* + (x + B_{11})\beta^2 U_1^* S^* - \sigma\psi\beta^2 U_1^* S^*\\
=&(x + B_{22})\sigma^2\beta^2 U_1^* V^* + \big(x + \mu + \beta U_1^* + (1 - \sigma)\psi\big)\beta^2 U_1^* S^* > 0.
\end{aligned}$$

It then follows that the real part of Z is positive, i.e., $\Re(Z) > 0$.

Appendix B.

To consider the roots of Equation (47), we let $\Re(\lambda) \geq 0$ and want to prove that $\Re(Z_1) > 0$, where

$$Z_1 = \frac{\beta^2 S^* U_1^*}{\lambda + \phi - \widehat{\Phi}(\lambda)} \tag{B.1}$$

Let $\lambda = x + iy$ with $x > 0$. By substituting $\lambda = x + iy$ into (B.1), we have that

$$Z_1 = \frac{\beta^2 S^* U_1^*}{x + \phi - \int_0^\infty \Phi(\theta) e^{-(x+iy)\theta} d\theta + iy} = \frac{\beta^2 S^* U_1^*}{E_1 + iE_2},$$

and

$$\Re(Z_1) = \frac{E_1}{E_1^2 + E_2^2}\beta^2 S^* U_1^*.$$

where $E_1 = x + \phi - \int_0^\infty \Phi(\theta) e^{-x\theta}\cos(y\theta)d\theta$ and $E_2 = y + \int_0^\infty \Phi(\theta) e^{-x\theta}\sin(y\theta)d\theta$. It follows from

$$E_1 = x + \phi - \int_0^\infty \Phi(\theta) e^{-x\theta}\cos(y\theta)d\theta \geq x + \phi - \int_0^\infty \Phi(\theta) e^{-x\theta} d\theta \geq x \geq 0$$

we have that $\Re(Z_1)$ is nonnegative.

Appendix C.

If $\sigma = 1$. Set $V(t) = \int_0^\infty V(a, t)da$. It follows from the last equation of system (1) that we have

$$\begin{aligned}
&\frac{dV(t)}{dt} = \int_0^\infty \frac{\partial V(a, t)}{\partial t} da\\
=&\int_0^\infty \left(-\frac{\partial V(a, t)}{\partial a} - (\mu + \alpha(a) + \beta U_1(t))V(a, t)\right) da\\
=&V(a, t)\Big|_{a=\infty}^{a=0} - (\mu + \beta U_1(t)) \int_0^\infty V(a, t)da - \int_0^\infty \alpha(a)V(a, t)da
\end{aligned}$$

$$=\psi S(t) - (\mu + \beta U_1(t))V(t) - \int_0^\infty \alpha(a)V(a,t)da.$$

Denote that $\widehat{S}(t) := S(t) + V(t)$. By dropping the hat, we have that

$$\frac{dS(t)}{dt} = \Lambda - \mu S(t) - \beta S(t)U_1(t).$$

Then system (1) can be rewritten as the main system in [10] and the drug spread steady state E^* is locally stable.

Acknowledgments

We would be very grateful to anonymous referees for their comments and suggestions that helped to improve this paper. This work is supported partially by China Postdoctoral Science Foundation 2017M621523; X. Li is supported partially by the National Natural Science Foundation of China (11771017); M. Martcheva is supported partially through grant DMS-1515661. Part of this work was done when XD was a visiting scholar at the Department of Mathematics, University of Florida. XD would like to thank the Department for kind hospitality he received there.

Conflict of interest

The authors declare there is no conflict of interest.

References

1. NIDA InfoFacts: Heroin. Available from: http://www.nida.nih.gov/infofacts/heroin.html.
2. J. Arino, C. C. McCluskey and P. van den Sriessche, Global results for an epidemic model with vaccination that exhibits backward bifurcation, *SIAM J. Appl. Math.*, **64** (2003), 260–276.
3. P. T. Bremer, J. E. Schlosburg, M. L. Banks, F. F. Steele, B. Zhou, J. L. Poklis and K. D. Janda, Development of a clinically viable heroin vaccine, *J. Am. Chem. Soc.*, **139** (2017), 8601–8611.
4. C. Comiskey, *National prevalence of problematic opiate use in Ireland*, EMCDDA Tech. Report, 1999.
5. O. Diekmann, J. A. P. Heesterbeek and J. A. J. Metz, On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations, *J. Math. Biol.*, **28** (1990), 365–382.
6. P. van den Driessche and J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, *Math. Biosci.*, **180** (2002), 29–48.
7. X. Duan, S. Yuan and X. Li, Global stability of an SVIR model with age of vaccination, *Appl. Math. Comput.*, **226** (2014), 528–540.
8. X. Duan, S. Yuan, Z. Qiu and J. Ma, Global stability of an SVEIR epidemic model with ages of vaccination and latency, *Comp. Math. Appl.*, **68** (2014), 288–308.

9. *European Monitoring Centre for Drugs and Drug Addiction (EMCDDA): Annual Report*, 2005. Available from: http:// annualreport.emcdda.eu.int/en/homeen.html.
10. B. Fang, X. Z. Li, M. Martcheva and L. M. Cai, Global asymptotic properties of a heroin epidemic model with treat-age, *Appl. Math. Comput.*, **263** (2015), 315–331.
11. J. K. Hale, *Asymptotic Behavior of Dissipative Systems*, Mathematical Surveys and Monographs Vol 25, American Mathematical Society, Providence, RI, 1988.
12. W. Hao, Z. Su, S. Xiao, C. Fan, H. Chen and T. Liu, Longitudinal surveys of prevalence rates and use patterns of illicit drugs at selected high-prevalence areas in china from 1993 to 2000, *Addiction.*, **99** (2004), 1176–1180.
13. W. M. Hirsch, H. Hanisch and J. P. Gabriel, Differential equation models of some parasitic infections: methods for the study of asymptotic behavior, *Comm. Pure Appl. Math.*, **38** (1985), 733–753.
14. M. Iannelli, M. Martcheva and X. Z. Li, Strain replacement in an epidemic model with super-infection and perfect vaccination, *Math. Biosci.*, **195** (2005), 23–46.
15. M. Iannelli, *Mathematical theory of age-structured population dynamics*, CNR Applied Mathematics Monographs, Giardini, Pisa, Vol. 7, 1995.
16. A. Kelly, M. Carvalho and C. Teljeur, *Prevalence of Opiate Use in Ireland 2000-2001. A 3-Source Capture Recapture Study. A Report to the National Advisory Committee on Drugs*, Subcommittee on Prevalence. Small Area Health Research Unit, Department of Public.
17. C. M. Kribs-Zaleta and J. X. Velasco-Hernndez, A simple vaccination model with multiple endemic states, *Math. Biosci.*, **164** (2000), 183–201.
18. C. M. Kribs-Zaleta and M. Martcheva, Vaccination strategies and backward bifurcation in an age-since-infection structured model, *Math. Biosci.*, **177&178** (2002), 317–332.
19. X. Z. Li, J. Wang and M. Ghosh, Stability and bifurcation of an SIVS epidemic model with treatment and age of vaccination, *Appl. Math. Model.*, **34** (2010), 437–450.
20. X. Liu, Y. Takeuchi and S. Iwami, SVIR epidemic models with vaccination strategies, *J. Theor. Bio.*, **253** (2008), 1–11.
21. D. R. Mackintosh and G. T. Stewart, A mathematical model of a heroin epidemic: implications for control policies, *J. Epidemiol. Commun. H.*, **33** (1979), 299–304.
22. P. Magal, Compact attractors for time-periodic age-structured population models, *Electron. J. Differ. Eq.*, **65** (2001), 1–35.
23. P. Magal and H. R. Thieme, Eventual compactness for semiflows generated by nonlinear age-structured models, *Commun. Pure Appl. Anal.*, **3** (2004), 695–727.
24. R. K. Miller, *Nonlinear Volterra integral equations Mathematics Lecture Note Series*, W.A. Benjamin Inc., Menlo Park, CA, 1971.
25. K. A. Sporer, Acute heroin overdose, *Ann. Intern. Med.*, **130** (1999), 584–590.
26. H. R. Thieme, Semiflows generated by Lipschitz perturbations of non-densely defined operators, *Diff. Int. Eqns.*, **3** (1990), 1035–1066.

27. J. Wang, R. Zhang and T. Kuniya, The dynamics of an SVIR epidemiological model with infection age, *IMA J. Appl. Math.*, **81** (2016), 321–343.
28. W. D. Wang and X. Q. Zhao, Basic reproduction numbers for reactio-diffusion epidemic models, *SIAM J. Appl. Dyn. Syst.*, **11** (2012), 1652–1673.
29. Y. Xiao and S. Tang, Dynamics of infection with nonlinear incidence in a simple vaccination model, *Nonlinear Anal. Real World Appl.*, **11** (2010), 4154–4163.
30. J. Yang, M. Martcheva and L. Wang, Global threshold dynamics of an SIVS model with waning vaccine-induced immunity and nonlinear incidence, *Math. Biosci.*, **268** (2015), 1–8.

AIMS Press